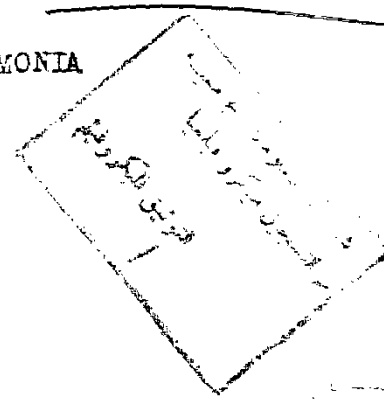
BACTERIAL CAUSES OF PNEUMONIA IN IMMUNOSUPPRESSED PATIENTS



Thesis

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By

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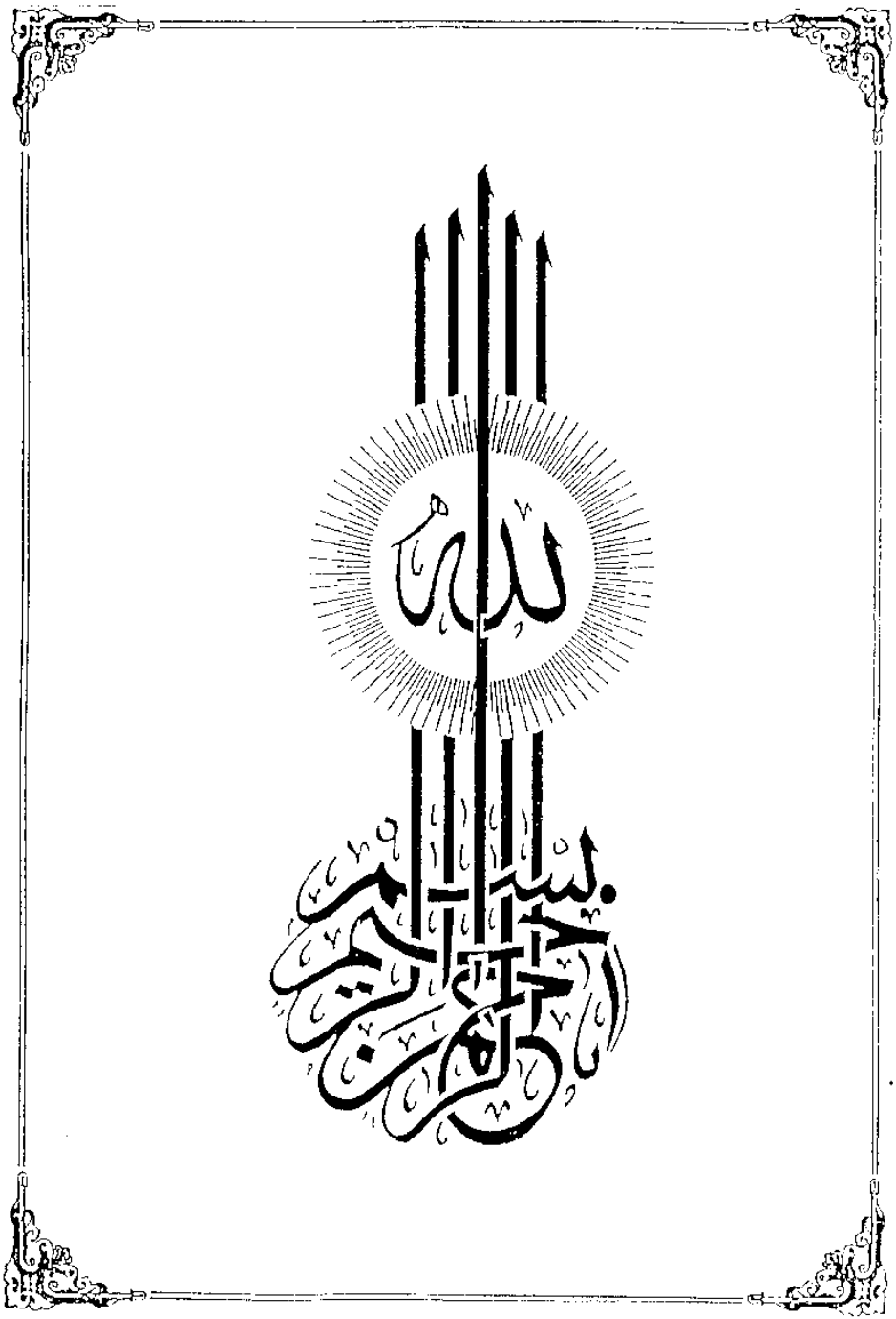

INTRODUCTION & AIM OF THE WORK

I N T R O D U C T I O N

With the development of intensive immunosuppressive therapy for patients with neoplastic diseases and organ transplants, infection has become a major cause of morbidity and mortality. Pneumonia presents a major diagnostic and therapeutic problem (Armstrog D.,1976; Neiman P.E.et al., 1976; Wolff et al.,1977).

Pneumonia due to pneumocystitis carinii and other opportunistic organisms is a clinically significant threat to immunosuppressed and immunodeficient patients (Wolff et al., 1977).

Examination of the expectorated sputum is the most important step in the management of pneumonia (Verghese A. et al. 1983; Donowitz G.R. et al.,1985). The value of sputum cultures has been totally neglected in some studies because sputum samples are regularly contaminated with bacteria present in the upper respiratory tract (Barrett Conner E. 1971). However, it has been shown that thecausative bacteria can be isolated as often from sputum as from trans-tracheal aspirate (Murray,P.R. et al.,1975; Geckler, R.W. et al.,1977; E. Lobrovski et al.,1988).

AIM OF THE WORK

This work aims to make a comparative study between the most common bacterial causes of pneumonia in immunocompetent patients and patients suffering from diseases associated with immunosuppression.

REVIEW OF LITERATURE

NORMAL FLORA OF THE RESPIRATORY TRACT

The mucous membranes of the mouth and pharynx are often sterile at birth but may be contaminated by passage through the birth canal. Within 4-I2 hours after birth, Streptococcus viridans become established as the most prominent member of the resident flora and remains so for life. Early in life, aerobic and anaerobic staphylococci, gram-negative diplococci (Neisseriae), diphtheroids and occasional lactobacilli are added. When teeth begin to erupt, anaerobes as Spirochaetes, Bacteroids and Fusobacterium species establish themselves. Yeast (Candida species) are also present in the mouth (Ernset et al.,I987).

The pharynx and the trachea contain a similar flora as the mouth (Ernset et al.,I987). Klebsiella pneumonia occurs commensally in the oropharynx of I-6% of healthy people. (Montgomerie,I979). Also, Pseudomonas aeruginosa is present as a commensal organism in the oropharynx of 5% of healthy people (Morrison et al.,I984).

The flora of the nose consist of prominent Corynebacteria, Staphylococci (S. aureus and S. epidermidis) and non-hemolytic and alpha-hemolytic streptococci. The bronchi contain few bacteria whereas the small bronchi and alveoli are sterile (Ernest et al., I987).

Natural Defences of the Respiratory System

A- The upper respiratory tract:

The nasal mucociliary mechanism propels mucus and deposited particles posteriorly to the pharynx where they are disposed of by swallowing (Crofton et al.,I989). The mucus secreted in the nose may contain specific secretory Ig A antibody (Butler et al. I970) as well as other non-specific antibacterial substances (Crofton et al., I989). In addition, the tonsils are important lymphoid organs that trap microorganisms (Tizard, I984).

B- The lower respiratory tract

I- Non-immunological defence mechanisms

I. The mucociliary escalator is the primary pulmonary mechanism for clearing airway surfaces of foreign materials (Crofton, et al.,I989).

II. The cough reflex: exists both as a protective and as a clearance mechanism for disposing of excessive secretions from the airways (Crofton et al.,I989).

III. Alveolar macrophages: are the probable explanation for the usual sterility of the alveolar surface (Brain et al.,I978). They ingest particulate matter (Warr et al.,I977), bacteria, fungi and viruses (Harris et al.,I970) and this ingestion is optimal following opsonization by immunoglobulins or complement (Reynolds et al.,I975).

Following ingestion of particulate matter or organisms,

alveolar macrophages become activated and these activated macrophages have an increased content of lysosomal enzymes (Mason., I977) and are better microbial killers (Brain et al.,I977).

IV. A number of non-specific humoral substances are present in the bronchial secretions and serve to protect the bronchial mucosa. These include:-

a) Lysozyme which is secreted by macrophages. It directly hydrolyses the B-I,4 linkageof the peptidoglycan layer of the cell wall of Gram-positive bacteria and can work in concert with complement and secretory Ig A to attack Gram-negative bacteria (Adinolfi et al.,I966).

b) Interferons: are a family of glycoproteins falling into 3 general groups: IFN-α, IFN-β and IFN-γ. They are produced rapidly by many cells in response to virus infections and T-cell activation. They act by promoting the synthesis of certain proteins actually inhibit virus replication (Crofton et al.,I989). Also, they are immunostimulants and antitumour agents.

c) Lactoferrin is a protein formed within the bronchial mucous glands (Masson et al.,I966) and can bind iron and has a bacteriostatic effect by competing for this element (Crofton et al.,I989).

II- Immunological defence mechanisms

I. Non-specific: Serum may contain natural antibodies against a variety of natural pathogens even in the absence of known previous exposure to these pathogens (Crofton et al.,I989).

II. Specific mechanisms:

a) Humoral Immunity: The respiratory tract possesses a considerable amount of lymphoid tissue in the form of nodules in the bronchi as well as lymphocytes distributed diffusely throughout the lung and the walls of the airways. The immunoglobulin synthesis in these tissues is mainly secretory Ig A, particularly in the upper regions of the respiratory tract. In the bronchioles and alveoli, however, the secretions contain a relatively large amount of Ig G, the concentration of which is intermediate between the levels in the trachea and in serum. Ig E is also synthesized in significant amounts in the lymphoid tissues of the upper respiratory tract. As in other body surfaces, Ig A in the respiratory tract is thought to protect by preventing adherence of antigenic particles, including microorganisms, whereas Ig G is probably of major importance only when acute inflammation and transudation of serum protein occur. This situation will arise, for example, following a type I hypersensitivity reaction mediated by locally produced Ig E, and it is tempting to suggest that the combination of Ig A and Ig E synthesis at mucosal surfaces is, therefore, not entirely fortuitous. It is possible that these immunoglobulins work in concert, so that Ig A produces a surface immunity serving to prevent antigen adherence and penetration. If, in spite of the presence of Ig A, antigen gains access to the tissues, then the subsquent Ig E mediated hypersensitivity reaction may serve to increase vascular permeability and make available large quantities of potent Ig G in the resulting fluid exudate (Tizard,I984).

b) Cell mediated immunity: It provides the main defence against intracellular organisms as Tubercle bacilli, Leprosy bacilli and viruses (Roitt,1980). Large numbers of cells may be washed out of the lungs by saline lavage. These include alveolar macrophages and lymphocytes. The lymphocytes are largely T-cells'. (Tizard, 1984).

c) Macrophages: Apart from their phagocytic function, macrophages play an important role in presenting antigens to B and T-lymphocytes. Also, the activated macrophages have many potential activities as release of interleukin I, neutrophil chemotactic factor, interferon, fibronectin, lysozyme acid hydrolase and lactoferrin (Crofton et al., 1989).

d) Complement: The complement consists of a series of serum proteins which activate each other serially, the reaction being initiated by the interaction of membrane antigen with antibody and result, by its end products, in lysis and phagocytosis of viruses and bacteria (Crofton et al., 1989).

PNEUMONIA

Defenition: Pneumonia is a syndrome caused by acute infection, usually bacterial, that is characterized by clinical and/or radiographic signs of consolidation of a part or parts of one or both lungs (Crofton et al.,I989).

Incidence and mortality:

The incidence of pneumonia varies between I and IO cases per IOOO of the population, being highest in infants and in elderly (Macfarlane,I987). This rate becomes 2 to 8 times greater in subjects of similar age living in the institutions. (Bently, I98I).

Also, pneumonia is the most common hospital acquired infection accounting for death, occurring with an estimated frequency of 0.5 to 5% of admissions(Podnos et al., I985).

Death rates from pneumonia may be affected by several factors, being greater in cold winter rather than in the summer, in lower socio-economic groups, overcrowding and poor ventilation (Crofton et al., I989).

Pathogenesis: The lungs are repeatedly inoculated by microorganisms from the upper airways and inhaled aerosoles, yet pneumonia rarely occurs due to the existence of efficient mechanisms of defence which are capable of elimination of microorganisms before their multiplication leads to clinical disease . The net bacterial clearance is actually the net result of three independent processess: the physical transport out of the lungs,

phagocytosis and in situ killing and bacterial multiplication. Using radiolabelled organisms, it has been found that different species of bacteria are cleared at markedly different rates and that the rate of bacterial killing greatly exceeds the rate of mucociliary transport. Some microorganisms e.g Pseudomonas aeruginosa and Klebsiella pneumoniae show resistance to phagocytosis and slow intrapulmonary killing (Goldstein et al.,I974).

Inoculum size and bacterial virulence are important determinants of the pathogenic potential of a bacterial challenge. Inoculum size is an important determinant of not only the rate of bacterial clearance but also of the cell type and the magnitude of the phagocytic defence against bacteria. Efficient numbers of alveolar macrophages are present on the alveolar surfaces to successfully ingest and kill certain inocula of bacteria, but larger inocula or Gram negative organisms overwhelm the resident alveolar macrophages requiring granulocytes for effective, although delayed, clearance. The different degrees of pathogenicity are thought to be related to the virulence of the bacterial species. The mucopolysaccharide which prevents phagocytosis by macrophages and neutrophils in the absence of an effective opsonin is one of the most important virulence factors e.g Pneumococci, Haemophilus and Klebsiella pneumoniae. The fact that some strains of pneumococci do not generate an effective opsonin and others do not activate the alternative complement pathway add to the virulence (Fine, I975).

Though bacteria may gain access to the pulmonary parenchyma

via the bloodfrom an extrapulmonary sources, or by inhalation of aerosolized bacterial particles, the majority of bacterial pulmonary infections are thought to follow endogenous aspiration of oropharyngeal bacteria (Woods,I983). Nocturnal aspiration is a common event; approximately 50% of normal subjects and 70% of subjects with impaired conciousness aspirate during sleep. It may, even, be proposed that everyone aspirates during deep sleep (Huxley et al.,1978). Inhaled bacteria are cleared by the lungs much more efficiently than these introduced by aspiration, this oropharyngeal secretions containing a significantly large number of organisms (approximately 10^7 organisms/ml) present a large challenge and their bacterial composition may be an important determinant of the aetiology of pneumonia. (Woods, I983).

Evidence has accumulated in recent years to suggest that the initial event in bacterial colonization and invasion is the adherence of microorganisms to epithelial cells of the mucosal surfaces. Organisms that fail to adhere to mucosal surfaces fail to colonize because they are removed by the secretions which bath the mucosal surfaces. Such adherence process is dependent upon specific recognition systems between bacteria and epithelial cells. Ig A in the oral secretions coats various bacteria preventing their adherence. Glycoproteins in saliva, receptor analogs, specifically inhibit the adherence of specific bacteria. Also, the availability of specific binding sites in a particular environment serve to select a certain population for any mucosal surface. This may explain the resistance