Antibiotic Resistance in the Intensive Care Unit

Essay

Submitted for Partial Fulfillment of Master Degree in Intensive Care

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2013

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Introduction

The development of antimicrobial resistance is a growing problem worldwide, and infections due to multi-resistant pathogens, both Gram-positive and Gram-negative, have steadily increased over the years ***(Raineri et al., 2010).***

Resistance is a measure of decreased ability of an antimicrobial agent to kill or inhibit the growth of a microbial organism ***(Henry and Constantine, 2011).*** Infections with these organisms have been associated with greater mortality , prolonged hospitalization and increased costs ***(Raineri et al., 2010).***

Infections caused by drug-resistant and multidrug-resistant microbial pathogens pose tremendous challenges to health care systems, including challenges related to the diagnosis, treatment, and containment of these infections ***(Livermore, 2009***). These challenges are amplified in the intensive care unit (ICU), where pressures for selection and emergence of resistance and risks of transmission of resistant pathogens are highest, and where the threat of resistance drives selection of empiric antimicrobial regimens ***(Henry and Constantine, 2011).***

Intensive care units are unique because they house seriously ill patients in confined environments where antibiotic use is extremely common ***(Kollef and Fraser, 2001).*** They have been focal points for the emergence and spread of antibiotic-

resistant pathogens. Several investigators have demonstrated a close association between previous use of antibiotics and the emergence of subsequent antibiotic resistance in both gram-negative and gram-positive bacteria ***(Kollef et al., 1995).*** The experience with scheduled antibiotic class changes also demonstrates how rapidly antibiotic-resistant bacteria can emerge in the ICU and in hospitals as patterns of antibiotic use change ***(Kollef and Farser, 2001).*** At least 7 days of mechanical ventilation, previous anti-biotic use, and previous use of broad-spectrum antibiotics (third-generation cephalosporin, fluoroquinolone, carbapenem, or a combination) are the most important risk factors associated with the development of ventilator-associated pneumonia caused by antibiotic-resistant pathogens. Other risk factors, such as prolonged length of hospital stay, also seem to predispose patients to infection with antibiotic-resistant bacteria ***(Trouillet et al., 1998).***

Multidrug resistant organisms (MDROs) continue to proliferate and spread in both the hospital and community, but the hospital remains the primary source for emergence and spread of MDROs. Controlling the emergence and spread of MDROs presents many challenges to physicians, hospital epidemiologists, and infection preventionists. Several interventions and strategies are currently available and reasonably effective, but further studies are needed to determine the best methods for controlling antimicrobial resistance (***Anderson and Kaye, 2009) .***

Different mechanisms of antibiotic resistance have been described in bacteria. These include enzymatic inhibition, decreased permeability, antibiotic efflux, Target modification (ribosomes, cell walls, enzymes), and development of alternative targets or pathways. They may be present singly, or in any combination, within a particular bacterial species ***(Varley et al., 2009)***.

Biomarkers guide antibiotic use in patients with ventilator associated pneumonia(VAP) caused by multidrug resistant pathogens pathogens(MDR). One of these markers is procalcitonin biomarker with the most convincing data: a rapid procalcitonin serum -level decline is associated with good outcomes, whereas its increase or stabilization is associated with poor outcomes (death, multiorgan failure) or denotes inappropriate antibiotic regimen, or superinfection ***(Charles et al., 2011).***

It is apparent that no single measure can be effective in the prevention of infection due to antibiotic resistant organisms or reduction of resistance. Knowledge of the mechanism of transmission of resistance enables targeted efforts to control outbreaks. For example, if resistance is being imported, greater isolation and screening measures should be employed. Alternatively if resistance is being disseminated from within the unit, better adherence to infection control measures should be enforced. A wide range of non-pharmacological methods are employed to try and limit the spread of resistant infections ***(Varley et al., 2009)***.

Introduction

The hospital has historically been regarded as the epicenter for antimicrobial resistance. In many ways, it represents the ‘‘perfect storm’’ for emergence and spread of antimicrobial resistance ***(Anderson and Kaye, 2009).***

Resistance is a measure of decreased ability of an antimicrobial agent to kill or inhibit the growth of a microbial organism ***(Fraimow and Tsigrelis , 2011).***

The epidemiology of resistance is extremely local. Most outbreaks and clusters involve a few patients in a unit, and the prevalence of resistance is often highest in those units where the most vulnerable patients are congregated and where antibacterial use consequently is heaviest ***(Voss et al., 1994).***

Outbreaks of antibiotic-resistant bacterial infection due to inadequate infection control practices, failure to recognize the presence of antibiotic resistance, or use of contaminated equipment are also important factors promoting the spread of resistance ***(Alfieri et al., 1999).***

Bacteria may use or combine multiple mechanisms against a single agent or class of agents or a single change may result in development of resistance to several different agents ***(Kaye et al., 2000).***

Strategies incited some investigators to explore whether use of biologic markers could improve identification of patients with true ventilator-associated pneumonia (VAP) and facilitate the decision about whether to treat, monitor the response to antibiotics, and shorten treatment duration ***(Luyt et al., 2011).***

Major efforts are needed to slow down the rising problem of multidrug-resistant bacteria. Prevention of infections, proper diagnosis and treatment, prudent and rational use of antimicrobials; and prevention of transmission are the milestones of facing the problem ***(Carlet et al., 2007).***

Antimicrobial resistance is an important determinant of outcome for patients in the intensive care unit. In addition, the problem has substantially increased overall health care costs ***(Kollef and Fraser, 2001).***

Antibacterial Resistance

GENERAL CONCEPTS:

Resistance is a measure of decreased ability of an antimicrobial agent to kill or inhibit the growth of a microbial organism. In practice, this is determined by testing a patient isolate against an antimicrobial in an in vitro assay system ***(Fraimow and Tsigrelis, 2011).***

For bacteria, the common in vitro testing systems are automated liquid media microdilution systems, disc diffusion, and the epsilometer test (E-test). For quantitative systems like broth microdilution or E test, the measure of drug activity is the minimum inhibitory concentration (MIC) ***(Fraimow and Tsigrelis, 2011).***

Minimum inhibitory concentration (MIC) is the lowest concentration of an antimicrobial drug that will inhibit the visible growth of a microorganism after overnight incubation. Minimum inhibitory concentrations are important in diagnostic laboratories to confirm resistance of microorganisms to an antimicrobial agent and also to monitor the activity of new antimicrobial agents ***(Andrews, 2001).*** A lower MIC is an indication of a better antimicrobial agent. MIC is generally regarded as the most basic laboratory measurement of the activity of an antimicrobial agent against an organism ***(Turnidge et al., 2003).***

From testing of large numbers of isolates, breakpoints that define the thresholds of susceptibility for each organism-drug combination are established by groups such as the US Clinical and Laboratory Standards Institutes (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Breakpoints are included in the US Food and Drug Administration (FDA)-approved product labeling for new antibacterial agents ***(Fraimow and Tsigrelis, 2011).***

A strain reported as susceptible in vitro has an MIC value at or below the defined susceptibility breakpoint, which is believed to correlate with high likelihood of therapeutic success ***(Fraimow and Tsigrelis, 2011).***

For strains reported as intermediate or indeterminate, therapeutic effect is uncertain; for strains reported as resistant, use of that agent is associated with high likelihood of therapeutic failure ***(Woodford and Sundsfjord, 2005).***

Some resistance traits are not reliably detected by standard methods, and require additional microbiologic or molecular confirmatory testing, which may lead to delay and increased cost for correctly identifying resistant organisms ***(Woodford and Sundsfjord, 2005).***

Intrinsic resistance is an inherent feature of a species resulting in the lack of activity of a drug or drug class. Intrinsic resistance may be due to such factors as lack of the appropriate antimicrobial target, inability of the drug to access target, or

presence of species-wide antimicrobial inactivating enzymes ***(Fraimow and Tsigrelis, 2011).***

An example is the intrinsic resistance of gram-negative organisms to the glycopeptides vancomycin and teicoplanin, which cannot penetrate the outer membrane to reach their target. Circumstantial resistance reflects the disparity between in vitro and in vivo activity. Antibiotics that are active in vitro may not be clinically effective, due to lack of drug penetration to protected sites such as the cerebrospinal fluid, or the inactivity of drug at low pH or in an anaerobic environment ***(Fraimow and Tsigrelis, 2011).***

Focusing in acquired resistance: a change in phenotypic characteristics of an organism resulting in decreased effectiveness of a previously active drug. Acquired resistance is a natural consequence of genetically adaptable microorganisms responding to the selective pressure of antimicrobial agents ***(Fraimow and Tsigrelis, 2011).***

The phenotype of acquired resistance has a genotypic correlate, although the genetics of some resistance traits remain poorly characterized. Some important acquired resistance traits can be directly selected for in vitro and in vivo via one or several point mutations in antimicrobial target genes.There are many important resistance phenotypes, such as methicillin resistance in *Staphylococci*, that cannot be selected for in vitro or in vivo, and only occur through susceptible organisms

acquiring exogenous genetic material***(Fraimow and Tsigrelis, 2011).***

Molecular genetics of antibiotic resistance

Analysis of bacteria collected before widespread introduction of antibiotics reveals, excluding intrinsic resistance, almost complete sensitivity. Organisms with intrinsic resistance are often of low virulence but do become a problem in vulnerable patients managed in selection pressure environments (*Pseudomonas*, *Acinetobacter*). Acquisition is based on the mechanisms of genetic mutation and inter-cell transfer. Mutation is often disadvantageous to the bacteria but will, infrequently, affect antibiotic resistance. However, the transfer of resistance between bacteria is of greater importance, the mechanisms of which are not mutually exclusive ***(Varley et al., 2009).***

1. Naked DNA (transformation)

Naked DNA is released from killed bacteria and as such is common in the ICU patient on antibiotics. DNA in this form is unprotected and is quickly degraded. Bacteria have a varying ability to take up this DNA. Transformation is the process where this DNA is incorporated into the genome of another bacterium ***(Varley et al., 2009).***

2. Bacteriophages (transduction)

These are viruses that infect bacteria. A protein coat protects the DNA within and the virus relies on the bacteria's

cellular machinery to propagate it. The DNA within the virus may be exchanged or transferred to the host, and through this mechanism can transfer genetic information encoding resistance. This is known as transduction. Bacteria vary in their susceptibility to infection with bacteriophages; *Coryne-bacterium diptheriae* and *Vibrio cholerae* are examples of bacteria that commonly receive genetic information through this route ***(Varley et al., 2009).***

3. Plasmids (conjugation)

These are self-replicating circles of DNA that exist within the bacteria but are separate from the chromosome **Figure (1)**. They lack the protective coat of the bacteriophage and are unable to move independently of the bacteria. Despite these limitations, they are the most important routes of transmission of genetic information within the intensive care unit ***(Varley et al., 2009).***

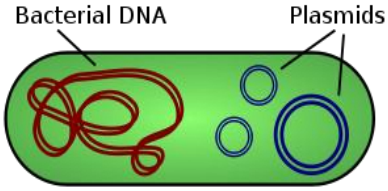

Figure (1): Illustration of a bacterium with plasmid enclosed showing chromosomal DNA and plasmids *(Varley et al., 2009).*

4. Transposons

These are small segments of DNA that can encode resistance genes. They also encode for their mobility, thus allowing them to move from plasmid to plasmid, or within the

main genotype. As such they can transmit resistance between cells ***(Varley et al., 2009).***

Evolution and Spread of Antimicrobial Resistant Organisms

In a patient exposed to an antimicrobial agent, resistant organisms can emerge by selection for and expansion of subpopulations of spontaneously generated, less susceptible mutants of antimicrobial target ***(Martinez et al., 2007).***

More commonly, colonization or infection with drug-resistant organisms results from super infection rather than by evolution of resistance in the original target organism. New drug-resistant "invaders" are selected from organisms already part of the patient's endogenous flora, living on mucosal surfaces or in the gastrointestinal tract, or are newly acquired from the health care environment ***(Plesiat, 2010).***

Emergence of resistant organisms and superinfection are both concerns in patients failing to respond to antimicrobial therapy, but there are multiple other reasons for therapeutic failure: inadequate source control, host immune status, and pharmacologic issues of drug bioavailability and optimal dosing are only a few of these. Bacteria employs several basic strategies for evading the effects of antibiotics, including enzymatic modification and inactivation of antimicrobial agents, restriction of drug access to the cellular targets, and

modification or even complete elimination of the target ***(Plesiat, 2010).***

The most important classes of inactivating enzymes are the many b-lactamases in gram-positive and gram-negative bacteria and the aminoglycoside- modifying enzymes (AME) ***(Jacoby and Munoz-Price, 2005).***

Restriction of drug target access can occur from alterations in membrane permeability to decrease drug entry, Or by "trapping" of an antimicrobial agent before accessing the target ***(Jacoby and Munoz-Price, 2005).***

Target modification occurs through mutations in target genes, such as the gyrase and topoisomerase targets of fluoroquinolones, by enzymatic modification of target genes, by introduction of new, non susceptible targets such as the MecA protein in *Staphylococcus aureus* **[**The MecA gene is a gene found in bacterial cells. The MecA gene allows a bacterium to be resistant to antibiotics such as methicillin, penicillin, erythromycin, tetracycline and other penicillin-like antibiotics**]** ***(Ubukata et al., 1989),***or through novel synthetic pathways like the *Enterococcal* vanA and vanB clusters that eliminate the bacteria's need for the original antimicrobial target ***(Jacoby and Munoz-Price, 2005).***

Levels of resistance are magnified by combining different mechanisms. For example, permeability changes and efflux pumps that decrease intracellular b-lactam concentrations

enhance effectiveness of b-lactamases present in the gram-negative priplasmic space ***(Jacoby and Munoz-Price, 2005).***

Organisms expressing acquired resistance traits can clonally disseminate, transmitting their resistance traits to their multiple descendants. The extra "work" required for maintaining resistance traits may result in decreased fitness of the organism, thus resistance may ultimately disappear in the absence of selective pressure. However, other resistances traits are relatively stable and persist even in the absence of antibiotic exposure ***(Andersson and Hughes, 2010).***

Resistance genes or gene clusters can also be transmitted horizontally between organisms, as well as between species. Resistance genes are typically carried on transposons, which are mobile genetic elements that can move in and out of the bacterial chromosome and into plasmids, facilitating horizontal gene transfer. Unrelated resistance genes are often clustered together, enabling transfer of multiple resistances as a single package. Transfer of resistance occurs among gram-negative flora in the human gastrointestinal tract, and exchange of vanA resistance clusters in vivo from *Enterococci* to *Staphylococcus aureus* has led to emergence of highly vancomycin- resistant *Staphylococcus aureus* (VRSA) ***(Rice, 2010).***