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ORIGINAL ARTICLE

Antibiotic resistance and extended spectrum beta-lactamases: Types, epidemiology and treatment

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Abstract Antibiotic resistance is a problem of deep scientific concern both in hospital and community settings. Rapid detection in clinical laboratories is essential for the judicious recognition of antimicrobial resistant organisms. Production of extended-spectrum β-lactamases (ESBLs) is a significant resistance-mechanism that impedes the antimicrobial treatment of infections caused by *Enterobacteriaceae* and is a serious threat to the currently available antibiotic armory. ESBLs are classified into several groups according to their amino acid sequence homology. Proper infection control practices and barriers are essential to prevent spread and outbreaks of ESBL producing bacteria. As bacteria have developed different strategies to counter the effects of antibiotics, the identification of the resistance mechanism may help in the discovery and design of new antimicrobial agents. The carbapenems are widely regarded as the drugs of choice for the treatment of severe infections caused by ESBL-producing *Enterobacteriaceae*, although comparative clinical trials are scarce. Hence, more expeditious diagnostic testing of ESBL-producing bacteria and the feasible modification of guidelines for community-onset bacteremia associated with different infections are prescribed.

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1. Introduction

Resistance of pathogenic organisms to countenance antibiotics has become a worldwide problem with serious consequences on the treatment of infectious diseases. The heightened use/misuse of antibiotics in human medicine, agriculture and veterinary is primarily contributing to the phenomenon. There

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is an alarming increase of antibiotic resistance in bacteria that cause either community infections or hospital acquired infections. Of particular interest are the multidrug resistant pathogens, *e.g. Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Streptococcus pneumoniae*, vancomycin-resistant *Enterococcus*, and extensively drug-resistant *Mycobacterium tuberculosis* (Alekshun and Levy, 2007).

Beta-lactam antimicrobial agents exhibit the most common treatment for bacterial infections and continue to be the prominent cause of resistance to β-lactam antibiotics among Gram-negative bacteria worldwide. The persistent exposure of bacterial strains to a multitude of β-lactams has induced dynamic and continuous production and mutation of β-lactamases in these bacteria, expanding their activity even against the newly developed β-lactam antibiotics. These enzymes are known as extended-spectrum β-lactamases (ESBLs) (Pitout and Laupland, 2008; Paterson and Bonomo, 2005). Treatment of these multiple drug resistant organisms is a deep scientific concern. At the level of a wider geographic scale, the incidence of ESBL-producing organisms is difficult to resolve due to various reasons, difficulty in detecting ESBL production and inconsistencies in reporting (Steward et al., 2000). Recently, a significant increase in the incidents of ESBL-related infections has been observed throughout the globe (Rupinder et al., 2013; Abhijit et al., 2013; Majda et al., 2013; Meeta et al., 2013; Kritu et al., 2013; Fatemeh et al., 2012; Gupta, 2007).

2. How do antibiotics work?

There are five major modes of antibiotic mechanisms of activity and here are some examples.

2.1. Interference with cell wall synthesis

Beta-lactam antibiotics like penicillin and cephalosporin impede enzymes that are responsible for the formation of peptidoglycan layer (Benton et al., 2007).

2.2. Inhibition of protein synthesis

Oxazolidinones, the newest class of antibiotics, interact with the A site of the bacterial ribosome where they should interfere with the placement of the aminoacyl-tRNA. Tetracyclines interfere with protein synthesis by binding to 30S subunit of ribosome, thereby weakening the ribosome-tRNA interaction. Macrolides bind to the 50S ribosomal subunit and inhibit the elongation of nascent polypeptide chains. Chloramphenicol binds to the 50S ribosomal subunit blocking peptidyl transferase reaction. Aminoglycosides inhibit initiation of protein synthesis and bind to the 30S ribosomal subunit (Leach et al., 2007).

2.3. Interference with nucleic acid synthesis

Rifampicin interferes with a DNA-directed RNA polymerase. Quinolones inhibit DNA synthesis with interference of type II topoisomerase, DNA gyrase and type IV topoisomerase during replication cycle causing double strand break (Strohl, 1997).

2.4. Inhibition of a metabolic pathway

Sulfonamides (e.g. sulfamethoxazole) and trimethoprim each block the key steps in the folate synthesis, which is a cofactor in the biosynthesis of nucleotides, the building blocks of DNA and RNA (Strohl, 1997).

2.5. Disorganizing of the cell membrane

The primary site of action is the cytoplasmic membrane of Gram-positive bacteria, or the inner membrane of Gram-negative bacteria. It is hypothesized that polymyxins exert their inhibitory effects by increasing bacterial membrane permeability, causing leakage of bacterial content. The cyclic lipopeptide daptomycin displays rapid bactericidal activity by binding to the cytoplasmic membrane in a calcium-dependent manner and oligomerizing in the membrane, leading to an efflux of potassium from the bacterial cell and cell death (Straus and Hancock, 2006). Antibiotic resistant versus antimicrobial activity mechanism is shown in Fig. 1.

3. Antibiotic resistance mechanism

Antibiotic resistance is the reduction in effectiveness of a drug such as an antimicrobial or an antineoplastic in curing a disease or condition. When the antibiotic is not intended to kill or inhibit a pathogen, then the term is equivalent to dosage failure or drug tolerance. More commonly, the term is used in the context of resistance that pathogens have "acquired", that is, resistance has evolved. When an organism is resistant to more than one drug, it is said to be multidrug-resistant (Fisher and Mobashery, 2010). Bacterial strains may possess different types of resistant mechanisms which are shown in Fig. 2 and are explained as follows.

3.1. Antibiotic inactivation

3.1.1. By hydrolysis

Many antibiotics have chemical bonds such as amides and esters which are hydrolytically susceptible. Several enzymes are known to ruin antibiotic activity by targeting and cleaving these bonds. These enzymes can often be excreted. Extended-spectrum β-lactamases (ESBLs) mediate resistance to all penicillins, third generation cephalosporins (e.g. ceftazidime, cefotaxime, and ceftriaxone) and aztreonam, but not to cephamycins (cefoxitin and cefotetan) and carbapenems (Bonnet, 2004).

3.1.2. By redox process

The pathogenic bacteria infrequently exploited oxidation or reduction of antibiotics. However, there are a few examples of this strategy (Yang et al., 2004). One is the oxidation of tetracycline antibiotics by the TetX enzyme. *Streptomyces virginiae*, a producer of the type A streptogramin antibiotic virginiamycin M1, protects itself from its own antibiotic by reducing a critical ketone group to an alcohol at position 16.