Optimizing antibiotic therapy in ICU.

An essay submitted for partial fulfillment of master degree in ICU.

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2010

ACKNOWLEDGEMENT

First of all and above all great thanks to Allah blessings on me cannot be counted.

I would like to express my deepest appreciation, great admiration and sincerest thanks to ***Prof. Dr. Yosry Robin Ghattas*** Professor of anaesthesia and intensive care, faculty of medicine, Ain Shams University for his generous advice, appreciable encouragement, fruitful criticism, kind assistance and experienced cooperation during this work.

It is difficult for me to express my sincere appreciation and my great thanks to ***Prof. Dr., Bahaa EL Dien Owis*** professor of anaesthesia and intensive care**,** faculty of medicine, Ain Shams University for his great help , valuable instructions ,continuous support and encouragement to complete this work .

I am especially grateful to ***Dr. Amal Hamed Rabie*** lecturer of anaesthesia and intensive care**,** faculty of medicine, Ain Shams University for her keen supervision, creative suggestions, creative criticism, unlimited cooperation, scientific advices and experienced guidance.

Finally, I would like to thank all members of anaesthesia department, faculty of medicine, Ain Shams University for their help and cooperation.

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Introduction

Infection is an everyday problem in **intensive care units** (ICUs) and **antibiotics** are therefore commonly used in this setting ***(Alberti et al., 2002).*** The high prevalence of infection in ICU involves heavy consumption of antimicrobial agents 10 times that in general wards ***(Roder et al., 1993).***

Besides treatment of infections, **antibiotics** are administered as prophylaxis to prevent or limit major infections in critically ill patients. There is a great distinction between surgical and non surgical patients ***(Mangram et al., 1999).***

It was found that first-line empirical therapy in critically ill patients is often inadequate and needs to be changed once the antimicrobial sensitivity test AST results are known ***(Alvarez, 1996)***. A number of factors may contribute to inappropriate empirical antibiotic choice in ICUs.

First, few ICUs have a well-organized infection surveillance system, and it would be difficult to base antibiotic choice on the local epidemiology of microbial resistance.

Second, although a scheduled cycling of antibiotics has been proposed within ICUs**,** it is not clear which antibiotics should be rotated ***(Raymond et al., 2001)***. Guidelines for coping with specific situations, like ventilator-associated pneumonia (VAP) are available but many important infections like bacteraemia, peritonitis and urinary tract infection remain uncovered.

Third ,the decisions to start and stop antibiotic therapy are usually taken by intensive care clinicians alone in over 95% of cases and the contribution from microbiologists and infectious diseases specialists are very low ***(corona et al.,2003).*** Thus, appropriate use of antibiotics in ICUs is important in ensuring an optimal clinical outcome, besides controlling the emergence of resistance among pathogenic microorganisms and in containing costs ***(Hoffken et al., 2002).***

List Of Abbreviations

AST:	the antimicrobial sensitivity test.
AmB:	amphotericin B
VAP:	ventilator-associated pneumonia.
CSF:	Cerebrospinal fluid.
CPmax::	maximum plasma concentration.
PBP-3:	penicillin-binding protein 3.
AHFS:	American Society of Health-System Pharmacists.
MRSE:	multi-resistant Staphylococcus epidermidis.
MRSA:	methicillin-resistant Staphylococcus aureus.
LPS:	lipopolysaccharide
IARC:	International Agency for Research on Canc
CN:	Coagulase-negative.
HAP:	hospital acquired pneumonia .
CAP :	community-acquired pneumonia.
NUTI:	nosocomial urinary tract infections.
HIV:	human immunodeficiency virus.
VRSA:	Vancomycin-resistant S. aureus.
MSSA:	Methicillin-susceptible *S.aureus.*
TMP/SMX:	Trimethoprim/sulfamethoxazol
PTSAgs:	Pyrogenic toxin superantigens
TSS:	toxic shock syndrome
SSSS:	staphylococcal scalded-skin syndrome.
PVL:	Panton-Valentine leukocidin.
EC:	E. coli
ETEC:	Enterotoxigenic E. coli
cGMP	cyclic guanosine monophsphate.
EPEC:	Enteropathogenic E. coli.
EIEC :	Enteroinvasive E. coli.
EHEC:	Enterohemorrhagic E. coli.
EAggEC:	Enteroaggregative E. coli.
VRE:	Vancomycin-resistant enterococcus,
Hib:	influenzae type b.
PRP	polyribosyl ribitol phosphate.
NAC	non-albicans Candida,
RSV,	respiratory syncytial virus.

NIs:	nosocomial infections
para-aminobenzoic acid PABA:	
HGT:	horizontal gene transfer
ESBLs:	Extended spectrum beta-lactamases producing Gram-negative bacteria
PRSP:	Penicillin resistant streptococcus pneumoniae
PPE:	personal protective equipments
HCWs:	healthcare workers
SARS:	severe acute respiratory syndrome

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Antibiotic Resistance

Antibiotic resistance is the ability of a micro-organism to withstand the effects of an antibiotic. It evolves naturally via natural selection acting upon random mutation, but it can also be engineered by applying an evolutionary stress on a population of micro-organisms. When a bacterium carries several resistance genes, it is called multiresistant or, informally, a superbug. If a microbe is resistant to many drugs, treating the infections it causes can become difficult or even impossible. In some cases, the illness can lead to serious disability or even death ***(Cirz et al., 2005).***

Almost all infections could be controlled, but finding an effective antibiotic typically requires 2-3 days as bacterial cultures with extensive growth are needed to test antibiotic susceptibility and resistance. With critically ill patients in the ICU, the physicians cannot wait for lab results before attempting to control an infection, therefore antibiotic therapy is started within a few hours of symptoms onset in the form of antibiotic combinations. These empiric antibiotic combinations fail in approximately 20- 40% of cases and even switching drugs after receiving lab results fails to improve the outcome ***(Cirz et al., 2005).***

There is a gene pool in nature for resistance to antibiotics as well as there is one for antibiotic production. Most microbes that are antibiotic producers are resistant to their own antibiotic and over the years, almost every known bacterial pathogen has developed resistance to one or more antibiotics in clinical use**.**

Types of antibiotic resistance:

Antibiotic resistance in bacteria may be an inherent trait of the organism that renders it naturally resistant, or it may be acquired by means of mutation in its own DNA or acquisition of resistance-conferring DNA from another source.

1*Inherent (natural) resistance:

Bacteria may be inherently resistant to an antibiotic. For example, an organism lacks a transport system for an antibiotic; or an organism lacks the target of the antibiotic molecule; or, as in the case of Gram-negative bacteria, the cell wall is covered with an outer membrane that establishes a permeability barrier against the antibiotic.

2*Acquired resistance:

Several mechanisms are developed by bacteria in order to acquire resistance to antibiotics. All require either the modification of existing genetic material (mutation) or the acquisition of new genetic material from another source ***(Todar, 2004).***

Researchers have recently demonstrated that the bacterial protein LexA may play a key role in the acquisition of bacterial mutations ***(Cirz et al., 2005).***

Mechanisms of antibiotic resistance:

Resistence mechanisms to most common antimicrobials are shown in (table 9)

antibiotic	**Mechanism of resistance**
Chloramphenicol, aminoglycosides	reduced uptake into cell
Tetracycline	active efflux from the cell
β-lactams, Erythromycin, Lincomycin,tetracyclines	eliminates or reduces binding of antibiotic to cell target
β-lactams, Aminoglycosides, Chloramphenicol	enzymatic cleavage or modification to inactivate antibiotic molecule
Sulfonamides, Trimethoprim	metabolic bypass of inhibited reaction overproduction of antibiotic target (titration)

Table (9): Mechanisms of antibiotic resistance ***(Todar, 2004)***

There are mainly four mechanisms (fig.28). They include:

1. *Drug inactivation or modification*: e.g. enzymatic deactivation of Penicillins through the production of β-lactamases.
2. *Alteration of target site*: e.g. alteration of penicillin binding proteins (PBP) the binding target site of penicillins in MRSA and other penicillin-resistant bacteria.
3. *Alteration of metabolic pathway*: e.g. some sulfonamide-resistant bacteria do not require para-aminobenzoic acid (PABA), an important precursor for the synthesis of folic acid and nucleic acids in bacteria inhibited by sulfonamides.

Instead, like mammalian cells, they turn to utilizing preformed folic acid.

4. *Reduced drug accumulation*: by decreasing drug permeability and/or increasing active efflux (pumping out) of the drugs across the cell surface ***(Daum et al., 2007).***

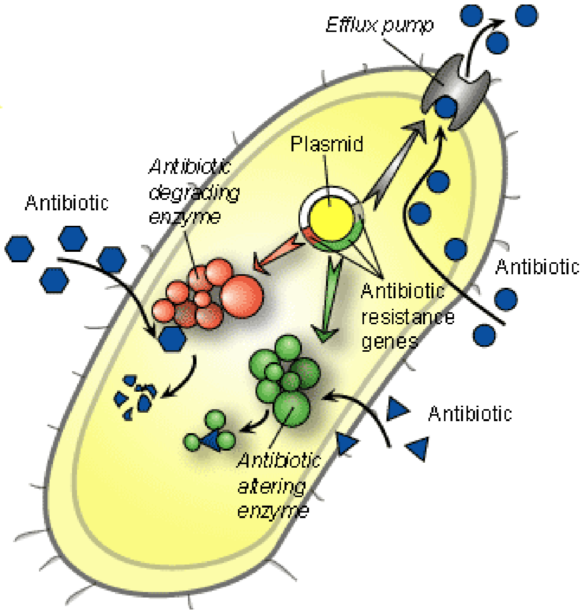

Fig (28): mechanisms of antibiotic resistance ***(Todar, 2004).***

Spread of antibiotic resistance genes is either vertical or horizontal.

1-Vertical gene transfer:

In vertical gene transefer or vertical evolution, once the resistance genes have developed, they are transferred directly to all the bacteria's progeny during DNA replication.

The very fast growth rate of bacteria and the absolute number of cells attained means that it doesn't take long before resistance is developed in a population.

2*Horizontal gene transfer:

In horizontal gene transfer (HGT) or lateral gene transfer, genetic material contained in small packets of DNA can be transferred between individual bacteria of the same species or even between different species. There are three possible mechanisms of HGT (fig 29), including transduction, transformation or conjugation ***(Todar, 2004)***.

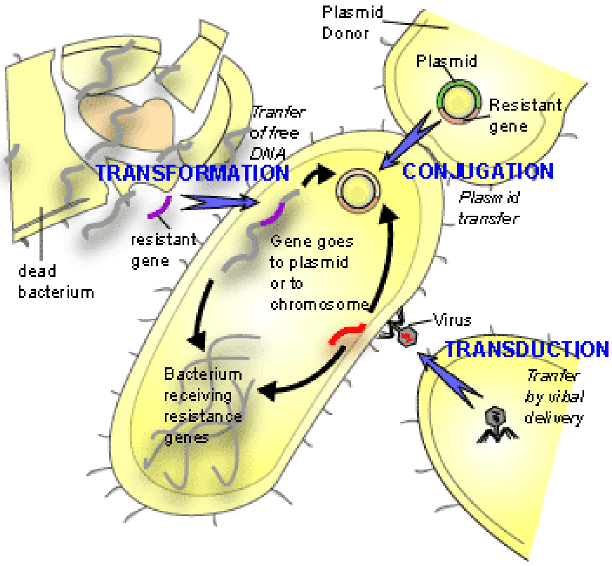

Fig (29): Horizontal gene transfer ***(Todar, 2004)***

a- *Conjugation* occurs when there is direct cell-cell contact between two bacteria (which need not be closely related) and transfer of small pieces of DNA called plasmids takes place. This is thought to be the main mechanism of HGT.

b- *Transformation* is a process where parts of DNA are taken up by the bacteria from the external environment. This DNA is normally