Antibiotic Resistance in the Intensive Care Unit

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Introduction

Antibiotic resistance is an increasingly common problem in the contemporary health care system, and in particular, in the intensive care unit (ICU) [1, 2]. Critically ill patients are five to ten times more likely to develop a hospital-acquired infection than patients on a general hospital ward, and antibiotic-resistant pathogens are responsible for more than half of these infections [3, 4]. A better understanding of the factors responsible for the emergence of resistant pathogens in hospitalized patients is fundamental to the control, or reversal of this trend.

Definition and Mechanisms of Antibiotic Resistance

Penicillin and streptomycin, introduced into clinical practice approximately 65 years ago, were the first antibiotics available to treat bacterial infections. The phenomenon of antibiotic resistance emerged at the same time. In 1940, Abraham and Chain [5] described a bacterial enzyme called beta-lactamase that could inactivate penicillin. Since then, almost all strains of bacteria responsible for human illness have developed resistance to one or more classes of antimicrobial agents.

However, the origins of antimicrobial resistance extend much farther back, and are not entirely related to the introduction of antibiotics. It would be teleologically improbable that the energetic and metabolic disadvantage, and the biological complexity of the processes necessary to express factors providing antibiotic resistance, would have emerged over the three billion year history of bacterial evolution, unless resistance genes served other roles that supported bacterial survival. It is known, for example, that antibiotic-producing microorganisms that are not agents of human disease also express genes encoding antibiotic resistance factors [6] that provide an adaptive advantage in limiting the growth of other microbial competitors. Thus it is most probable that innate and conserved mechanisms of antibiotic resistance in bacteria have become more prevalent under the powerful selective pressure provided by widespread antimicrobial exposure.

Antibiotic resistance at the cellular level is mediated through several biologic mechanisms, and may be intrinsic or acquired. Some strains of bacteria are naturally resistant to certain antibiotics (for example, enterococci are resistant to fluoroquinolones and cephalosporins), because they do not express the appropriate molecular target of the antibiotic, or because the cell wall is impermeable to penetration by the agent. These organisms behave clinically as opportunistic pathogens,
since they selectively proliferate in the presence of antibiotics that suppress other components of the normal flora. In addition to enterococci, coagulase-negative staphylococci, Acinetobacter baumannii and Stenotrophomonas maltophilia are frequently resistant to multiple antimicrobials and emerge as common causes of ICU-acquired infections, particularly in the chronic critically ill patient who has received multiple courses of broad spectrum antibiotics [6].

Antibiotic resistance is acquired through one of two principle mechanisms: spontaneous mutation and DNA transfer [3, 6, 7]. Genetic mutations can result in structural modification of proteins, and in the up- or down-regulation of proteins relevant to the antibiotic effect, for example, porins, active transporters, and gene promoters or repressors. If mutations occur in the genes that regulate DNA replication or repair, the mutants can become ‘hypermutators’ – bacteria characterized by a mutation rate 200 times higher than the usual. This phenomenon, triggered in part by a stress response system, increases the capacity of the microorganism to adapt to the surrounding environment, and thus to develop resistance to antibiotics that are present [8].

Antibiotic resistance can also be acquired through DNA transfer. Genes encoding antibiotic resistance factors can reside in chromosomes or in plasmids, circular structures of nucleic acid that are transferable from one bacterium to another. DNA transfer is responsible for the spread of antibiotic resistance from one species of bacteria to another [6, 7].

Most Gram-negative, and some Gram-positive bacteria (for example, Staphylococcus aureus), are able to inactivate antibiotics through the synthesis of specific enzymes, such as beta-lactamases that hydrolyze the beta-lactam ring present in penicillins and cephalosporins. There are a number of beta-lactamases, with differing affinity for different types of beta-lactam antibiotics. Moreover, over the past few decades, antibiotic exposure has resulted in a much broader spectrum of beta-lactamase enzymatic activity including activity against third generation cephalosporins. More than 150 extended spectrum beta-lactamases (ESBL) have been identified; some are highly resistant to third generation cephalosporins and to beta-lactamase inhibitors (clavulanic acid, tazobactam) [9].

Another mechanism of bacterial antibiotic resistance derives from modification of the antibiotic target, altering the affinity for the antimicrobial drug. For example, S. aureus, streptococci and enterococci, synthesize a modified penicillin-binding protein that has a low affinity for beta-lactam antibiotics and so renders them inactive [3].

Modification of porin channels in the bacterial cell wall can prevent the movement of antibiotic across the bacterial outer membrane, a phenomenon that has been documented in some Gram-negative bacteria, such as Pseudomonas aeruginosa. P aeruginosa and other enterobacteriaceae possess an energy dependent system that can actively remove drugs or other undesirable substances from the organism before they exert their biologic effects. Some of these pumps are drug specific; others are active across a broad spectrum of agents [7].

In addition to intrinsic cellular mechanisms of resistance, multiple other factors are relevant to the emergence of antibiotic resistance, including the site of the infection, the pharmacodynamic properties of the antibiotic used and its concentration in the infectious focus, and the immunocompetence of the human host. Bacteria that are sensitive in vitro to a certain dose of antibiotic may be completely resistant in vivo because of the particular distribution of the drug in the body, or the inaccessibility of the drug to the infected tissue. Sub-therapeutic doses of anti-