ANTIBIOTICS IN THE TREATMENT OF BACTERIAL INFECTIONS OF THE LOWER RESPIRATORY TRACT

" A LIMITED STUDY FOR EVALUATION OF THE EFFICACY AND SAFETY OF THE USE OF [ENOXACIN] IN THE TREATMENT OF SUCH INFECTIONS"

THESIS

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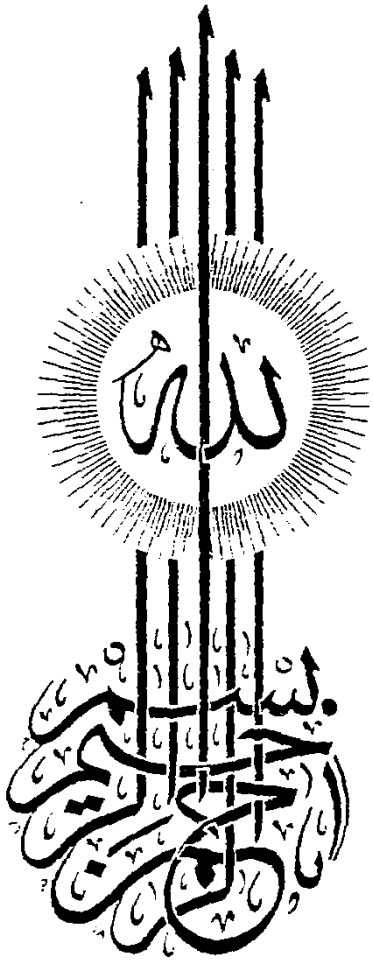

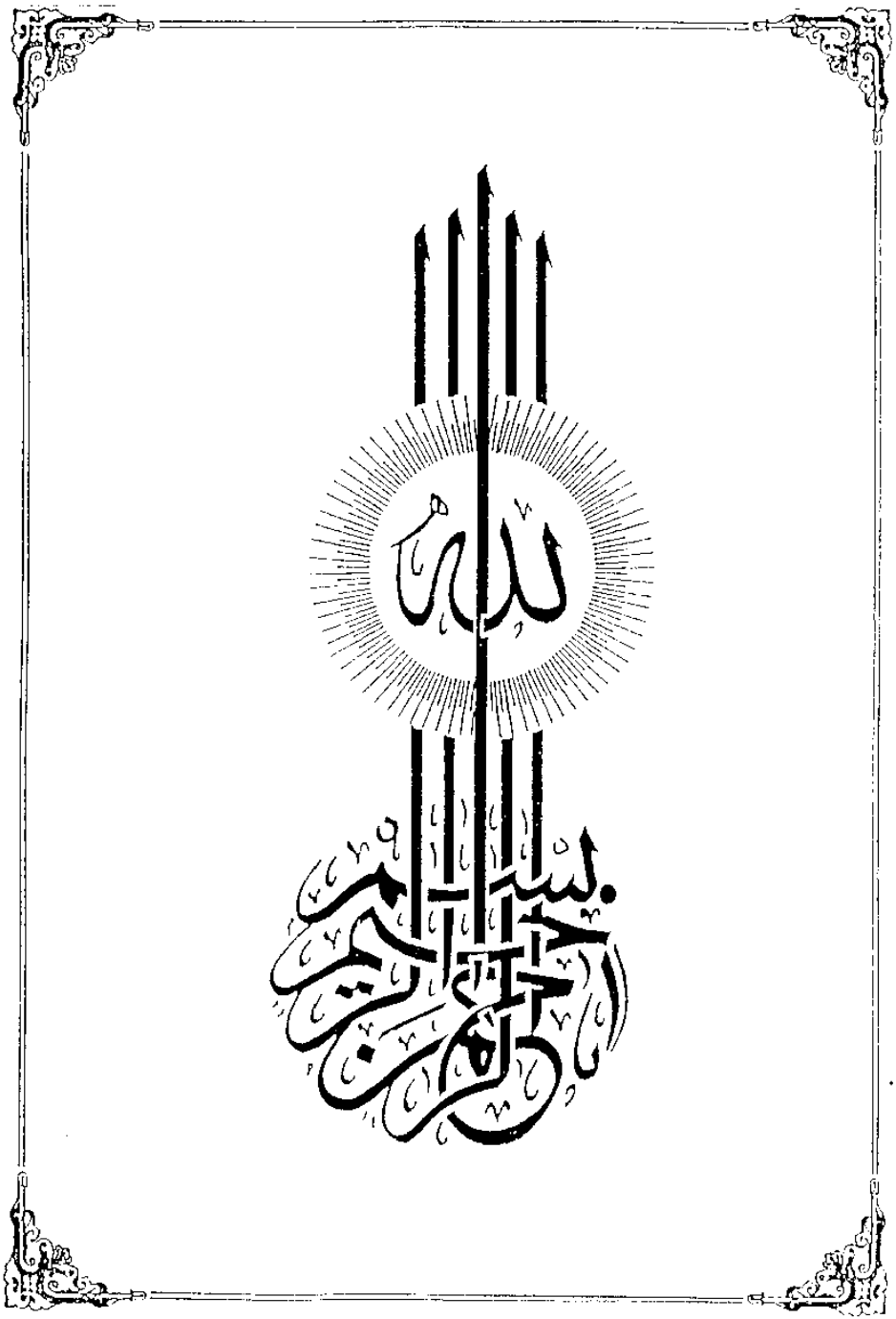

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INTRODUCTION

The development of the power to control infections is considered as one of the most important developments in the history of medicine. Following the discovery of penicillin a rush of antibiotics have been discovered and manipulated in a trial to have more potent and less toxic genrations. However,in spite of the increasing number of available antibiotics the rate of infections does not seem to decrease . Rather , with the increasing numbers of immunocompromized patients under medical care, there was a change in the pattern of infectious diseases. The principal etiologic agents in the former times, predominantly Gram-positive aerobic cocci, were replaced by predominantly Gram negative aerobic and anerobic bacilli, rarely encountered as pathogens in the intact human host. The widespread misuse of available antibiotic adds to the problem by enhancing the emergence of resistant strains ; calling for newer antimicrobial agents.

AIM OF THE STUDY

The aim of this study is to review the literatures concerning the use of antibiotics in lower respiratory tract infections. A trial of "Enoxacin" is also included, comprising a limited number of 11 patients to study its efficacy and safety in treating lower respiratory tract infections.

REVIEW
OF
LITERATURE

The modern era of chemotherapy has begun since the initial use of sulphonamides in 1936. This was followed in 1940s by the discovery of the therapeutic value of penicilline and streptomycin. Over the last 40 years several antibiotics have been developed. Antibiotics continue to be grossly over-used, and this has led to the present vicious circle of increasing bacterial resistance and increasing treatment with newer drugs.

DEFINITION OF ANTIBIOTICS

Antibiotics are chemical substances produced by various species of microorganisms [bacteria, fungi and actinomy cetes] that suppress the growth of other microorganisms and may eventually destroy them. [Sande and Mandell, 1980].

CLASSIFICATION OF ANTIBIOTICS

Sametimes deep knowledge is required to chocse the proper antimicrobial therapy. Several classfications, which might help, have been applied.

1) According to the primary action, antibiotics can be classified into:-
   a) bacteriostatic drugs which act primarily by stopping bacterial growth. Of these are the sulphonamides, tetracyclines, chloramphenicol,

erythromycin [in low concentrations], lincomycin, clindamycin, P.A.S. and fusidic acid.

b) bactericidal drugs which act primarily by killing the bacteria. This group includes the beta-lactams, aminoglycosides, Co-trimoxazole, polymxin, colistin, vancomycin and erythro mycin [in high concentrations]

This classification, however, is arbitrary because some drugs are becteriostatic or bactericidal according to concentration. This is particularly true of Co-trimoxazole, erythromycin, novobiocin, fusidic acid, lincomycin and clindamycin [Laurence and Bennet, 1980].

Another classification has been based on chemical structure and proposed mechanism of action:-

a) Agents that inhibit synthesis of, or activate enzymes that disrupt bacterial cell walls to cause loss of viability and often cell lysis. Such cell wall is essential to withstand the osmotic gradient between the cytoplasm and the surrounding medium.

Penicilins, cephalosporins, cycloserin, vancomycin, novobiocin and bacitracin contain groups simulating chemical groups concerned with the building up of the wall of

the bacterial cell and so interfere with the new synthesis of cell wall of the growing bacteria. Mammalian cells are lacking this cell wall, that is why penicillines are not toxic to human cells. The difference in structure and more complexity of the cell wall of gram negative bacteria explains the insensitivity of these microorganisms to benzyl penicilline. Failure of antibiotics to penetrate may also contribute. to their resistance to some antibiotics.

b) Agents that act directly on the cell membrane, affecting permeability and leading to leakage of intracellular compounds; these include the detergants, polymyxin and the polyene antifungal agents, nystatin and amphotericin-B, that bind to cell wall sterols.

c) Agents that affect the function of bacterial ribosomes to cause a reversible inhibition of protein synthesis; these bacteriostatic drugs include chloramphenicol, the tetracyclines and the macrolide antibiotics.

D) Agents that bind to the 30s ribosomal subunit and causes accumulation of protein synthetic initiation complexes, misreading of the mRNA code, and the production of abnormal peptides; those include the aminoglycoside group which are bactericidal.

e) Agents that affect the nucleic acid metabolism, such as rifampicin, which inhibit DNA- dependent RNA polymerase.

f) Agents that block specific antibiotic steps that are essential to the microoganisms; these include trimethoprim and sulphonamides [Sande and Mandell, 1980].

A 3rd classfication is based on the general antimicrobial activity of the various groups of drugs:

a) drugs primarily effective against the Gram-positive cocci and bacilli, which tend to have a narrow spectrum of activity, include penicillin-G, the semisynthetic penicillinase resistant penicillins, the macrolides, the lincomycins, vancomycin, and bacitracin.

b) drugs primarily effective against the aerobic Gram-negative bacilli, include the aminoglycosides and polymyxins.

c) drugs with relatively broad spectrum activity affecting both the Gram-positive cocci and Gram negative bacilli, these include the broad spectrum penicillins, the cephalosporins, the tetracyclines, chloramphenical, trimethoprim and the sulphonamides.

Although this classification has many important exceptions, it does help the physcian to remember the antibiotic spectrum of each drug [Sande and Mandell, 1980].

* * *

incorporate into their own substance part of the host's genetic material. The modified phage reproduces and its offspring escapes from the now dead host to infect other bacteria. The new host receives the genetic material derived from the organism that was infected in the first place. The modified phages are less virulent and they do not necessarily kill the bacteria they infect. If the material they transfer contains genes that determine drug resistance, the infected cells will also acquire resistance. The material transferred by the transduction process is occasionally derived from chromosomes but more commonly it takes the form of plasmids. Phage transduction occurs in both Gram-negative and Gram-positive organisms. [Crossland, 1980].

Some Gram-negative bacteria can conjugate with other members of the same or related species by a process that is reminiscent of sexual union. The "male" member of each pair carries a hair-like projection called sex pilus which comes into contact with its partner. the conjugation bridge so formed, permits the passage of plasmids from "male" to the "female cell [Crossland, 1980].

There is increasing agreement that is the main mechanism whereby bacteria have acquired resistance in vivo is by the acquisition of plasmids. With most bacteria, change in the bacterial DNA, that is mutation, occurs

infrequently except to a few antibiotics, notably streptomycin, fusidic acid, novobiocin and rifamicin [Lacey,1980]

ROLE OF PLASMIDS:

The plasmid is a small extrachromosomal piece of genetic material, usually in the form of a circular piece of double stranded DNA. It has many of the properties of a small chromosome. Plasmids carry genes that cause the cell, using its normal synthetic mechanisms, to produce proteins, chiefly enzymes, that inactivate individual antibiotics in various ways. They occasionally carry genes that cause the cell to produce toxins and virulence factors or resistance factors to antimicrobial drugs [Lacey, 1980].

MECHANISMS OF RESISTANCE

Regardless of the genetic background involved, the mechanisms of antimicrobial resistance include:

[1] Elaboration of enzymes that inactivate the antibiotics. Beta- Lactamase are the best known example, and is considered as the commonst resistance mechanism that results from the carriage of plasmids. Enzymes of this groups are seen in the majority of hospital strains of Staph. aureus, E. Coli, Klebsiella, Proteus, Pseudomonas,