Alcohol Abuse, Immunosuppression, and Pulmonary Infection

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Abstract: Excessive alcohol consumption predisposes the host to a wide range of infectious complications, particularly pulmonary infections. Factors that contribute to the development of pulmonary infections in alcohol-abusing patients include dysfunction of the protective barriers in the respiratory tract, aspiration of oropharyngeal contents, nutritional deficiencies, liver disease, and impairment of host defense mechanisms. This review discusses the complex host-pathogen interactions in the airways with an emphasis on how alcohol consumption adversely affects these mechanisms and predisposes the host to infections. Potential immunomodulatory strategies for enhancing host defense function in alcohol-consuming patients are also discussed.

Keywords: Alcohol abuse, lung, infection, pneumonia, immunity, host defense.

INTRODUCTION

Alcohol abuse predisposes the host to a wide range of infectious diseases, particularly pneumonia [1, 2]. Accumulated *in vivo* and *in vitro* studies have shown that alcohol alters/compromises the immune system, thereby increasing the susceptibility of the host to pulmonary infections. Other factors that contribute to pulmonary infections in alcohol abusers include dysfunction of protective barriers in the respiratory tract, aspiration of oropharyngeal contents, nutritional deficiencies, and liver disease. Alcohol-abusing patients with pulmonary infections are characterized by severe symptoms, frequent complications, and poor outcomes. Treatment of infection in these immunocompromised hosts has continued to be a major challenge to modern medicine. This review discusses the complex host-pathogen interactions that occur in the airways with an emphasis on how alcohol consumption adversely affects these interactions resulting in lung infections. Potential immunomodulatory strategies for improving host defenses against pulmonary infections in alcoholic patients are also discussed.

EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

It has long been recognized that excessive alcohol consumption is associated with an increased risk of developing infections. 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 1785, in which he reported that alcohol abusers were vulnerable to yellow fever, tuberculosis, pneumonia, and abscesses [3]. In 1905, Sir William Osler stated that alcohol abuse was "perhaps the most potent predisposing factor to lobar pneumonia" [4]. Shortly thereafter, Capps and Coleman reported that the mortality rate of pneumonia was more than doubled in alcoholics compared to nonalcoholics [5]. Consistent with these early observations, subsequent large cohort studies have repeatedly shown that alcohol abuse significantly increases the incidence and severity of pulmonary infections. One study of 1722 alcoholic patients in Oslo from 1925 to 1940 reported that the age-specific death rates caused by pneumonia were more than three times higher in alcohol abusers compared to those in the general population [6]. Another study of 1298 patients with lobar pneumonia from 1927 to 1935 showed that the mortality rate in alcohol-abusing patients was approximately twice that of nonalcoholic patients [7]. 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 [8]. Fernandez-Sola reported a two-phase study in 1995 [9]. Among the risk factors analyzed, excessive alcohol consumption was the only independent risk factor for community-acquired pneumonia. Alcoholic patients with pneumonia showed more severe clinical symptoms, required longer duration of intravenous antibiotics and hospital stays, and had more multilobar involvement and pleural effusions with slower resolution of pulmonary infiltrates. In addition, high alcohol intake was the only prognostic factor for mortality. Similarly, a cohort study of 23,198 pneumonia patients hospitalized in 1992 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 [10]. Another recent study in patients with severe community-acquired pneumonia presenting with septic shock reported that alcohol abuse predisposes patients to pulmonary infections with *Pseudomonas aeruginosa* and *Acinetobacter* species, both of which are frequently fatal (82%) [11]. In 2000, Musher and colleagues reported a prospective study identifying predisposing factors for pneumococcal pneumonia with and without bacteremia. Their investigation 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 [12]. In addition to community-acquired pneumonia, alcohol abuse has also been shown to be a sig-

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nificant risk factor for hospital-acquired pneumonia. Everts and colleagues reported a one-year prospective study of consecutive patients hospitalized for general medical and surgical diseases [13]. Nosocomial pneumonia developed in 126 patients representing 6.1 per 1000 admissions. Fourteen patients (11%) died as a consequence of pneumonia. Alcohol abuse was identified as one of the most powerful predictors of a fatal outcome. In 2004, Bochicchio and colleagues reported 204 cases of pneumonia in 714 trauma patients admitted to the intensive care unit. Alcohol abuse was listed as a leading premorbid risk factor in this series [14].

Pulmonary infection caused by a wide range of bacterial pathogens, including Gram-positive, Gram-negative, aerobic, anaerobic, as well as mycobacteria, occur more frequently in alcohol abusers than in the general population. Alcohol abusers are also susceptible to lung infections caused by fungi and viruses. Unique features of pulmonary infections in alcoholic patients include a younger age of occurrence, more severe symptoms, higher incidence of complications, more frequent recurrence, greater likelihood of developing resistant pathogens, and poorer outcomes. Alcoholic patients with cirrhosis or bone marrow suppression have the poorest prognosis. A prominent phenomenon in alcohol abusers suffering from bacterial pneumonia is that these patients frequently present with granulocytopenia, which is an indicator of increased mortality. McFarland and Libre reported 10 alcohol abusers with 12 episodes of infections [15]. Bacterial pneumonia accounted for 11 of them. Leukopenia was present in 6 episodes on admission and the remaining 6 cases developed leukopenia within 24 hours after hospitalization. Fruchtman and colleagues identified 10 leukopenic patients with *S. pneumoniae* pneumonia [16]. Eight of them were alcoholics. All of these patients developed the adult respiratory distress syndrome (ARDS) with a mortality rate at 50%. Perlino and Rimland analyzed 95 episodes of pneumococcal bacteremia in 93 patients [17]. Pneumonia was identified in 80 of these patients. The most common pre-existing illness was alcoholism (in 52 patients) which was significantly associated with leukopenia. Patients with alcoholism, leukopenia, and pneumococcal sepsis (the ALPS syndrome) constituted 12.6% of this series and had a mortality rate greater than 80%.

Similar to that in the general population, *Streptococcus pneumoniae* has been reported to be the most frequent pathogen causing lung infections in individuals consuming excess alcohol [18, 19]. A recent study of 1511 hospitalized patients with community-acquired pneumonia showed that *S. pneumoniae* was isolated in 27% of alcoholic patients in this series [18]. *Hemophilus influenzae* and *Klebsiella pneumoniae* are also frequent pathogens causing pneumonia in alcoholic patients. Pulmonary infection caused by *K. pneumoniae* is usually life-threatening and associated with a high frequency of complications and death. Alcoholic patients have been reported to have a high incidence of pulmonary infections with *Pseudomonas aeruginosa* and *Acinetobacter* species which frequently result in death. Because alcohol is a potent inhibitor of the central nervous system and the cough reflex, aspiration of oropharyngeal bacteria is common in alcohol abusers. Accordingly, anaerobic lung infections with *Fusobacterium nucleatum*, *Bacteriodes melaninogenicus*, and *Bacteriodes fragilis* are frequently observed in alcohol abusing patients in the form of simple pneumonitis, necrotizing pneumonia, lung abscess, and empyema [20]. In fact, studies have shown that about 30% of all anaerobic pulmonary infections occur in heavy alcohol consumers [20, 21].

Pulmonary tuberculosis occurs more frequent in alcohol abusers than in the general population. Alcoholic patients with pulmonary tuberculosis usually have more extensive disease and a higher risk of death during the initial hospitalization. Alcohol addiction is an independent risk factor for mortality in tuberculosis patients. A study of 1493 tuberculosis patients has shown that patients who excessively consume alcohol are at increased risk of hospitalization during treatment [22]. Lack of patient compliance is a significant problem for the effective treatment of tuberculosis in these individuals. High rates of relapse and the development of multiple drug-resistant strains are common in alcohol abusers. The HIV epidemic, especially among substance abusers and alcoholics, has played an important role in the worldwide resurgence of tuberculosis during the last two decades.

Pneumocystis carinii (also known as *Pneumocystis jirovecii*), is a common pathogen causing pulmonary infections in immunocompromised hosts. In recent years, the etiological significance of these opportunistic pathogens in alcohol abusers has come to attention because of the increased incidence of HIV infection in this population. *P. carinii* pneumonia occurs frequently in hosts with impaired cell-mediated immunity and is a common opportunistic infection in HIV-infected individuals. Alcohol suppresses cell-mediated immunity. Studies have shown that intrapulmonary challenge with *P. carinii* in mice on a chronic alcohol-containing diet significantly increases *P. carinii* infection in the lung (greater than 60% in the alcohol-fed group *vs* none in control group) [23]. *P. carinii* pneumonia has been observed in patients with alcoholic hepatitis and cirrhosis [24].

NORMAL IMMUNE DEFENSE MECHANISMS OF THE RESPIRATORY TRACT

The human respiratory tract has developed a sophisticated defense system that effectively protects the host from infections. The host defense mechanisms in the respiratory tract include both innate (nonspecific) and acquired (specific) immunity. Innate immunity consists of mechanical defenses, antimicrobial molecules generated in the airways, and phagocytic defenses provided by the resident alveolar macrophages and the polymorphonuclear leukocytes (PMNs) that are recruited into the lung in response to infection. Mechanical host defenses include the structural barriers in the respiratory tract and mucociliary blanket lining the surface of the airways. Mucins in the mucociliary fluid trap airborne particles and microorganisms. The mucus containing trapped particles and microbes is propelled to the oropharynx by ciliary movement. Clearance of secretions from the airways is facilitated by coughing. Particles with sizes smaller than 5 μm in diameter can bypass these mechanical defense mechanisms and deposit in the alveoli. This size discrimination is particularly relevant to the pathogenesis of pulmonary infection as most pathogenic microbes are within this size range. In addition to mechanical defenses, airways produce a variety of antimicrobial molecules including lysozyme, complement, immunoglobulin A and G, fibronectin, lactoferrin, transferrin, LPS-binding protein, defensins, cathelicidins, and collectins. Some of these molecules possess direct an-

timicrobial activity while others facilitate phagocytes in the elimination of pathogenic microbes.

Alveolar macrophages are the resident phagocytes in the alveolar space. Under normal conditions, approximately one alveolar macrophage is found in each alveolus [25]. These cells constitute the major cell type recovered by bronchoalveolar lavage (BAL). In normal individuals, approximately 85 to 95 percent of cells obtained by BAL are alveolar macrophages with the remainder being lymphocytes and other cell types [25, 26]. Alveolar macrophages typically exhibit a lobulated nucleus surrounded by vacuolated cytoplasm containing abundant mitochondria and electron-dense secondary lysosomes. Under certain circumstances such as chronic inflammation, these phagocytes may merge and form multinucleated cells. The size of alveolar macrophages varies widely from 12 μm (similar to blood monocytes) to 50 μm (as seen in multinucleated cells or those in smokers). The size change in the alveolar macrophage population is associated with different disease states. In acute inflammation, the number of small, monocyte-like macrophages is usually increased. In contrast, chronic lung disorders are often associated with an increase in large, more mature macrophage numbers in the alveolar space. These resident alveolar macrophages constitute the first line of phagocytic defense in the terminal airways. They are avidly phagocytic and responsible for the clearance of daily air-borne particles and small loads of pathogenic microbes in order to maintain the sterility of the air-exchange surface in the lung. Certain pathogens, such as *Mycobacterium spp* and *Legionella spp,* are resistant to the microbicidal activities of alveolar macrophages. They can proliferate intracellularly. Other immune defense mechanisms such as cell-mediated immunity are required for eliminating these pathogens. When alveolar macrophages are confronted with invading pathogens that are either too virulent or of too large an inoculum, these cells are capable of generating numerous mediators that orchestrate the recruitment of PMNs from the systemic circulation into the alveolar space. These recruited PMNs provide auxiliary phagocytic defenses to reinforce the immune response against offending pathogens. 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, complement fragments including C3a and C5a, and arachidonic acid metabolites such as leukotriene B4.

Cytokines are responsible for communication among different cellular components of the immune system. Based on their functional activities, these mediators can be largely divided into pro- and anti-inflammatory subgroups. Both pro-inflammatory and anti-inflammatory cytokines are critical in the regulation of the pulmonary host defense response. They mediate functional adjustment of various effector cell types in the immune system during different stages of the immune defense response.

A number of pro-inflammatory cytokines have been identified to play an important role in pulmonary host defense. These mediators include tumor necrosis factor-α (TNF-α), interleukin-8 (IL-8), macrophage inflammatory protein-2 (MIP-2), granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), interleukin-12 (IL-12), and interferon-γ (IFN-γ). TNF-α is an early response cytokine rapidly produced by alveolar macrophages following exposure to infectious stimulants. TNF-α activates alveolar macrophages and, perhaps, other cell types in the alveoli such as type II epithelial cells. It enhances functional activities of these cells and stimulates the release of other cytokines and chemokines by different types of pulmonary cells. CXC chemokines, including IL-8 and MIP-2 in humans, as opposed to cytokine-induced neutrophil chemoattractant (CINC) or keratinocyte-derived chemokine (KC) and MIP-2 in rodents, are potent chemoattractants for PMNs. In response to bacterial infection, pulmonary cells produce large amounts of these chemokines which provide chemotactic signals in the lung for PMN recruitment. CXC chemokines have also been shown to enhance PMN activities including the expression of surface adhesion receptors, phagocytosis, and production of reactive oxygen species. Several CXC chemokines including IL-8, MIP-2, and KC have also been shown to stimulate granulocyte mobilization from hematopoietic tissues into the circulation [27-30].

G-CSF is a lineage-specific hematopoietic growth factor that selectively stimulates the proliferation and maturation of myeloid progenitor cells to PMNs. Cells at all stages of granulocyte lineage, including their up-stream precursors (CD34+CD33-, and lin-ckit+Sca-1+), have G-CSF receptors (G-CSFR) and respond to G-CSF with increased proliferation [31-34]. In addition to stimulating myeloid cell proliferation and neutrophil maturation, G-CSF also enhances the release of PMNs and their progenitors from the bone marrow into the systemic circulation [35-37]. Under normal conditions, G-CSF plays a critical role in maintaining the regular level of PMNs in the blood stream. During lung infection, pulmonary cells including alveolar macrophages and epithelial cells increase their production of G-CSF, resulting in a rapid elevation of G-CSF level in the systemic circulation. Clinical studies have shown that G-CSF in the circulation is significantly increased in patients with bacterial pneumonia [38, 39]. Studies from our group have shown that animals challenged with intrapulmonary bacteria rapidly increase G-CSF production in the lung [31, 40]. We have also shown that exogenous G-CSF instilled into the lung rapidly enters the blood stream. The granulopoietic activity in hematopoietic tissues and mobilization of PMNs and their progenitors into the circulation are enhanced in animals either challenged with intrapulmonary bacteria or treated with recombinant G-CSF [31, 41]. Thus, G-CSF produced from tissue sites of infection and inflammation plays a crucial role in the initiation and regulation of the granulopoietic response [41, 42]. In addition to stimulating granulopoiesis in hematopoietic tissues, G-CSF enhances the functional activities of mature PMNs including adhesion molecule expression, chemotaxis, oxygen metabolism, phagocytosis, and intracellular bacterial killing.

GM-CSF is a 23-kDa secreted polypeptide that functions as a growth factor predominantly stimulating bone marrow cells of myeloid lineages. Compared to G-CSF, GM-CSF has a broader spectrum of leukocyte stimulation that includes neutrophils, eosinophils, monocytes, macrophages, and dendritic cells. In addition, this cytokine also stimulates bone marrow production of erythrocytes and megakaryocytes and influences the growth of alveolar epithelium of the lung. Since the function of GM-CSF on hematopoietic cells over-

laps with other hematologic cytokines, impairment of hematopoiesis or myelopoiesis does not occur in animals with targeted ablation of the GM-CSF gene or its receptor gene ($GM^{-/-}$ or $GMR_{\beta c}^{-/-}$ mice) [43]. In the respiratory tract, GM-CSF is expressed by a variety of pulmonary cells including epithelial cells, alveolar macrophages, fibroblasts, and activated T lymphocytes [43-46]. It plays a crucial role in stimulating the terminal differentiation of alveolar macrophages and accumulation of these cells in the lung [43]. GM-CSF up-regulates alveolar macrophage Fcγ receptor expression and enhances antibody- and complement-mediated phagocytosis [47, 48]. Other functional activities of macrophages that are enhanced by GM-CSF include antigen presentation, cytokine production, oxygen metabolism, and intracellular killing of microbes. Intrapulmonary challenge with bacteria causes a significant increase in lung leukocyte production of GM-CSF in mice [49]. Mice with GM-CSF deficiency show defects in alveolar macrophage phagocytosis, bacterial killing, and hydrogen peroxide production. These animals are also defective in production of leukotrienes, prostaglandin E_2, TNF-α, IFN-γ, MIP-2, and KC by lung leukocytes post-infection. In addition to these defects, GM-CSF deficient mice have higher bacterial loads in the lung, spleen, and systemic circulation with a decreased survival rate following intrapulmonary challenge with *P. aeruginosa* compared to normal control mice.

Other pro-inflammatory cytokines, such as IL-12 and IFN-γ also have important immunoregulatory functions. IL-12 promotes Th1-type immune responses and enhances cell-mediated immunity against airway infections caused by viruses, mycobacteria, fungi, and parasites. In addition, IL-12 promotes innate immunity in the lung against bacterial pathogens in experimental models of infection. Patients with IL-12 deficiency develop recurrent pneumococcal pneumonia with sepsis and other infections. IFN- γ exerts profound effects on various aspects of host defense against a wide range of pathogens including viruses, bacteria, fungi, and parasites [50]. IFN- γ enhances cytokine and chemokine production by alveolar macrophages and other types of leukocytes. It also stimulates the respiratory burst and release of lysosomal enzymes from PMNs, and actively modulates antigen presentation, cell differentiation, and cytotoxicity of immune effector cells.

As named, anti-inflammatory cytokines down-regulate host immune responses. Interleukin-10 (IL-10) is a representative of these mediators. IL-10 inhibits the production of many proinflammatory cytokines including TNF-α, interleukin-1-β (IL-1β), IFN- γ, IL-12, MIP-2, and macrophage inflammatory protein-1α (MIP-1α). IL-10 also suppresses the functional activities of PMNs [51]. This cytokine plays an important role in modulating the intensity of the host response to an infection and affecting the resolution of inflammation when the infection is confined.

PMNs represent the largest phagocyte population in the circulation of humans. Under normal conditions, very few PMNs exist in the alveolar space. The marginated pool of PMNs in the pulmonary vasculature represents a large number of PMNs [52]. Mature PMNs have a characteristically segmented nucleus. The cytoplasm of PMNs contains a mixed population of granules, one-third of which are peroxidase positive. Peroxidase-positive (azurophilic or primary) granules contain myeloperoxidase and numerous lysosomal enzymes. These granules also contain bactericidal factors including the defensins, azurophil-derived bactericidal factors, and bactericidal permeability-increasing protein or cationic proteins. Peroxidase-negative granules include specific (secondary) granules and gelatinase granules. The former are rich in lactoferrin, B12 binding proteins, and other polypeptides, while the latter contain abundant gelatinase. All of these granules contain lysozyme. In addition to these granules, PMN cytoplasm contains secretory vesicles. The content of these vesicles include latent alkaline phosphatase and plasma proteins, such as albumin, that are endocytosed from the plasma.

In response to infectious stimuli, PMNs in the pulmonary vasculature rapidly migrate into the alveolar space to reinforce phagocytic and bactericidal defenses. Experimental studies have shown that intrapulmonary challenge with either bacteria or bacterial components, such as LPS, elicits a massive migration of PMNs from the vasculature into the alveolar space in animals. Several hours after the challenge, PMNs constitute 60% to 90% of the total cells recovered by BAL [53-55]. In patients with pulmonary infection, the alveolar space is also filled with large numbers of PMNs. PMN activation occurs during the recruitment of these cells as they are exposed to a variety of proinflammatory cytokines and mediators contained within the infected compartment. In addition to the ingestion and killing of invading microbes, recruited PMNs may participate in regulating the local defense response by producing different cytokines including TNF-α, IL-1β, IL-6, and MIP-2. S100A8 (calgranulin A or myeloid-related protein 8, MRP8) and S100A9 (calgranulin B, MRP14) are phagocyte-specific calcium-binding proteins belonging to the S100 family. During infection and inflammation, tissue recruited PMNs are able to release large amounts of S100 proteins into the surrounding environment [56]. Studies have shown that binding of S100A8/S100A9 complexes to carboxylated *N*-glycans on endothelial cells enhances the subsequent adhesion of phagocytes to the vascular endothelium [57]. Interaction of S100A9 with granulocytes increases the binding activity of β_2-integrins and up-regulates the expression of high affinity Mac-1 receptors on these cells [58]. In addition, S100A8 and S100A9 have been identified as potent chemoattractants for neutrophils and macrophages [59, 60]. The function of S100 proteins may serve as a positive feedback signal for the continued recruitment of PMNs into inflammatory sites [61]. Data suggest that the initial chemotactic signals for PMN migration into the lung are primarily the chemokines produced by alveolar macrophages following the infection. The release of S100 proteins by the first wave of recruited phagocytes promotes and facilitates the further recruitment of additional leukocytes into alveolar space. PMNs also trap and scavenge chemokines in the surrounding environment, which may play an important role in the resolution of the inflammatory response in the lung [62, 63].

During the process of PMN recruitment into the alveolar space in response to pulmonary infection, the number of PMNs in the circulatory system needs to be replenished or increased in order to support and/or reinforce the on-going tissue recruitment of PMNs. Hematopoietic tissues accelerate their release of mature PMNs from the marrow storage pool and increase the production of PMNs in order to main-

tain or increase the level of PMNs in the circulation. It has long been recognized that an increase in blood granulocyte counts frequently accompanies bacterial pneumonia. The increased production of granulopoietic cytokines such as G-CSF and certain CXC chemokines increase the rate of PMN production from their precursor cells, shorten PMN maturation time, reduce the retention time of granulocytes in the bone marrow, and enhance the release of these phagocytes into the circulation. The transit time of PMNs through the bone marrow mitotic (or proliferative) and postmitotic (maturation-storage) pools to blood is significantly reduced in both animals challenged with intrapulmonary *S. pneumoniae* and patients with lobar pneumonia [64, 65].

Dendritic cells represent another large population of resident phagocytes in the lung. The precursors of these cells are blood monocytes. After migrating into airway tissues, they differentiate into a distinct cell type with long processes bearing MHC class II receptors. These cells form a meshwork widely distributed within the respiratory tract. They exist in airway epithelial layer, submucosa, and lung parenchyma. Dendritic cells have also been identified on the alveolar surface, accessible by bronchoalveolar lavage [66]. Airway dendritic cells possess the ability to travel from tissue sites to regional draining lymph nodes *via* afferent lymphatic vessels or to the spleen *via* the bloodsteam [67]. In response to an inflammatory challenge, the number of dendritic cells can be rapidly increased in the local tissues [68]. Compared with alveolar macrophages, dendritic cells are relatively weak in phagocytic activity. These cells are able to ingest inhaled materials including particulate matter, viruses, bacteria, and fungi. At the present time, the contribution of phagocytosis conducted by dendritic cells to host innate immune defense of the airways remains poorly characterized. However, ingestion of antigen-bearing particles and pathogens by dendritic cells has been known as a critical component of antigen capturing and processing in the respiratory tract. Studies have shown that airway dendritic cells are efficient antigen-presenting cells [66]. They capture, process, and retain inhaled antigens while migrating to the regional lymph nodes where they present these antigens to T cells to initiate the acquired (or specific) immune response.

The acquired immune defense system in the human lung consists of both humoral and cellular components, which function as the major host defenses against pathogens that are capable of evading the innate immune defense system. Developing an effective specific immune response encompasses a complex interaction between antigen presenting cells or accessory cells (such as dendritic cells and alveolar macrophages) and lymphocytes (T and B lymphocytes). Antigens of invading pathogens are captured and processed initially by antigen presenting cells. The processed antigens together with class II major histocompatibility complex (MHC) molecules on the antigen presenting cell surface are then presented to helper T (Th) lymphocytes through binding of the class II MHC-antigen complexes to CD4 receptors expressed on the surface of helper T lymphocytes. Additional stimuli provided by the engagement of nonantigenic matching ligands and co-stimulatory receptors such as CD25, CD40, CD80, CD83, and CD86 expressed on the surface of helper T cells and antigen presenting cells, respectively, as well as cytokines (e.g., IL-1 and TNF) generated by the antigen presenting cells will help activation of the engaged CD4+ T lymphocytes. The activated CD4+ T lymphocytes subsequently develop into specific helper T cells to produce various types of cytokines which mediate the proliferation and activation of immune effector cells including B lymphocytes and cytotoxic T lymphocytes (CTL). The profile of cytokines produced by the helper T cells dictates which branch of specific immunity (i.e., humoral or cell-mediated) will become the predominant response.

In the respiratory tract, dendritic cells are considered to be the primary antigen presenting cells. Alveolar macrophages are weaker than dendritic cells at antigen presentation. It has been proposed that alveolar macrophages may play a role in antigen transfer. Alveolar macrophages initially take up the antigen and then transfer the processed peptides to dendritic cells for efficient presentation [69]. Antigens in the terminal airways may either directly diffuse into regional lymphoid tissues or be captured by antigen presenting cells which then migrate to regional lymph nodes. The primary immune response is initiated within these regional lymphoid tissues to produce a large number of immune effector cells including CTLs and antibody producing B cells. These effector B and T cells generated during the primary immune response then traffic back to the infected lung through the systemic circulation and eventually reside in the interstitium and alveolar space by means of their homing mechanisms. In general, it takes days to weeks to develop a specific immune response to a new antigen. During the primary immune response, memory B and T cells are generated. These memory cells can rapidly (hours to days) organize a response when the host is subsequently exposed to the same antigen [69]. Under normal conditions, memory cells constitute the predominant type of lymphocyte residing in the lung [70].

THE EFFECT OF ALCOHOL ON PULMONARY IMMUNE DEFENSE MECHANISMS

Excessive alcohol consumption impairs both the innate and acquired immunity. The most extensively characterized immune defect caused by alcohol is suppression of PMN function. In 1938, Pickrell observed that rabbits intoxicated with alcohol failed to mount an acute leukocytic response to pneumococcal infection in the lung [71]. Subsequent studies in experimental animals and human subjects have repeatedly shown that alcohol impairs tissue recruitment of PMNs during infection and inflammation. Green and colleagues documented that pulmonary clearance of bacteria was suppressed by alcohol intoxication [72]. Astry and colleagues studied the relationship between the alcohol-induced defects of PMN recruitment and pulmonary clearance of bacteria [73]. In their experiments, animals were challenged by aerosol inhalation of either Gram-positive (*Staphylococcus aureus*) or Gram-negative (*Proteus mirabilis*) bacteria in the presence and absence of acute alcohol intoxication. Pulmonary recruitment of PMNs in response to bacterial challenge was inhibited by alcohol intoxication in a dose-dependent manner. In association with impaired PMN recruitment, pulmonary clearance of both the Gram-positive and Gram-negative bacteria was suppressed by alcohol. Studies from our group have shown that acute alcohol intoxication causes a profound inhibition of PMN delivery to the alveolar space of rats challenged with intrapulmonary *S. pneumoniae*, which is assoc-

iated with more severe lung infection and increased mortality [54].

Tissue recruitment of PMNs in response to infection and inflammation is a complex process that involves PMN margination, adhesion, and transendothelial migration. An intricate interplay of various adhesion molecules on the surface of both PMNs and the endothelium of the microvasculature takes place during this multi-step process. Chemoattractants produced by infected tissues guide PMN migration from the vasculature into the infected tissue sites. Alcohol has been shown to inhibit several steps of this process. In response to infectious stimuli, circulating PMNs rapidly up-regulate β_2-integrin adhesion molecule CD11b/CD18 expression. CD11b/CD18 mediates PMN firm attachment to the endothelium and the subsequent transendothelial migration. Alcohol inhibits up-regulation of CD18 expression on PMNs in response to inflammatory stimuli [74] and suppresses PMN "hyperadherence" to endothelial monolayers following appropriate stimulation [75]. Our studies have shown that alcohol intoxication suppresses up-regulation of CD11b/c and CD18 expression on circulating PMNs in animals challenged with systemic LPS [76]. Other investigators have also reported that alcohol causes a dose-dependent inhibition of granulocyte adherence.

Appropriate response of PMNs to chemotactic signals is necessary for the directed migration of these phagocytes. Alcohol has been shown to impair the PMN response to chemoattractants. Rats intoxicated with alcohol show a significant decrease in PMN chemotaxis to LPS-activated normal rat serum [77]. PMNs from alcohol abusers also exhibit a decreased chemotactic response [78, 79]. In patients with alcoholic liver diseases, LPS absorbed from the portal system may gain access to the systemic circulation due to either the development of a shunt between these two systems or impaired Kupffer cell function. LPS in the systemic circulation may induce a chronic inflammatory reaction within the body. Chemoattractants such as CXC chemokines (IL-8) and complement fragments (C5a) are elevated in the peripheral circulation of patients with alcoholic liver diseases [80, 81]. This chronic *in vivo* activation of PMNs has been postulated to account for the blunted response of PMNs to chemoattractants in these hosts.

In addition to alcohol-induced impairment of the PMN response to chemotactic stimuli, acute alcohol intoxication also suppresses CXC chemokine production in the lung during pulmonary infection and inflammation [54, 56, 82]. This inhibition occurs at the level of both gene expression and protein production. Studies have shown that the increase in CINC and MIP-2 concentrations in BAL fluid of rats following intrapulmonary challenge with *S. pneumoniae* is markedly attenuated by acute alcohol intoxication [83]. Correspondingly, the chemotactic activity for PMNs in BAL fluid recovered from alcohol intoxicated rats challenged with intrapulmonary *S. pneumoniae* is markedly reduced as compared to those of control animals with *S. pneumoniae* pneumonia. Repleting these CXC chemokines in the BAL fluid of alcohol intoxicated animals partially restores chemotactic activity for PMNs. Alcohol intoxication suppresses the chemokine response in the lung and impairs the establishment of a chemotactic gradient across the alveolar-capillary membrane. Thus, the initial signals that trigger PMN migration into the infected focus are reduced. In a recent study, we also observed that acute alcohol intoxication suppressed the increase in S100A8 and S100A9 expression in the terminal airways of rats challenged with intrapulmonary LPS [56]. This suppression of S100 proteins decreases the reinforcement signals for PMN recruitment into the alveolar space, which may serve as an additional mechanism underlying the alcohol-induced impairment of PMN recruitment into the lung during pulmonary infection.

Enhanced granulopoiesis and increased PMN mobilization from the bone marrow are important mechanisms for the host to recruit additional PMNs in order to combat invading pathogens. Alcohol is known to injure hematopoietic tissues [84-88]. Studies of bone marrow from alcohol-abusing patients show a significant reduction in the number of mature granulocytes with vacuolization of myeloid progenitor cells. Exposure of bone marrow cells to alcohol at concentrations commonly observed in intoxicated patients suppresses granulocyte colony formation. Alcohol also likely impairs local production of granulopoietic growth factors and/or causes metabolic disorders in the hematopoietic microenvironment. We, and others, have shown that G-CSF and CXC chemokine levels in the peripheral circulation increase significantly during pulmonary infection. As stated previously, these cytokines mediate the granulopoietic response in hematopoietic tissues and enhance PMN mobilization from the bone marrow. Alcohol intoxication suppresses both the G-CSF and chemokine responses in experimental animals challenged with either pulmonary or systemic bacterial pathogens [54, 89, 90]. In addition, our studies have shown that alcohol inhibits increases in granulopoietic progenitor cell proliferation in mice challenged with intrapulmonary *S. pneumoniae* or G-CSF. *In vitro* exposure to alcohol causes a dose-dependent inhibition of myeloid progenitor cell proliferation in response to G-CSF stimulation (unpublished data). These observations show that alcohol damages the granulopoietic response at two different levels. In addition to suppressing granulopoietic cytokine production by infected tissues, alcohol also impairs the granulopoietic progenitor cell response to the cytokine stimulation. Mitogen activated protein kinase (MAPK) and Janus family tyrosine kinase and signal transducer and activator of transcription (Jak-STAT) pathways are involved in mediating G-CSF-induced granulopoiesis. G-CSF binding to its receptor activates the extracellular signal-regulated kinase (ERK1/2, or p44/42 MAPK) pathway which generates a strong signal for the proliferation of myeloid progenitor cells [91-93]. Ligand engagement of G-CSFR also causes activation of STAT3 which promotes expression of the cyclin-dependent kinase (cdk) inhibitor $p27^{Kip1}$. An increase in the intracellular level of $p27^{Kip1}$ causes G1 arrest of cell proliferation [94-97]. Studies have shown that alcohol inhibits the p44/42 MAPK signaling while enhancing the STAT3-$p27^{Kip1}$ signaling.

Alcohol has been known to impair the functional activities of PMNs. In addition to inhibiting adhesion molecule expression and the adherence of PMNs to endothelial cells, alcohol at clinically relevant levels inhibits 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 are also inhibited by alcohol at concentrations between 0.2% and 0.3% [98]. *In vivo* alcohol intoxication (blood alcohol concentra-

tion of 50-100 mM) significantly inhibits PMN phagocytic activity in experimental animals [82, 99]. PMNs from alcohol intoxicated patients have been reported to contain 31% less elastase activity compared to those from normal individuals and produce 25-27% less superoxide than controls in response to inflammatory stimuli [100]. Both acute alcohol intoxication and chronic alcohol consumption have been shown to significantly inhibit bacterial killing activity of the lung in rats infected with intrapulmonary *S. pneumoniae* [54, 101].

As stated previously, alveolar macrophages constitute the first line of phagocytic defense against invading pathogens in the terminal airways. Activated alveolar macrophages produce large amounts of TNF, which serves as a key proximal step in triggering the inflammatory response in the lung. Acute alcohol intoxication suppresses the pulmonary TNF response to bacterial challenge which is associated with an inhibition of PMN recruitment into the alveolar space and clearance of bacteria from the airways. Studies have shown that alcohol-induced inhibition of TNF production by alveolar macrophages primarily occurs at the post-transcriptional level. Exposure of alveolar macrophages from rhesus macaques to alcohol causes suppression of LPS-induced TNF protein production without affecting the up-regulation of TNF mRNA expression by these macrophages [102]. Alcohol also causes a significant increase in cell-associated TNF in macrophages following LPS stimulation [103, 104]. These studies suggest that alcohol likely impairs mechanisms involved in the release of TNF from these cells. In addition to a direct inhibition of pro-inflammatory cytokine production, alcohol also increases anti-inflammatory cytokine (IL-10) expression by human monocytes, which has been postulated to be one mechanism underlying the immunosuppressive effects of alcohol [105].

Other functional activities of macrophages including mobilization, adherence, phagocytosis, superoxide production, and microbicidal activity are also inhibited by alcohol. These alcohol-induced defects of alveolar macrophage function diminish the capacity of these cells to eliminate invading pathogens within the alveolar space. These harmful effects of alcohol may be of particular importance in tuberculosis where greater than 90% of inhaled mycobacteria are normally ingested and destroyed by alveolar macrophages [106]. 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. Studies have shown that exposure to alcohol enhances intracellular growth of mycobacteria in human macrophages [107, 108].

In recent years, the effect of alcohol on accessory cell function has drawn wide attention. A binge alcohol exposure (0.85 g/kg of body weight) in healthy volunteers causes inhibition of myeloid dendritic cell allostimulatory capacity [109, 110]. In vitro exposure to alcohol during dendritic cell differentiation significantly reduces allostimulatory activity in a mixed lymphocyte reaction using naïve CD4 T cells. Alcohol treatment also inhibits co-stimulatory receptor expression and tetanus toxoid antigen presentation by dendritic cells. IL-12 production by alcohol-treated dendritic cells is reduced. Naïve CD4 T cells primed with alcohol-treated dendritic cells show decreases in IFN-γ production, which can be restored by exogenous IL-12. These data indicate that alcohol impairs Th1 immune responses via inhibition of dendritic cell differentiation and accessory cell function. Patients with alcoholic liver cirrhosis have been shown to have decreased numbers of circulating dendritic cells [111]. Furthermore, active alcohol consumption in these patients causes inhibition of IL-1β and TNF-α production by peripheral blood dendritic cells. Experimental studies have shown that in vitro exposure to alcohol inhibits generation of bone marrow-derived dendritic cells in response to fms-like tyrosine kinase 3 ligand [112]. Chronic alcohol feeding causes inhibition of co-stimulatory receptor expression by splenic dendritic cells in response to in vivo CpG-DNA class B stimulation. Splenic dendritic cells induced naïve, allogeneic T cell proliferation is also impaired by chronic alcohol consumption in these animals.

Excessive alcohol consumption also exerts adverse effects on acquired immune defenses including both cell-mediated and humoral immunity. The ability to develop delayed hypersensitivity skin test reactions to various antigens is usually poor in alcohol-abusing patients. Chronic alcohol abusers, especially those with liver disease, frequently develop lymphopenia. Alcohol also suppresses lymphocyte blast transformation in response to mitogen stimulation. Lymphocyte proliferative responses to specific antibodies against T-cell receptors are blunted by alcohol [113]. Chronic alcohol feeding results in atrophy of the thymus and spleen in experimental animals. Chronic alcohol consumption causes a significant reduction in absolute numbers of CD4+ T lymphocytes in experimental animals. In addition, T lymphocytes isolated from alcoholic hosts have a diminished capacity to produce IFN- γ, an important cytokine that stimulates cell-mediated immunity [114]. Pulmonary recruitment of both CD4+ and CD8+ T lymphocytes in response to *P. carinii* infection in the lung is suppressed by alcohol consumption [115, 116]. An increase in plasma immunoglobulins has been observed in alcohol-abusing patients, especially those with alcoholic liver disease. These immunoglobulins do not appear to be protective. Interestingly, the ability to develop specific antibodies following new antigen challenges is impaired in animals chronically intoxicated with alcohol. Since specific antibodies are important for protecting the host from certain bacterial infections, such as *S. pneumoniae*, this defect may adversely affect the eradication of these pathogens in patients with pneumonia.

A subset of T helper cells known as Th17 cells produce cytokine IL-17 which serves as a link between acquired and innate immunities. IL-17 promotes the PMN response to bacterial infection [117]. Chronic alcohol consumption has been shown to inhibit IL-17 production in the lung during pulmonary infection with K. pneumoniae [118]. In vitro exposure to alcohol causes a dose-dependent inhibition of IL-17 expression by T lymphocytes in response to inflammatory stimuli. Treatment of animals with an adenoviral vector encoding IL-17 gene has been shown to improve lung host defense and survival of alcohol-intoxicated mice with pulmonary K. pneumoniae infection [119].

IMMUNOMODULATION AND TREATMENT OF PULMONARY INFECTIONS

Treatment of pulmonary infections in both alcoholic and nonalcoholic patients is based on effective antibiotic therapy.

The emergence of drug-resistant pathogens, particularly in alcohol abusing patients, is becoming a significant challenge to existing antibiotic therapy. Immunomodulation may be useful as an adjuvant therapy for the treatment of pulmonary infections in individuals who excessively consume alcohol.

Alcohol impairs multiple aspects of the innate immune response in the lung, particularly PMN recruitment into the alveolar space in response to bacterial infection, which facilitates the proliferation of invading pathogens. Strategies have been developed to enhance phagocytic defenses in the lung either by increasing the number of circulating PMNs or enhancing the chemotactic signals for PMN migration and activation in infected tissue sites. Administration of exogenous G-CSF has been shown to stimulate PMN mobilization from the bone marrow and augment PMN recruitment into the lung in response to infectious stimuli. Subcutaneous injections of G-CSF (50 μg/kg) twice daily for two days results in a 7-fold increase in circulating PMNs and 5-fold increase in PMN influx into the alveolar space in rats following an intratracheal LPS challenge [82]. This enhanced PMN recruitment is resulted from both an increase in the number of circulating PMNs and up-regulation of the PMN response to chemotactic signals [62]. G-CSF has been show to enhance pulmonary antibacterial defenses in rats infected with *K. pneumoniae* [120]. In these experiments, G-CSF augmented pulmonary recruitment of PMNs in infected control rats and significantly attenuated the adverse effects of alcohol on PMN delivery into the infected lung. G-CSF enhanced pulmonary clearance of bacteria in both control and alcohol-treated rats and improved the survival. G-CSF has also been shown to attenuate the adverse effects of alcohol on PMN functional activities, including the expression of adhesion molecules and phagocytosis [82, 121, 122].

A clinical trial of 756 patients with community-acquired pneumonia has shown that subcutaneous injection of G-CSF (300 μg/day) to patients for up to 10 days causes a 3-fold increase in the number of circulating PMNs [123]. G-CSF treatment is well-tolerated by these patients. Patients treated with G-CSF exhibit a faster resolution of X-ray abnormalities and fewer complications including the adult respiratory distress syndrome and disseminated intravascular coagulation. These observations suggest that G-CSF may be useful in the treatment of pulmonary infections in immunocompromised patients such as individuals who abuse alcohol.

GM-CSF is known to play an important role in promoting host defense against Gram-positive and Gram-negative bacteria, mycobacteria, *Pneumocystis carinii*, and fungi. Animal experiments have shown that alcohol consumption does not affect pulmonary production of GM-CSF. However, the expression of the GM-CSF receptor by alveolar macrophages and the alveolar epithelium is significantly reduced in rats fed an alcoholic diet [124, 125]. In parallel, cellular expression and nuclear binding of PU.1, a key transcription factor that drives a number of GM-CSF-dependent macrophage functions, are reduced by alcohol ingestion. Intrapulmonary administration of recombinant GM-CSF to alcohol-fed animals restores GM-CSF receptor expression as well as PU.1 protein expression and nuclear binding in alveolar macrophages. GM-CSF treatment also improves the functional activities of alveolar macrophages in alcohol-fed rats, as shown by LPS-stimulated TNF-α production and phagocytosis of bacteria. In addition, GM-CSF treatment restores alveolar epithelial barrier function that has been damaged by alcohol, even during acute endotoxemia [126]. In an experimental model of CD4 depleted mice with pulmonary *P. carinii* infection, administration of GM-CSF has been reported to reduce the intensity of *P. carinii* infection which is associated with enhanced alveolar macrophage TNF-α production [45, 127]. In a clinical trial of GM-CSF therapy for treatment of patients with sepsis, it has been shown that a 72-h period of infusion with GM-CSF at a dose of 125 $\mu g/m^2$ causes up-regulation of CD11b expression on circulating PMNs and monocytes with more frequent resolution of infection in these patients [128]. In another clinical trial of approximately 1200 neutropenic patients with pneumonia, it was reported that GM-CSF (mean dose of 5 μg/kg daily) administration for a mean period of 13 days (2 to 57 days) restored blood leukocyte counts [129]. Hematopoietic recovery was observed in 74% of the patients with a good clinical and/or radiologic improvement in 63% of these patients. This investigation also reported that GM-CSF was well-tolerated in the majority of patients (89%). These studies suggest that GM-CSF may be beneficial for improving host defense functions against pulmonary infection in immunocompromised hosts including patients who abuse alcohol. However, like many other immune modulating agents, GM-CSF may cause serious side effects. Nonspecific activation of the proinflammatory cascade may result in generalized inflammation and tissue injury. It has been reported that higher GM-CSF doses (i.e., greater than 15 μg/kg daily) are likely associated with more serious side effects [130, 131].

IFN-γ enhances host defenses against viruses, bacteria, fungi, and parasites. *In vitro* studies have shown that macrophages stimulated by IFN-γ are able to kill over 3 dozen different pathogens [132]. Administration of IFN-γ in conjunction with antibiotics generates synergistic or additive effects in the treatment of certain pulmonary infections (*S. aureus*, *P. carinii*, and *C. neoformans*) in immunocompromised hosts. Intratracheal instillation or aerosol inhalation of IFN-γ activates alveolar macrophages and enhances the microbicidal activities of the lung [52, 133, 134]. We have shown that administration of a recombinant adenoviral vector encoding the murine IFN- γ complementary DNA to rat lung produces prolonged expression of biologically active IFN- γ in the airways. Pulmonary TNF production, PMN recruitment, and bactericidal activity are significantly augmented in both normal and alcohol-intoxicated animals [135, 136]. Intrapulmonary administration of IFN- γ has been shown to enhance the pulmonary CXC chemokine response in experimental animals [137]. Alcohol-induced suppression of MIP-2 and CINC production in the lung following intrapulmonary LPS challenge is also attenuated by IFN- γ treatment.

Clinical investigations have shown that IFN- γ administered either locally or systemically for the treatment of pulmonary and other infections is well-tolerated by patients. In patients with disseminated atypical mycobacterial infection (*Mycobacteria avium complex*), IFN- γ administration in combination with antimycobacterial chemotherapy results in clinical improvement. The treated patients rapidly clear the infection and become afebrile [138]. Similar results have been seen in patients with AIDS. A study of patients with multidrug resistant tuberculosis has shown that aerosol-

administration of 500 μg IFN- γ three times a week for 1 month eradicates mycobacteria in sputum in all patients [139]. Based on data obtained from animal experiments and clinical studies, IFN-γ therapy may be a promising approach in the management of pulmonary infection in patients immunocompromised by alcohol.

SUMMARY

Alcohol abuse profoundly impairs the host defense mechanisms in the respiratory tract and increases host susceptibility to a wide spectrum of pulmonary infections. Bacterial pneumonia and other lung infections are more common and severe in individuals who abuse alcohol. Treatment of lung infections in these patients is quite difficult. While aggressive antibiotic therapy remains the mainstay for the treatment of these infections, a combination of immunomodulatory agents with antibiotic therapy may provide a new effective approach for the treatment of lung infections in alcohol-abusing patients.

Key Learning Objectives:

Alcohol is the most frequently abused drug. Alcohol abuse predisposes the host to infectious diseases, particularly pulmonary infections. The respiratory tract possesses a sophisticated immune defense system which effectively protects the host from infections. The immune system in the airways consists of both innate and specific immunity. Alcohol impairs both components of immune defense. Treatment of pulmonary infections in immunocompromised patients is a major challenge to our health care system. Adjuvant therapy with immunomodulatory agents may provide a new approach in the management of alcohol-abusing patients with severe lung infections.

Future Research Questions:

Future studies will focus on the molecular mechanisms by which alcohol injures specific components of the immune system. Investigations into the actions of immunomodulatory mediators will form a foundation for developing new therapeutic strategies to treat alcohol abusing patients with pulmonary infections.

ACKNOWLEDGEMENTS

This work was supported by NIH grant AA-09803.

ABBREVIATIONS

AIDS = Acquired immunodeficiency syndrome
ALPS syndrome = Alcoholism, leucopenia, and pneumococcal sepsis syndrome
ARDS = Adult respiratory distress syndrome
BAL = Bronchoalveolar lavage
cdk = Cyclin-dependent kinase
CINC = Cytokine-induced neutrophil chemoattractant
CTL = Cytotoxic T lymphocytes
ERK = Extracellular signal-regulated kinase
G-CSF = Granulocyte colony-stimulating factor
GM-CSF = Granulocyte macrophage colony-stimulating factor
G-CSFR = Granulocyte colony-stimulating factor receptors
HIV = Human immunodeficiency virus
IFN-γ = Interferon-γ
IL-1β = Interleukin-1-β
IL-8 = Interleukin-8
IL-10 = Interleukin-10
IL-12 = Interleukin-12
IL-17 = Interleukin-17
Jak = Janus family tyrosine kinase
KC = Keratinocyte-derived chemokine
LPS = Lipopolysaccharide
MAPK = Mitogen activated protein kinase
MIP-1α = Macrophage inflammatory protein-1-α
MIP-2 = Macrophage inflammatory protein-2
MHC = Major histocompatibility complex
PBMC = Peripheral blood mononuclear cells
PMNs = Polymorphonuclear leukocytes or neutrophils
STAT = Signal transducer and activator of transcription
S100A8 = Calgranulin A or myeloid-related protein 8, MRP8
S100A9 = Calgranulin B or myeloid-related protein 14, MRP14
Th = Helper T lymphocyte
TNF-α = Tumor necrosis factor-α

REFERENCES

[1] Macgregor RR, Loubia DB. Alcohol and infection. Curr Clin Top Infect Dis 1997; 17: 291-315.
[2] Zhang P, Bagby GJ, Happel KI, Summer WR, Nelson S. Pulmonary host defense and alcohol. Front Biosci 2002; 7: d1314-30.
[3] Rush B. An inquiry into the effects of ardent spirits upon the human body and mind. Q J Stud Alcohol 1943; 4: 321-41.
[4] Olser W. The Principles and Practice of Medicine. Appleton, New York. 1905.
[5] Capps JA, Coleman GH. Influence of alcohol on prognosis of pneumonia in Cook County Hospital. JAMA 1923; 80: 750-2.
[6] Sundby P. Alcoholism and mortality. Oslo, Universitetsforlaget, National Institute for Alcohol Research. 1976; Publ. No. 6.
[7] Painton JF, Ulrich HJ. Lobar pneumonia; an analysis of 1298 cases. Ann Intern Med 1937; 10: 1345-64.
[8] Schmidt W, De Lint J. Causes of death of alcoholics. Q J Stud Alcohol 1972; 33: 171-85.
[9] Fernandez-Sola J, Junque A, Estruch R, Monforte R, Torres A, Urbano-Marquez A. High alcohol intake as a risk and prognostic factor for community-acquired pneumonia. Arch Intern Med 1995; 155: 1649-54.
[10] Saitz R, Ghali WA, Moskowitz MA. The impact of alcohol-related diagnoses on pneumonia outcomes. Arch Intern Med 1997; 157: 1446-52.
[11] Marik P E. The clinical features of severe community-acquired pneumonia presenting as septic shock - Norasept II Study Investigators. J Crit Care 2000; 15: 85-90.
[12] Musher DM, Alexandraki I, Graviss EA, *et al*. Bacteremic and nonbacteremic pneumococcal pneumonia - a prospective study. Medicine 2000; 79: 210-21.
[13] Everts RJ, Murdoch DR, Chambers ST, *et al*. Nosocomial pneumonia in adult general medical and surgical patients at Christchurch Hospital. N Z Med J 2000; 113: 221-24.

[14] Bochicchio GV, Joshi M, Bochicchio K, Tracy K, Scalea TM. A time-dependent analysis of intensive care unit pneumonia in trauma patients. J Trauma 2004; 56:296-303.

[15] McFarland W, Libre EP. Abnormal leukocyte response in alcoholism. Ann Intern Med 1963; 59: 865-77.

[16] Fruchtman SM, Gombert ME, Lyons HA. Adult respiratory distress syndrome as a cause of death in pneumococcal pneumonia - report of ten cases. Chest 1983; 83: 598-601.

[17] Perlino CA, Rimland D. Alcoholism, leukopenia and pneumococcal sepsis. Am Rev Respir Dis 1985; 132: 757-60.

[18] De Roux A, Cavalcanti M, Marcos MA, *et al*. Impact of alcohol abuse in the etiology and severity of community-acquired pneumonia. Chest 2006; 129: 1219-25.

[19] Paganin F, Lilienthal F, Bourdin A, *et al*. Severe community-acquired pneumonia: assessment of microbial aetiology as mortality factor. Eur Respir J 2004; 24: 779-85.

[20] Bartlett JG, Finegold SM. Anaerobic infections of the lung and pleural space. Am Rev Respir Dis 1974; 110: 56-77.

[21] Kharkar RA, Ayyar VB. Aetiological aspects of lung abscess. J Postgrad Med 1981; 27: 163-6.

[22] Taylor Z, Marks SM, Rios Burrows NM, *et al*. Causes and costs of hospitalization of tuberculosis patients in the United States. Int J Tuberc Lung Dis 2000; 4: 931-9.

[23] D'Souza NB, Mandujano JF, Nelson S, Summer WR, Shellito JE. Alcohol ingestion impairs host defenses predisposing otherwise healthy mice to *Pneumocystis carinii* infection. Alcohol Clin Exp Res 1995; 19: 1219-25.

[24] Ikawa H, Hayashi Y, Ohbayashi C, Tankawa H, Itoh H. Autopsy case of alcoholic hepatitis and cirrhosis treated with corticosteroids and affected by *Pneumocystis carinii* and cytomegalovirus pneumonia. Pathol Int 2001; 51: 629-32.

[25] Gordon SB, Read RC. Macrophage defenses against respiratory tract infections. Brit Med Bullet 2002; 61: 45-61.

[26] Welsh DA, Mason CM. Host defense in respiratory infections. Med Clin N Am 2001; 85: 1329-47.

[27] Wang JB, Mukaida N, Zhang Y, Ito T, Nakao S, Matsushima K. Enhanced mobilization of hematopoietic progenitor cells by mouse MIP-2 and granulocyte colony-stimulating factor in mice. J Leukoc Biol 1997; 62: 503-9.

[28] Laterveer L, Lindley IJD, Hamilton MS, Willemze R, Fibbe WE. Interleukin-8 induces rapid mobilization of hematopoietic stem cells with radioprotective capacity and long term myelo-lymphoid repopulating ability. Blood 1995; 85: 2269-75.

[29] Laterveer L, Lindley IJD, Heemskerk DPM, *et al*. Rapid mobilization of hematopoietic progenitor cells in rhesus monkeys by a single intravenous injection of interleukin-8. Blood 1996; 87:781-8.

[30] Martin C, Burdon PCE, Bfidger G, Gutierrez-Ramos JC, Williams TJ, Rankin SM. Chemokines acting *via* CXCR2 and CXCR4 control the release of neutrophils from the bone marrow and their return following senescence. Immunity 2003; 19:583-93.

[31] Shahbazian LM, Quinton LJ, Bagby GJ, Nelson S, Wang G, Zhang P. Escherichia coli pneumonia enhances granulopoiesis and the mobilization of myeloid progenitor cells into the systemic circulation. Crit Care Med 2004; 32: 1740-6.

[32] Demetri GD, Griffin JD. Granulocyte colony-stimulating factor and its receptor. Blood 1991; 78: 2791-2808.

[33] Chatta GS, Andrews RG, Rodger E, Schrag M, Hammond WP, Dale DC. Hematopoietic progenitors and aging: alterations in granulocytic precursors and responsiveness to recombinant human G-CSF, GM-CSF, and IL-3. J Gerontol 1993; 48: M207-12.

[34] Tsuji K, Ebihara Y. Expression of G-CSF receptor on myeloid progenitors. Leuk Lymphoma 2001; 42:1351-7.

[35] Semerad CL, Liu F, Gregory AD, Stumpf K, Link DC. G-CSF is an essential regulator of neutrophil trafficking from the bone marrow to the blood. Immunity 2002;17: 413-23.

[36] Dale DC, Liles WC, Summer WR, Nelson S. Granulocyte colony-stimulating factor – role and relationships in infectious diseases. J Infect Dis 1995; 172: 1061-75.

[37] Van de Geijn GJM, Arats LHJ. Erkeland SJ, Prasher JM, Touw IP. Granulocyte colony-stimulating factor and its receptor in normal hematopoietic cell development and myeloid disease. Rev Physiol Biochem Pharmacol 2003; 149: 53-71.

[38] Kragsbjerg P, Jones I, Vikerfors T, Holmberg H. Diagnostic value of blood cytokine concentrations in acute pneumonia. Thorax 1995; 50: 1253-7.

[39] Pauksen K, Elfman L, Ulfgren AK, Venge P. Serum levels of granulocyte-colony stimulating factor (G-CSF) in bacterial and viral infections, and in atypical pneumonia. Br J Haematol 1994; 88: 256-60.

[40] Quinton LJ, Nelson S, Boé DM, *et al*. The granulocyte colony-stimulating factor response following intrapulmonary and systemic bacterial challenges. J Infect Dis 2002; 185: 1476-82.

[41] Zhang P, Quinton LJ, Gamble L, Bagby GJ, Summer WR, Nelson S. The granulopoietic cytokine response and enhancement of granulopoiesis in mice during endotoxemia. Shock 2005; 23: 344-52.

[42] Basu S, Dunn A, Ward A. G-CSF: function and modes of action. Int J Mol Med 2002; 10: 3-10.

[43] Trapnell BC, Whitsett JA. GM-CSF regulates pulmonary surfactant homeostasis and alveolar macrophage-mediated innate host defense. Annu Rev Physiol 2002; 64: 775-802.

[44] Zhang Z, Harkiss GD, Hopkins J, Woodall CJ. Granulocyte macrophage colony stimulating factor is elevated in alveolar macrophages from sheep naturally infected with maedi-visna virus and stimulates maedi-visna virus replication in macrophages *in vitro*. Clin Exp Immunol 2002; 129: 240-6.

[45] Paine RIII, Preston AM, Wilcoxen S, *et al*. Granulocyte-macrophage colony-stimulating factor in the innate immune response to *Pneumocystis carinii* pneumonia in mice. J Immunol 2000; 164: 2602-9.

[46] Charbeneau RP, Christensen PJ, Chrisman CJ, *et al*. Impaired synthesis of prostaglandin E2 by lung fibroblasts and alveolar epithelial cells from GM-CSF-/- mice: implications for fibroproliferation. Am J Physiol Lung Cell Mol Physiol 2003; 284: L1103-11.

[47] Bercilaz PY, Shibata Y, Whitsett JA, Trapnell BC. GM-CSF, *via* PU.1, regulates alveolar macrophage FcγR-mediated phagocytosis and the IL-18/IFN-γ-mediated molecular connection between innate and adaptive immunity in the lung. Blood 2002; 100: 4193-4200.

[48] Collins HL, Bancroft GJ. Cytokine enhancement of complement-dependent phagocytosis by macrophages: synergy of tumor necrosis factor-alpha and granulocyte-macrophage colony-stimulating factor for phagocytosis of *Cryptococcus neuformans*. Eur J Immunol 1992; 22: 1447-54.

[49] Ballinger MN, Paine RIII, Serezani CHC, *et al*. Role of granulocyte macrophage colony-stimulating factor during Gram-negative lung infection with Pseudomonas aeruginosa. Am J Respir Cell Mol Biol 2006; 34: 766-74.

[50] Murray HW. Current and future clinical applications of interferon-gamma in host antimicrobial defense. Intensive Care Med 1996; 22: S456-61.

[51] Laichalk LL, DanforthJM, Standiford TJ. Interleukin-10 inhibits neutrophil phagocytic and bactericidal activity. FEMS Immunol Med Microbiol 1996; 15: 181-7.

[52] Nelson S, Mason MC, Kolls J, Summer WR. Pathophysiology of pneumonia. Clin Chest Med 1995; 16: 1-12.

[53] Nelson S, Bagby GJ, Bainton BG, Wilson LA, Thompson JJ, Summer WR. Compartmentalization of intraalveolar and systemic lipopolysaccharide-induced tumor necrosis factor and the pulmonary inflammatory response. J Infect Dis 1989; 159: 189-94.

[54] Boé DM, Nelson S, Zhang P, Bagby GJ. Acute ethanol intoxication suppresses lung chemokine production following infection with *Streptococcus pneumoniae*. J Infect Dis 2001; 184: 1134-42.

[55] Zhang P, Nelson S, Holmes MC, Summer WR, Bagby GJ. Compartmentalization of macrophage inflammatory protein-2, but not cytokine-induced neutrophil chemoattractant, in rats challenged with intratracheal endotoxin. Shock 2002; 17: 104-8.

[56] Zhang P, Zhong Q, Bagby GJ, Nelson S. Alcohol intoxication inhibits pulmonary S100A8 and S100A9 expression in rats challenged with intratracheal lipopolysaccharide. Alcohol Clin Exp Res 2007; 31: 113-21.

[57] Srikrishna G, Panneerselvam K, Westphal V, Abraham V, Varki A, Freeze HH. Two proteins modulating transendothelial migration of leukocytes recognize novel carboxylated glycans on endothelial cells. J Immunol 2001; 166: 4678-88.

[58] Newton RA, Hogg N. The human S100 protein MRP-14 is a novel activator of the β_2-integrin Mac-1 on neutrophils. J Immunol 1998; 160: 1427-35.

[59] Lackmann M, Cornish CJ, Simpson RJ, Moritz RL Geczy CL. Purification and structural analysis of a murine chemotactic cyto-

kine (CP-10) with sequence homology to S100 proteins. J Biol Chem 1992; 267: 7499-504.

[60] Ryckman C, Vandal K, Rouleau P, Talbot M, Tessier PA. Proinflammatory activities of S100: proteins S100A8, S100A9, and S100A8/A9 induce neutrophil chemotaxis and adhesion. J Immunol 2003; 170: 3233-42.

[61] Roth J, Vofl T, Sorg C, Sunderkötter C. Phagocyte-specific S100 proteins: a novel group of proinflammatory molecules. Trends Immunol 2003; 24: 155-8.

[62] Zhang P, Bagby GJ, Kolls JK, *et al*. The effects of granulocyte colony-stimulating factor and neutrophil recruitment on the pulmonary chemokine response to intratracheal endotoxin. J Immunol 2001; 165: 458-68.

[63] Holmes MC, Zhang P, Nelson S, Summer WR, Bagby GJ. Neutrophil modulation of the pulmonary chemokine response to lipopolysaccharide. Shock 2002; 18: 555-60.

[64] Terashima T, Wiggs B, English D, Hogg JC, Van Eeden SF. Polymorphonuclear leukocyte transit times in bone marrow during streptococcal pneumonia. Am J Physiol 1996; 271: L587-92.

[65] Cronkite EP. Analytical review of structure and regulation of hemopoiesis. Blood Cells 1998; 14: 313-28.

[66] Stumbles PA, Upham JW, Holt PG. Airway dendritic cells: coordinators of immunological homeostasis and immunity in the respiratory tract. APMIS 2003; 111: 741-55.

[67] Steinman RM. The dendritic cell system and its role in immunogenicity. Annu Rev Immunol 1991; 9: 271-96.

[68] McWilliam AS, Napoli S, Marsh AM, *et al*. Dendritic cells are recruited into the airway epithelium during the inflammatory response to a broad spectrum of stimuli. J Exp Med 1996; 184: 2429-32.

[69] Twigg PHIII. Pulmonary host defenses. J Thorac Imag 1998; 13: 221-33.

[70] Saltini C, Kirby M, Trapnell BC, Tamura N, Crystal RG. 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 1990; 170: 1123-40.

[71] Pickrell KL. The effect of alcoholic intoxication and ether anesthesia on resistance to pneumococcal infection. Bull Johns Hopkins Hosp 1938; 63: 238-60.

[72] Green GM, Kass EH. Factors influencing the clearance of bacteria by the lung. J Clin Invest 1964; 43: 769-76.

[73] Astry CL, Warr GA, Jakab GJ. Impairment of polymorphonuclear leukocyte immigration as a mechanism of alcohol-induced suppression of pulmonary antibacterial defenses. Am Rev Respir Dis 1983; 128: 113-7.

[74] Nilsson E, Lindström P, Patarroyo M, *et al*. Ethanol impairs certain aspects of neutrophil adhesion *in vitro*: comparisons with inhibition of expression of the CD18 antigen. J Infect Dis 1991; 163: 591-7.

[75] MacGregor RR, Safford M, Shalit M. Effect of ethanol on functions required for the delivery of neutrophils to sites of inflammation. J Infect Dis 1988; 157: 682-9.

[76] Zhang P, Bagby GJ, Xie M, Stoltz DA, Summer WR, Nelson S. Acute ethanol intoxication inhibits neutrophil β_2-integrin expression in rats during endotoxemia. Alcohol Clin Exp Res 1998; 22: 135-41.

[77] Lister DD, Gentry MJ, Preheim LC. Ethanol impairs neutrophil chemotaxis *in vitro* but not adherence or recruitment to lungs of rats with experimental pneumococcal pneumonia. J Infect Dis 1993; 167: 1131-7.

[78] Gluckman SJ, Dvorak VC, MacGregor RR. Host defenses during prolonged alcohol consumption in a controlled environment. Arch Intern Med 1977; 137: 1539-43.

[79] MacGregor RR, Gluckman SJ, Senior JR. Granulocyte function and levels of immunoglobulins and complement in patients admitted for withdrawal from alcohol. J Infect Dis 1978; 138: 747-53.

[80] Cook RT. Alcohol abuse, alcoholism, and damage to the immune system - a review. Alcohol Clin Exp Res 1998; 22: 1927-42.

[81] Sheron N, Bird G, Koskinas J, *et al*. 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 1993; 18: 41-6.

[82] Zhang P, Bagby GJ, Stoltz DA, Summer WR, Nelson S. Granulocyte colony-stimulating factor modulates the pulmonary host response to endotoxin in the absence and presence of acute ethanol intoxication. J Infect Dis 1999; 179: 1441-8.

[83] Boé DM, Nelson S, Zhang P, Quinton L, Bagby GJ. Alcohol-induced suppression of lung chemokine production and the host defense response to *Streptococcus pneumoniae*. Alcohol Clin Exp Res 2003; 27: 1838-45.

[84] Heermans EH. Booze and blood: the effects of acute and chronic alcohol abuse on the hematopoietic system. Clin Lab Sci 1998; 11: 229-32.

[85] Ballard HS. Hematological complications of alcoholism. Alcohol Clin Exp Res 1989; 13: 706-20.

[86] Michot F, Gut J. Alcohol-induced bone marrow damage. A bone marrow study in alcohol-dependent individuals. Acta Haematol 1987; 78: 252-7.

[87] Ballard HS. Alcohol-associated pancytopenia with hypocellular bone marrow. Am J Clin Pathol 1980; 73: 830-4.

[88] Liu YK. Effects of alcohol on granulocytes and lymphocytes. Semin Hematol 1980; 17: 130-6.

[89] Bagby GJ, Zhang P, Stoltz DA, Nelson S. Suppression of the granulocyte colony-stimulating factor response to *Escherichia coli* challenge by alcohol intoxication. Alcohol Clin Exp Res 1998; 22: 1740-5.

[90] Zhang P, Bagby GJ, Boé DM, *et al*. Acute alcohol intoxication suppresses the CXC chemokine response during endotoxemia. Alcohol Clin Exp Res 2002; 26: 65-73.

[91] Srinivasa SP, Doshi PD. Extracellular signal-related kinase and p38 mitogen-activated protein kinase pathways cooperate in mediating cytokine-induced proliferation of a leukemic cell line. Leukemia 2002; 16: 244-53.

[92] Rausch O, Marshall CJ. Cooperation of p38 and extracellular signal-regulated kinase mitogen-activated protein kinase pathways during granulocyte colony-stimulating factor-induced hemopoietic cell proliferation. J Biol Chem 1999; 274: 4096-105.

[93] Kamezaki K, Shimoda K, Numata A, *et al*. Roles of STAT3 and ERK in G-CSF signaling. Stem Cell 2005; 23: 252-63.

[94] De Koning JP, Soede-Bobok AA, Ward AC, *et al*. STAT3-mediated differentiation and survival of myeloid cells in response to granulocyte colony-stimulating factor: role for the cyclin-dependent kinase inhibitor p27(Kip1). Oncogene 2000; 19: 3290-8.

[95] Mangan J, Reddy EP. Activation of the Jak3 pathway and myeloid differentiation. Leuk Lymphoma 2005; 46: 21-7.

[96] Rane SG, Mangan JK, Amanullah A, *et al*. Activation of the Jak3 pathway is associated with granulocytic differentiation of myeloid precursor cells. Blood 2002; 100: 2753-62.

[97] Lee CK, Raz R, Gimeno R, *et al*. STAT3 is a negative regulator of granulopoiesis but is not required for G-CSF-dependent differentiation. Immunity 2002; 17: 63-72.

[98] Tamura DY, Moore EE, Partrick DA, *et al*. Clinically relevant concentrations of ethanol attenuate primed neutrophil bactericidal activity. J Trauma 1998; 44: 320-4.

[99] Zhang P, Nelson S, Summer WR, Spitzer JA. Acute ethanol intoxication suppresses the pulmonary inflammatory response in rats challenged with intrapulmonary endotoxin. Alcohol Clin Exp Res 1997; 21: 773-8.

[100] Sachs CW, Christensen RH, Pratt PS, Lynn WS. Neutrophil elastase activity and superoxide production are diminished in neutrophils of alcoholics. Am Rev Respir Dis 1990; 141: 1249-55.

[101] Vander Top EA, Perry GA, Snitily MU, Gentry-Nielsen MJ. Smoke exposure and ethanol ingestion modulate intrapulmonary polymorphonuclear leukocyte killing, but not recruitment or phagocytosis. Alcohol Clin Exp Res 2006; 30: 1599-1607.

[102] Stoltz DA, Nelson S, Kolls JK, *et al*. *In vitro* ethanol suppresses alveolar macrophage TNF-α during simian immunodeficiency virus infection. Am J Res Crit Care Med 2000; 161: 135-40.

[103] Zhang Z, Cork J, Ye P, *et al*. Inhibition of TNF-alpha processing and TACE-mediated ectodomain shedding by ethanol. J Leukoc Biol 2000; 67: 856-62.

[104] Kolls JK, Xie J, Lei D, Greenberg S, Summer WR, Nelson S. Differential effects of *in vivo* ethanol on LPS-induced TNF and nitric oxide production in the lung. Am J Physiol 1995; 268: L991-8.

[105] Szabo G, Mandrekar P, Girouard L, Catalano D. 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 1996; 20: 900-7.

[106] Dannenberg AM. Immune mechanisms in the pathogenesis of pulmonary tuberculosis. Rev Infect Dis 1989; 11: S369-78.

[107] Bermudez L, Young LS. Ethanol augments intracellular survival of *Mycobacterium avium* complex and impairs macrophage responses to cytokines. J Infect Dis 1991; 163: 1286-92.

[108] Bermudez LE. Effect of ethanol on the interaction between the macrophage and *Mycobacterium avium.* Alcohol 1994; 11: 69-73.

[109] Mandrekar P, Catalano D, Dolganiuc A, Kodys K, Szabo G. Inhibition of myeloid dendritic cell accessory cell function and induction of T cell anergy by alcohol correlates with decreased IL-12 production. J Immunol 2004; 173: 3398-7.

[110] Szabo G, Catalano D, White B, Mandrekar M. Acute alcohol consumption inhibits accessory cell function of monocytes and dendritic cells. Alcohol Clin Exp Res 2004; 28: 824-8.

[111] Laso FJ, Vaquero JM, Almeida J, Marcos M, Orfao A. Chronic alcohol consumption is associated with changes in the distribution, immunophenotype, and the inflammatory cytokine secretion profile of circulating dendritic cells. Alcohol Clin Exp Res 2007; 31: 846-54.

[112] Lau AH, Abe M, Thomson AW. Ethanol affects the generation, cosignaling molecule expression, and function of plasmacytoid and myeloid dendritic cell subsets *in vitro* and *in vivo*. J Leukoc Biol 2006; 79: 941-53.

[113] Domiati-Saad R, Jerrells TR. The influence of age on blood alcohol levels and ethanol-associated immunosuppression in a murine model of ethanol consumption. Alcohol Clin Exp Res 1993; 17: 382-8.

[114] Chadha KC, Stadler I, Albini B, Nakeeb SM, Thacore HR. Effect of alcohol on spleen cells and their functions in C57BL/6 mice. Alcohol 1991; 8: 481-5.

[115] Shellito JE. Alcohol and host defense against pulmonary infection with *Pneumocystis carinii*. Alcohol Clin Exp Res 1998; 22: 208S-11.

[116] Shellito JE, Olariu R. 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 1998; 22: 658-63.

[117] Ye P, Rodriguez FH, Kanaly S, *et al*. Requirement of interleukin 17 receptor signaling for lung CXC chemokine and granulocyte colony-stimulating factor expression, neutrophil recruitment and host defense. J Exp Med 2001; 194: 519-27.

[118] Shellito JE, Quan ZM, Ye P, Ruan S, Shean MD, Kolls J. Effect of alcohol consumption on host release of interleukin-17 during pulmonary infection with *Klebsiella pneumoniae*. Alcohol Clin Exp Res 2001; 25: 872-81.

[119] Ye P, Garvey PB, Zhang P, *et al*. Interleukin-17 and lung host defense against *Klebsiella pneumoniae* infection. Am J Respir Cell Mol Biol 2001; 25: 335-40.

[120] Nelson S, Summer W, Bagby GJ, *et al*. Granulocyte colony-stimulating factor enhances pulmonary host defenses in normal and ethanol-treated rats. J Infect Dis 1991; 164: 901-6.

[121] Zhang P, Bagby GJ, Stoltz DA, Spitzer JA, Summer WR, Nelson S. Modulation of the lung host response by granulocyte colony-stimulating factor in rats challenged with intrapulmonary endotoxin. Shock 1997; 7: 193-9.

[122] Stoltz DA, Zhang P, Nelson S, Bohm RP, Jr., Murphey-Corb M, Bagby GJ. Ethanol suppression of the functional state of polymorphonuclear leukocytes obtained from uninfected and simian immunodeficiency virus infected rhesus macaques. Alcohol Clin Exp Res 1999; 23: 878-84.

[123] Nelson S, Belknap SM, Carlson RW, *et al*. 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 1998; 178: 1075-80.

[124] Joshi PC, Applewhite L, Ritzenthaler JD, *et al*. Chronic ethanol ingestion in rats decreases granulocyte-macrophage colony-stimulating factor receptor expression and downstream signaling in the alveolar macrophage. J Immunol 2005; 175:6837-45.

[125] Joshi PC, Applewhite L, Mitchell PO, *et al*. GM-CSF receptor expression and signaling is decreased in lungs of ethanol-fed rats. Am J Physiol Lung Cell Mol Physiol 2006; 291: L1150-8.

[126] Pelaez A, Bechara RI, Joshi PC, Brown LAS, Guidot DM. Granulocyte/macrophage colony-stimulating factor treatment improves alveolar epithelial barrier function in alcoholic rat lung. Am J Physiol Lung Cell Mol Physiol 2004; 286: L106-11.

[127] Mandujano JF, D'Souza NB, Nelson S, Summer WR, Beckerman RC, Shellito JE. Granulocyte-macrophage colony stimulating factor and *Pneumocystis carinii* pneumonia in mice. Am J Respir Crit Care Med 1995; 151:1233-8.

[128] Rosenbloom AJ, Linden PK, Dorrance A, *et al*. Effect of granulocyte-monocyte colony-stimulating factor therapy on leukocyte function and clearance of serious infection in nonneutropenic patients. Chest 2005; 127: 2139-50.

[129] Dierdorf R, Kreuter U, Jones TC. A role for granulocyte-macrophage colony-stimulating factor (GM-CSF) in the treatment of neutropenic patients with pneumonia. Braz J Infect Dis 1997; 1: 68-76.

[130] Arning M, Kliche KO, Schneider W. GM-CSF therapy and capillary-leak syndrome [letter]. Ann Hematol 1991; 62: 83.

[131] Lieschke GJ, Cebon J, Morstyn G. Characterization of the recombinant human granulocyte-macrophage colony-stimulating factor. Blood 1989; 74: 2634-43.

[132] Murray HW. Interferon-γ and host antimicrobial defense. Am J Med 1994; 97: 459-67.

[133] Beck JM, Liggitt HD, Brunette EN, Fuchs HJ, Shellito JE, Debs RJ. Reduction in intensity of *Pneumocystis carinii* pneumonia in mice by aerosol administration of gamma interferon. Infect Immun 1991; 11: 3859-62.

[134] Jaffe HA, Buhl R, Mastrangeli A, *et al*. 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 1991; 88: 279-302.

[135] Kolls JK, Lei D, Stoltz D, *et al*. Adenoviral-mediated interferon-gamma gene therapy augments pulmonary host defense ethanol-treated rats. Alcohol Clin Exp Res 1998; 22: 157-62.

[136] Lei D, Lancaster JR, Jr., Joshi MS, *et al*. Activation of alveolar macrophages and lung host defenses using transfer of the interferon-gamma gene. Am J Physiol 1997; 272: L852-9.

[137] Zhang P, Quinton LJ, Bagby GJ, Summer WR, Nelson S. Interferon-γ enhances the pulmonary CXC chemokine response to intratracheal lipopolysaccharide challenge. J Infect Dis 2003; 187: 62-9.

[138] Gallin JI, Farber JM, Holland SM, Nutman TB. Interferon-γ in the management of infectious diseases. Ann Intern Med 1995; 123: 216-24.

[139] Condos R, Rom WN, Schluger NW. Treatment of multidrug-resistant pulmonary tuberculosis with interferon-gamma *via* aerosol. Lancet 1997; 349: 1513-5.

Received: August 24, 2007 Revised: September 24, 2007 Accepted: October 1, 2007