15

Mechanisms of Antibiotic Resistance in *Corynebacterium* spp. Causing Infections in People

Alina Olender
Department of Medical Microbiology, Medical University of Lublin
Poland

1. Introduction

In recent years we can observe an increasing number of publications describing different incidents of infections, where species of *Corynebacterium* are isolated as the etiological factor of infection (Anderson et al., 2008; Campanile et al., 2009; Chiner et al., 1999; Dela et al., 2008; Fernandez-Roblas et al., 2009; Funke et al., 1997a; Funke et al., 1997b; Lagrou et al., 1998; Otsuka et al., 2005; Ostuka et al., 2006; Williams et al., 1993). It is a large and very diverse group of microorganisms, in which *Corynebacterium diphtheriae* is the most important species, with the most important human-pathogenic significance (Gomes et al., 2009; Wagner et al., 2011; Wilson, 1995). Strains of this species produce a strong exotoxine and are responsible for causing diphtheria. Well-developed procedures for diagnosis of diphtheria and conducted large-scale vaccinations resulted in erradication of diphtheria in most countries. Beside the typical human-pathogenic *C. diphtheriae,* the genus *Corynebacterium* comprises more than 85 different species of pathogenic significance. This type includes species pathogenic for animals, e.g. *C. pseudotuberculosis* (Baird & Fontanie, 2007; Nieto et al., 2009), *C. kutscheri* (Amao et al., 2008; Suzuki et al., 1988), *C. canis* (Funke et al., 2009) and a very large group of species colonizing the skin and mucous membranes of man, which in favorable circumstances, may become the cause of serious infections in humans. These opportunistic organisms, e.g. *C. jeikeium* (Ifantidou et al., 2010; Pitcher et al., 1990; Rosato et al., 2001), *C. urealyticum* (Funke et al., 1997b; Garcia-Bravo et al. 1996; López-Medrano et al., 2008), *C. amycolatum* (Anderson et al., 2008; Dela et al., 2008; Funke et al., 1997b), *C. striatum* (Campanile et al., 2009; Funke et al., 1997b; Martinem-Martinez et al., 1995; Ostuka et al., 2006; Roberts et al., 1992), *C. pseudodiphtehriticum* (Chiner et al., 1999; Dorello et al., 2006; Freman et al., 1994; Olender & Niemcewicz, 2010), may cause infections of various course: mild, chronic and acute, as well as of invasive nature, life-threatening to a patient. The genus *Corynebacterium* includes also species unrelated to the human organism, e.g. *C. glutamicum*, producing L-glutamic acid and lysine, used in biotechnological processes on the industrial scale and in genetic studies (Katsumata et al., 1984; Serwold-Davis et al., 1987; Tauch et al., 1998; Wendisch et al., 2006; Valbuena et al., 2007, Yague Guirao et al., 2005).

Application of modern molecular biology techniques in genetic studies of unknown strains isolated from infections resulted in the detection and description of new species such as: *C. singulare* (Riegel etal., 1997), *C. auriscanis* (Collins et al., 1999), *C. resistens* (Otsuka et al. 2005),

C. imitans (Funke at al., 1997a), *C. sputi* (Yassin & Siering, 2008) and the reclassification of previously inaccurately determined ones, e.g.: *C. cystitidis*, *C. pilosum* (Takahashi et al., 1995).

In view of a widely conducted taxonomic research of species belonging to the genus *Corynebacterium*, the term "dyphteroids" has also been changed, which was used commonly for the opportunistic species, suggesting a direct relationship with *C. diphtheriae*. Nowadays taxonomists more and more replace it by a more universal name for this group of bacteria "coryneform" (Anderson et al., 2008; Balci et al., 2002; Funke et al., 1996; Funke et al., 1997b; Gomez-Garces et al., 2007; Lagrou et al., 1998; Ostuka et al., 2005), which seems fully justified.

Many opportunistic strains of the genus *Corynebacterium*, isolated from clinical materials, belong to species whose characteristics determining the pathogenic effect on the human body have not been thoroughly recognised and characterized yet. Therefore, the assessment of their role as pathogens is often very difficult. Undoubtedly, the common occurrence of coryneform on mucous membranes and the skin may cause doubts in interpretation of their contribution to infections, especially when the material is sampled from places non-sterile physiologically and there might be a suspicion of its contamination.

An increasing number of recognized and described incidents of infections and the observed increase in the number of publications on this topic is probably connected with the microbiological diagnostics currently carried out at a higher level and development of quick commercial tests for identification of species based on their biochemical properties. In reference to strains difficult to identify or requiring verification of uncertain biochemical determination, oftener methods of molecular biology are used, which has resulted in detection of new species and the reclassification of ones previously poorly assayed.

Infections caused by opportunistic *Corynebacterium spp.* generally refer to a group of people, who experience symptoms of immunodeficiency. The group of patients with a particular risk of infection includes primarily people with immunodeficiency due to disorders of bone marrow activity, the ongoing processes of cancer, post surgery or urological surgery, invasive diagnostic procedures and patients with AIDS. The risk of infection is increased by long-term hospitalization, antibiotic therapy, radiotherapy, treatment with cytostatics or steroids. A disturbing fact is occurrence of such infections in a group of people called "immunocompetent", in whom no symptoms of immunodeficiency were reported before (Chiner et al., 1999; Frejman et al., 1994).

The basis for treatment of infections caused by *Corynebacterium spp*. is taking up of an effective antibiotic therapy. For this group of microorganisms, until recently an obstacle in the evaluation of drug resistance was use of different criteria of interpretation that were recommended for other groups of microorganisms and determination of drug resistance with various methods, yet results presented by different authors have become the basis for information about occurrence of strains with high resistance to antibiotics among opportunistic *Corynebacterium spp*., which indicate existence of different mechanisms of resistance in these strains.

The described multidrug-resistant strains of *C. jeikeium* (Rosato et al., 2001; Yagye Guirao et al., 2005) *C. amycolatum* (Yagye Guirao et al., 2005; Yoon et al., 2011), *C. striatum* (Campanile et al., 2009; Martinem-Martinez et al., 1995; Otsuka et al., 2006; Roberts et al., 1992) i *C. resistens* (Otsuka et al., 2005) confirm presence in *Corynebacterium spp.* of different

mechanisms of resistance and genes, which may be differently located. Phenotypic tests of resistance to antibiotics have become the basis for search of the genes responsible for them and their transmission paths. They have also contributed to analyses and study of similarity in occurrence of resistance genes in other groups of microorganisms, often unrelated to the genus *Corynebacterium*, such as *Staphylococcus spp.* (Roberts et al., 1999), *Enterococcus* spp.(Power et al., 1995), *E. coli* (Deb & Noth,1999; Serwold-Davis et al., 1990; Serwold-Davis et al., 1987).

2. Mechanisms of resistance to antibiotics most commonly occurring in *Corynebacterium* spp.

The conducted study characterizing resistance to antibiotics isolated from clinical material of different species of the genus *Corynebacterium* (Anderson et al., 2008; Fernandez-Roblas et al., 2009; Funke et al., 1997a; Funke et al., 1997b; Garcia-Bravo et al., 1996; Gomez-Garceset al., 2007; Martinem-Martinez et al., 1995; Otsuka et al., 2006; Roberts et al., 1992, Troxler R et al., 2001, Weiss et al., 1996) draw attention to the most frequently occuring mechanisms of resistance to antibiotics in this group of microorganisms. The results show participation of extrachromosomal genetic elements in transmission of resistance genes in both pathogenic and potentially pathogenic - opportunistic and typically nonpathogenic ones, e.g. present in the soil or strains of *Corynebacterium spp.* (Kono et al., 1983; Vertes et al., 2005).

Antibiotic resistance genes in species of *Corynebacterium spp.* are often located on large plasmids, e.g. resistance to tetracycline, chloramphenicol, erythromycin and streptomycin on plasmid pTP10 in *C. xerosis* (Deb & Nath, 1999; Hodgson et al., 1990), but also on trensposons (Delal et al., 2008).

2.1 Resistance to macrolides, lincosamides and streptogramins B

The occurrence of simultaneous resistance to three groups of antibiotics: macrolides, lincosamides and streptogramins B, determined in short as MLSB, is characteristic mainly of staphylococci and streptococci. It is connected with occurrence of three different mechanisms of the effects of activity: modification of the ribosome binding site associated with methylation or mutation, the mechanism of active efflux of antibiotic from the cell and the least significant - enzymatic inactivation of the antibiotic. The first two MLSB resistance mechanisms are of the highest importance.

Methylation of the binding site causes conformational changes of the subunit 23S rRNA, which prevents binding of the antibiotic molecules in the peptidyltransferase center within the 50S ribosome subunit and leads to the blockade of the mRNA translation and inhibition of bacterial protein synthesis. In species of the genus *Corynebacterium* it is connected with presence of genes belonging to class *erm* (erythromycin ribosome methylation), encoding the rRNA methylase enzyme, which causes dimethylation of adenine present in the 23S rRNA (Arthur et al., 1990). The gene *erm* occurring in *Corynebacterium spp,* responsible for this mechanism of resistance has been classified as class X of genes *erm* (Roberts et al., 1999). Despite a high degree of homology between genes *ermX* isolated from different species of *Corynebacterium* (*C. diphtheriae, C. jeikeium and C. xerosis*), it has been found that they exhibit different locations. The gene *ermX* in *C. diphtheriae* was found within the 14.5-kbp plasmid pNG2 (Coyle et al., 1979), while the gene *erm*X in *C. xerosis* turned out to be located on

transposon Tn5432, whose carrier is the 50-kbp plasmid pTP10 (Delal et al., 2008). In the strain *C. jeikeium* (Pitcher et al., 1990) and *C. striatum* (Roberts et al., 1992), the gene *ermX* was found on the chromosome, which has been confirmed also in other analysed strains of *C. jeikeium* (Rosato et al., 2001). Despite detection of different locations of genes *ermX* in certain strains of *C. jeikeium* and *C. xerosis,* it is assumed that its most typical location is primarily the transposon Tn*5432*. At the same time in other examined *Corynebacterium spp.*, in which the MLSB mechanism is not related to the location of genes *ermX* on transposon Tn*5432*, interesting results of research were obtained, indicating the possibility of reorganization of fragments of the transposon Tn*5432* and presence of all its components in the strain genome (Hall et al., 1999).

It is possible that mobile transpositional elements IS*1249* containing *ermX* may create new composite transposons containing other multidrug- resistant genes. This phenomenon is particularly disturbing since transposition of the insertional sequence IS*1249* is known for its capabilities to insert and transfer Tn*5432* from genomes of unrelated bacteria (Rosato et al., 2001).

Different results of studies suggesting different locations of the detected genes *ermX* referred to the species of *Corynebacterium*, which were isolated from strains coming from different geographical regions, which may explain such diversified locations in the genome. The strain of *C. diphthariae,* containing pNG2 and *C. striatum* came from patients from the north-western USA (Coyle et al., 1979; Hodgson et al., 1990; Roberts et al., 1992), *C. xerosis* from pTP10 from Japan (Tauch et al.1995), *C. jeikeium* from France (Rosato et al.2001) and *C. jeikeium* and *C. amycolatum* from Spain (Yague Guirao et al., 2005).

It is very likely that different locations of genes *ermX* may indicate the possibility of acquiring resistance genes by multidrug-resistant strains of *Corynebacterium spp.* from microorganisms colonizing the skin or mucous membranes. *ErmX* occurring in *C. diphtheriae* is contained in plasmid pNG2, similar to plasmids isolated from *Corynebacterium spp.* occurring on the skin (Serwold-Davis & Groman, 1986). The replicon 2.6-kb EcoRI-ClaI fragment (oriR) may be possessed by many microorganisms, including a popular commensal *E. coli* (Deb & Nath, 1999; Serwold-Davis et al., 1990; Serwold-Davis et al., 1987).

At the same time, as research indicates, the plasmid pNG2 seems an unlikely place of origin for genes *erm* occurring in *Corynebacterium spp*. More likely is transposon Tn*5432* associated with the chromosome, which may be mobile (Trauch et al., 1995). Tn*5432* was also found in the occuring on the skin strains of *Propionibacterium acnes, P. granulosum* and P. *avidum*, which suggests that multidrug –resistant strains of the genus *Corynebacterium* may be an important source in horizontal transfer of resistance genes to other human pathogens (Ross et al., 2002). Another source, from which strains may be derived or to which they may arrive, is bacterial flora occurring in animals. It may be confirmed by detection of gene *ermX* in the strain of *Corynebacterium spp*. isolated from pasteurized milk. It showed resistance to erythromycin and/or spiromycin (Perrin-Guyomard et al., 2005).

Beside gene *ermX*, in strains of *Corynebacterium* Group A with the MLSB mechanism of resistance, also gene *erm* class B has been found (Luna et al., 1999), which occurs in *Enterococcus spp.* and *Streptococcus spp.,* which may also suggest the participation of these microorganisms in spread of the MLSB mechanism in *Corynebacterium spp*.

The expression of the MLSB resistance may be constitutive or induced. In the case of the constitutive type of resistance, active mRNA, permitting synthesis of methylase, is created without an inducer, while the induced MLSB - inactive mRNA is synthesized, which is activated only under the influence of an inducer, which allows synthesis of the enzyme. Occurrence of the constitutive MLSB resistance mechanism is very popular in strains of *C. pseudodiphtheriticum,* present in mucous membranes of the upper respiratory tract in humans (Olender & Niemcewicz, 2010).

Formation of cross-resistance associated with the MLSB mechanism is also accompanied by the process of active efflux of antibiotic from the cell. In staphylococci they are transporters of the membrane protein nature (ETP - binding cassette), encoded by genes *msrA* (macrolide streptogramin resistance), carried on plasmids. These transporters act as a specific pump removing macrolides of 14 - and 15-membered lactone ring and streptogramins B from the bacterial cell. Macrolides of 16-membered lactose ring, lincosamides and telithromycin are not transported. In this case, this mechanism is referred to as MSB (Leclercq, 2002; Douthwaite &Champney, 2001)

It was found that presence of gene *msrA* is also associated with resistance to macrolides and streptogramins B in strains of *Corynebacterium spp.* (Ojo et al., 2006) and similarly with production of an active transport system of the antibiotic pumped out from the cell (macrolide efflux proteins). Gene *msrA* had been previously found only in *Staphylococcus spp*. (Roberts et al., 1999). It encodes the ATP relay needed by the cell to gain energy from hydrolysis ATP for active transport of erythromycin and streptogramin B, and enables synthesis of the ABC family of transporters, i.e. multiprotein systems to actively pump out the antibiotic from the cell.

In turn in reference to *S.pneumoniae, S. pyogenes, S. agalactiae* and other species of streptococci and enterococci, the efflux mechanism is associated with presence of the MCF transporters (macrolide-specific efflux) and refers only to macrolites with 14 - and 15-membered lactose rings. It does not apply to macrolites with a 16-membered lactose ring, ketolides, linkosamides and streptogramin B. It is associated with low levels of resistance to macrolides (Appelbaum, 2002).

Gene *mef*, causing active efflux of macrolides from the bacterial cell was also found in *Corynebacterium* group A, *C. jeikeium* and strains of *Corynebacterium spp.* (Luna et al., 1999).

2.2 Resistance to fluoroquinolones

In species of the genus *Corynebacterium,* resistance has been also observed to fluoroquinolones. It is associated with point mutations within the structural gene region of the gyrase subunit A, which is defined as the region determining resistance to quinolones (QRDR - quinolone resistance determining region).

Mutations are of the spontaneous nature, leading to changes in the amino acid sequences, on which depends the range of resistance to certain fluoroquinolones. The resulting level of resistance depends largely on the type of the amino acid that has been built-in as a result of mutation in place of the pre-existing one. Some of them cause a small loss of affinity and a slight decrease in sensitivity, other reduce potently the affinity and activity of fluoroquinolones. It is confirmed by studies of strains of *C. macginleyi*, in which resistance

has been found to norfloxacin, ciprofloxacin and levofloxacin. By analyzing gene *gyraA* encoding the gyrase subunit A, a change of the amino acid in position 83 in the QRDR region was found (Serine to Arginine), which resulted in resistance in *C. macginleyi* to norfloxacin. A double mutation has been also found, leading to amino acid changes in positions 83 and 87, which conditioned resistance to all fluoroquinolones. It was observed that double mutations occurred in Ser-83 and Asp-87 in all strains of *C. macginleyi* with a high level of resistance (Eguchi et al., 2008).

Studies of the gene *gyr*A sequence were also conducted in strains of *C. striatum* and *C. amycolatum* (Sierra et al., 2005). A high resistance to quinolones in *C.amycolatum* resulted from a double mutation and amino acid changes in positions 87 and 97 or 87 and 88 (unusual location of mutation in *gyr*A). In the case of *C. striatum* mutations of amino acids in positions 87 and 91 occurred in *gyr*A, corresponding to resistance characterized by very high MIC values for ciprofloxacin and levofloxacin, while only moderately increased MIC values for moxifloxacin.

These studies showed various complex and intricate mechanisms of resistance to quinolones in the studied species of *Corynebacterium spp.* (Sierra et al., 2005), which depend on the number of mutations and the type of changed amino acids.

2.3 Resistance to tetracyclines

Phenotypic studies constituted the basis for detection of resistance to tetracycline in *Corynebacterium spp.* In the case of *C. striatum,* it was found in 97% of the tested strains (Martinem-Martinez, 1995). These observations were confirmed by detection of the gene *tet*M, responsible for resistance to all tetracyclines, which is due to the protective effect on the protein ribosome with the mass of about 72-72.5 kDa (Roberts et al., 1992).

In strains of *C. striatum* M82B resistance to tetracycline is associated with the region 50-kb R-plasmid pTP10. An analysis of the nucleotide sequence revealed two reading frames called *tet*A and *tet*B. For analysis of the *tet*AB genes function, their expression in *C. glutamicum* was used and thus it was confirmed that they are responsible for resistance to tetracycline, oxytetracycline, and at a low level to other derivatives, such as chlortetracycline, minocycline and doxycycline. At the same an increased MIC value for oxacycline was found in this strain. This effect is associated with participation of the *tet*AB genes that determine resistance of the transport nature. It creates a powerful mechanism of active transport (efflu) causing pumping out of drugs from the cell via specific transport protein localized in the cytoplasmic membrane (Tauch et al., 1999).

R-plasmid pTP10 found in *C. xerosis* also contains determinants of resistance to tetracycline with parallel resistance to other antibiotics, such as chloramphenicol, kanamycin and erythromycin (Kono et al., 1983; Tauch et al., 1995) whereas, in strains of *C. melassecola*, the species used to produce glutamate, the resistance gene to tetracycline was found on another mobile element - plasmid pAG1 (Deb & Nath, 1999).

2.4 Resistance to beta-lactam antibiotics

The common susceptibility to penicillin in toxic and nontoxic strains of *C. diphtheriae* made it one of the most frequently prescribed antibiotics in treatment of diphtheria (Wilson, 1995).

Despite this opinion, there have been cases observed in which it showed no efficacy. Phenotypic tests consisuted the basis (Von Hunostein et al., 2002), in which penicillin sensitivity of 24 nontoxic strains of *C. diphtheriae* biotype *gravis* was determined in the broth microdilution method and by Etests. The research conducted with two methods showed a high 98% consistency of results. MIC values for penicillin were in the range from 0.064 to 0.250 mg/l, with simultaneous very low values for erythromycin (MIC ≤ 0.016 mg/l), whereas MBC (Minimal Bactericidal Concentaration) - MBC50 and MBC90 for penicillin were respectively 2.0 and 8.0 mg/l and 17.0 and 24.0. In 71% of the tested strains the ratio MBC/MIC was ≥ 32. The results of the study indicated the insensitivity (tolerance) to penicillin, which was confirmed by a lack of a positive effect of treatment despite the MIC values indicating sensitivity of the tested strains to this antibiotic. Such an effect was also observed in the case of tolerance to amoxicillin in the strain *C. diphtheriae* isolated from the case of *endocarditis* (Dupon et al., 1995).

In other strains of *Corynebacterium spp.* a similar situation was found, i.e. creation of insensitivity to oxacillin with low MIC values. This effect was not associated with the existing mechanism of resistance to beta-lactam antibiotics, but with a very high phenotypic expression and activity of a pair of genes *tet*A and *tet*B present on the Tn3598-transposon Class II - 12kb, which determined resistance to tetracycline. The activity of these genes, which consists of powerful active pumping, resulted also in removal of a structurally different antibiotic, which was oxacillin (Tauch et al., 2000).

Based on the analysis of results of phenotypic and genotypic studies of different species of the genus *Corynebacterium* showing resistance to beta-laktam antibiotics, it can be concluded that both resistance mechanisms organisms occur in these microorganisms, i.e. production of beta-laktamases and modification of penicillin-binding proteins. It is confirmed by e.g. resistance to penicillin (MIC 90> 4 μg/ml) in strains of *C. jeikeium* and *C. urealyticum*, ampicillin (MIC90> 8 μg/ml) (Gomez-Garces et al., 2007), in *C. resistens* to penicillin, cefazolin, cefotiam, cefmetazol, cefepime (MIC> 64 μg/ml) and imipenem (MIC> 32 μg/ml) (Otsuka et al., 2005), in strains of *C. striatum* to penicillin, ampicillin (MIC90 = 16 μg/ml), cefazolin, cefotiam, cefotaxime, imipenem (MIC90> 32 μg/ml) (Otsuka et al., 2006). Just like in hospital strains of *C. urealyticum*, in which resistance to penicillin and cefotaxime was particularly high (MIC90> 512 μg/ml) (Garcia-Bravo et al., 1996).

It can be also confirmed by an analysis of the genome sequence of *C. glutamicum*, which showed presence of four genes encoding proteins PBP (Penicillin Binding Proteins) HMW (high-molecular-weight), i.e. PBP1a, PBP1b, PBP2a, PBP2b, two genes encoding PBP4, PBP4b (low-molecular-weight) and two probably encoding beta-laktamases (Valbuena et al., 2007).

2.5 Resistance to glycopeptides

An antibiotic recommended by many authors in the empirical treatment of invasive infections caused by species of the genus *Corynebacterium* is vancomycin. It is connected with the common sensitivity to this antibiotic of even multidug-resistant species, which pose the greatest problems in infections. It refers to such species as *C. jeikeium*, *C. resistant*, *C. amycolatum* and *C. striatum* (Wiliams et al., 1993). Unfortunately, still cases of isolated strains of *C. aquaticum* and *C. group B1* resistant to vancomycin have been reported.

Only single cases are described, in treatment of which other alternative antibiotics give very good results. An example might be a case of infection in a 44-year-old patient with *endocarditis* 4 months after a prosthetic mitral valve (Barnas et al., 1991). The strain of *Corynebacterium spp.* isolated from the blood turned out resistant to vancomycin and penicillin G, erythromycin, gentamicin and rifampicin. The use of imipenem and ciprofloxacin resulted in an effective cure of the infection.

In related species of Coryneform *Oerskovia turbata 892* and *Arcanobacterium* (former *Corynebacterium*) *haemolyticum 872,* resistance to vancomycin and teicoplanin was found of the constitutive nature. Presence of the VanA gene was detected, found on plasmids of 15 and 20 kb. In strains of *A. haemolyticum 872* the VanA gene sequence turned out the same as in vancomycin-resistant *Enterococcus faecium BM4147*. In the case of *O. turbata* 892 a change of sequence occurred in three points. Species *A. haemoliticum* and *O. turbata* show a natural sensitivity to vancomycin and teicoplanin, and resistance found in the tested strains resulted from presence of the VanA gene (Power et al., 1995). The resistance phenotype associated with presence of the VanA gene is characterized by a high degree of resistance to vancomycin and teicoplanin.

2.6 Resistance to chloramphenicol

Resistance genes to chloramphenicol were detected on plasmids - in the strain *Corynebacterium spp.* on the pXZ10145 plasmid - 5.3 kb and in *C. xerosis* on pTP10 - 45.0 kb (Deb & Nath, 1999). In *C. striatum* strain M82B (former *C. xerosis* M82B) (Tauch et al., 1998) chloramphenicol resistance gene cmx (chloramphenicol and exports) was detected as an integral part of the transposon Tn5564, which contains a complete copy of the insertion sequence IS1513. The *cmx* gene is responsible for encoding of a specific protein (transmembran chloramphenicol efflux protein), which inhibits the passage of the antibiotic into the cytoplasm, and gives the bacetrial cell resistance to chloramphenicol.

3. Problems with diagnostic of infection by coryneform

The increasing isolation of multidrug-resistant strains of the genus *Corynebacterium* from clinical materials draws attention to the emerging issues related to treatment of infections caused by this group of opportunistic bacteria. The problem is all the more important since the infections often concern diagnostically difficult cases, long-hospitalized patients, the chronically ill, often with an accompanying disease causing immunosuppression. The underrated contribution of coryneform in infections may lead to therapeutic errors. Their common occurrence on the mucous membranes and skin causes doubts about their recognition as the etiologic factor of the infection.

The next problem, that may determine the accuracy of microbiology result as well as confirmation of the presence of opportunistic *Corynebacterium spp.* in infection, is a choice of appropriate culture method – bacterial culture media, which composition supports the growth of different coryneforms species. It is applied mostly for lipophilic species, as *C. jeikeium, C. urealyticum*. It is very important to identify the isolated strains precisely, as this enables tracking multi drug-resistance in specific strains, their existence on specific areas and routes of transmission. These informations are specifically important for hospital areas, facilitating to make proper decision on limiting these types of infections.

Accurate microbiological diagnostics of infections caused by species of the genus *Corynebacterium*, identification of strains of the isolated species and determination of antibiotic susceptibility with methods enabling determination of the MIC values permit assessment of the existing and emerging mechanisms of drug resistance and result in making right decisions about the most appropriate antibiotic therapy for a given case. It is extremely important to apply correct interpretation criteria of the determined drug resistance for species of the genus *Corynebacterium*, specific for this group of microorganisms, based on the established and generally accepted recommendations (Clinical and Laboratory Standards Institute [CLSI], 2006; Łętowska & Olender, 2010). Application of methods of molecular biology and examination of resistance genes, their locations and transmission paths is a very important direction of research on monitoring of resistance mechanisms in coryneform and gives the ability to track and determine their role in transmission of genes also among other species.

4. Antibiotic therapy used in infections of *Corynebacterium spp.*

The basis for monitoring of the emerging multi-drug resistant strains for all bacteria, as well as species of the genus *Corynebacterium,* is conducting research characterizing their sensitivity to antibiotics, which is potentially useful in treating infections. Publication of such data is extremely important due to tips received about the most effective antibiotic therapy for a given group of microorganisms.

An analysis of sensistivity to antibiotics of a large group of strains of *C. urealyticum, C. amycolatum, C. jeikeium, C. coyleae, C. striatum, C. aurimucosum* and *C. afermentans* was conducted with assays using Etests (Fernandez-Roblas et al., 2009). The authors found that strains of all tested species were susceptible to glycopeptides, linezolid, chinupristin/dalphopristin and daptomycin, which was also confirmed in other studies (Funke et al., 1997a; Funke et al., 1997b).

The results obtained from research done in Italy, involving strains of *C. striatum* isolated from different infections, also indicated the need of analysis of drug resistance in *Corynebacterium*. Genetic studies of strains of *C. striatum* MDR (multidrug-resistant) revealed presence of a multidrug-resistant clone, whose strains isolated from cases of pneumonia, catheter related bacteremia and wound infections showed, despite resistance to other classes of antibiotics, susceptibility to glycopeptides, tigecyclin, chinupristyn/dalphopristin, daptomycin and linezolid (Campanile et al., 2009).

One of the most resistant species, which causes the biggest problems in hospitals and is frequently isolated from infections in hospitalized patients, is *C. jeikeium*. The study of 66 strains of *C. jeikeium* (Johnson et al. 2004) showed resistance to penicillin in all of them, in 94% resistance to erythromycin, and in 74% to tetracycline. Twenty-two strains of other examined species of the genus *Corynebacterium* had a significantly lower level of the resistant. But what is extremely important, all examined strains were susceptible to vancomycin (MIC = 0.5-4.0 mg/l), linezolid (MIC = 0.5-2.0 mg/l) and daptomycin (MIC ≤ 1mg/l) with the exception of two isolates of *C. auaticum,* whose MIC for daptomycin was 8 mg/l. At the same time effecacy of daptomycin was confirmed in the successfully applied combination with rifampicin in a patient with *endocarditis* caused by *C. amycolatum* (Dala et al., 2008) i *C. striatum* (Shah & Murillo, 2005).

Linezolid, as shown in published works, was also characterized by a very good action. High activity of linezolid was found in studies of 190 strains of coryneform (Gomez-Garces et al.,2007). It confirmed the possibility of equally successful application of this antibiotic in infections caused by Coryneform.

Diversity of antibiotic resistance in species of the genus *Corynebacterium* is strictly connected with the locations, in which the tested strains occur. As found in the conducted studies (Garcia-Bravo et al., 1996) strains of *C. urealyticum* coming from hospitalized patients show significantly higher resistance to antibiotics than those isolated from outpatients, from outside of the hospital environment. An analysis of frequency and duration of antibiotic therapy used in patients from both groups of respondents was conducted. It confirmed unequivocally that the hospital environment and more frequently used antibiotics in the hospitalized patients is conducive to occurence of multidrug-resistant strains, and the hospital environment in which such patients stay is the place from which strains of *C. urealyticum* came, causing infections in the hospitalized patients. At the same time considerably lower resistance to antibiotics of isolates coming from the outpatients indicates that the strains of *C.urealyticum* most likely are derived from microflora colonizing the skin of the examined outpatients.

A very disturbing fact is discovery of new multidrug-resistant species of the genus *Corynebacterium*, which suggests a progressive character of multidrug-resistance occurring in this group. It is confirmed by a description of a new multidrug-resistant species of *C. resistens* in 2005. It is lipophilic, with low fermentation properties (it ferments glucose), does not reduce nitrates, does not produce urease and pyrazinamidase. It is characterized by resistance to penicillin and cephalosporins (MIC > 64 μg/ml), imipenem (MIC > 32 μg/ml), aminoglycosides (MIC > 3 μg/ml 2), macrolides (MIC > 16 μg/ml), quinolones (MIC > 32 μg/ml) and sensitivity to teicoplanin (MIC ≤ 0.5 μg/ml) and vancomycin (MIC = 2 μg/ml) (Otsuka et al., 2005).

5. Conclusion

Presented by several authors results of their studies on antibiotics resistance show, that even though *Corynebacterium spp*. are the members of the normal flora, they are not universally susceptible to antibiotics, as could be expected. Opportunistic *Corynebacterium spp*., until now considered as bacteria of low pathogenicity, may pose a diagnostic and therapeutic problems, as they are more and more commonly isolated from serious, life-threatening invasive infections. Observed in many cases multi drug-resistance may be connected with the possibility to acquire resistance genes by gene transfer within bacteria regarded as normal flora present in large number on a given body area (skin, mucous membranes). Drug resistance occurrence in opportunistic species is the result of antibiotics overuse. It is obvious that antibiotics used also influence on saprophytic bacteria. Resulting selection of resistant strains is commonly known and regarded as important process leading to multi drug-resistance. For these reasons, analysis of the process in opportunistic *Corynebacterium* is an important element in monitoring new multi drug-resistant strains derived from saprophytic flora, mostly in infections in patients from risk groups, under immunosuppression, hospitalized for long time. Studying mechanisms of drug resistance on the basis of phenotypic and genotypic expression is important for proper antibiotic therapies in infections caused by this group of microorganisms.

Studies on sensitivity to antibiotics of different multidrug-resistant species of the genus *Corynebacterium* indicate that the highest efficacy in treatment of infections is shown by glycopeptides, linezolid, daptomycin, tigecyclin and chinupristin/dalphopristin.

6. References

Adderson, E. E., Boudreaux, J. W. & Hayden, R. T. (2008). Infections caused by coryneform bacteria in pediatric oncology patients. *Pediatr Infect*. 27 (2): 136-141.

Amao, H., Moriguchi, N., Komukai, Y., Kawasami, H., Takahashi, S. & Sawada, T. (2008). Detection of *Corynebacterium kutscheri* in the feaces of subclinically infectied mice. *Lab Anim*. 42 (3): 376-382.

Appelbaum, P. C. (2002). Resistance among *Streptococcus pneumoniae*: Implications for drug selection. *Clin Infect Dis*. 34 (12): 1613-20.

Arthur, M., Nolinas, C., Mabilat, C. & Courvalin, P. (1990). Detection of erythromycin resistance by the Polymerase Chain Reaction using primers in conserved refion of *erm* rRNA methylase genes. *Antimicrob Agents Chemother*. 34 (10): 2024-26.

Baird, G. J., and Fontanie, M. C. (2007). *Corynebacterium pseudotuberculosis* and its role in ovine caseous lymphadenitis. *J Comp Pathol*. 137 (4): 179-210.

Balci, I., Esik, F., & Bayram, A. (2002). Coryneform bacteria isolated from blond cultures and their antibiotic susceptibilities. *J Intern Med Res*. 30 (4): 422-7.

Barnass, S., Holland, K. & Tabaqchali, S. K. (1991). Vancomycin-resistant *Corynebacterium species* causing prosthetic valve endocarditis successfully treated with imipenem and ciprofloxacin. *J Infect*. 22(2): 161-9.

Campanile, F., Carretto, E., Barbarini, D., Grigis, A., Falcone, M., Goglio, A., Venditti, M. & Stefani, S. E. (2009). Clonal multidrug - resistant *Corynebacterium striatum* strains, Italy. *Emerg Infect Dis*. 15(1): 75-78.

Chiner, E., Arriero, J. M., Signes-Costa, J., Marco, J., Corral, J., Gomez-Esparrago, A., Ortiz de la Tabla, V. & Martin, C. (1999). *Corynebacterium pseudodiphtheriticum* pneumonia in an immunocompetent patient. *Monaldi Arch Chest Dis*. 54 (4): 325-327.

Clinical and Laboratory Standards Institute. (2006). Method for antimicrobial dilution and disk susceptibility testing of infrequently isolated or fastidious bacteria. Approved standard M45-A. Wayne, PA. Clinical and Laboratory Standards Institute.

Collins, M. D., Hoyles, L., Lawson, P. A., Falsen, E., Robson, R. L. & Foster, G. (1999). Phenotypic and phylogenetic characterization of a new *Corynebacterium* species from dogs: description of *Corynebacterium auriscanis* sp.nov. *J Clin Microbiol*. 37(11): 3443-7.

Coyle, M. B., Minshew, B. H., Bland, J. A. & Hsu, P. C. (1979). Erythromycin and clindamycin resistance in *Corynebacterium diphtheriae* from skin lesion. *Antimicrob Agents Chemother*. 16 (4): 525-7.

Dalal, A., Urban, C. & Segal-Maurer, S. (2008). Endocarditis due *Corynebacterium amycolatum*. *J Med Microbiol*. 57 (10): 1299-1302.

Deb, J. K., and Nath, N. (1999). Plasmids of corynebacteria. *FEMS Microbiology Letters*. 175 (1): 11-20.

Dorella, F. A., Pacheco, L. G., Oliveira, S. C., Miyoshi, A. & Azevedo, V. (2006). *Corynebacterium pseudotuberculosis*: microbiology, biochemical properties, pathogenesis and molecular studies of virulence. *Vet Res*. 37 (2): 201-18.

Douthwaite, S., and Champney, W. S. (2001). Structures of ketolides and macrolides determine their mode of interaction with the ribosomal target site. *J Antimicrob Chemother*. 48 (Suppl T1): 1–8.

Dupon, C., Turner, L., Rouveix, E., Nicolas, M. H. & Dorra, M. (1995). Endocardite à *Corynebacterium diphtheriae* tolerant à l'amoxicillin. *Presse Med*. 24 (24): 1135.

Eguchi, H., Kuwahara, T., Miyamoto, T., Nakayama-Imaohji, H., Ichimura, M., Hayashi, T. & Shiota, H. (2008). High-level fluoroquinolone resistance in ophthalmic clinical isolates belonging to the species *Corynebacterium macginleyi*. *J Clin Microbiol*. 46 (2): 527-32.

Freeman, J. D., Smith, H. J., Haines, H. G. & Hellyar, A. G. (1994). Seven patients with respiratory infection due to *Corynebacterium pseudodiphtheriticum*. *Pathology*. 26 (3): 311-4.

Fernandez-Roblas, R., Adames, H., Martin-de-Hijas, N. Z., Garcia Almeida, D., Gadea, I. & Esteban, J. (2009). In vitro activity of tigecycline and 10 other antimicrobials against clinical isolates of the genus *Corynebacterium*. *Int J Antimicrob Agents*. 33 (5): 353-5.

Funke, G., Efstratiou, A., Kiklinska, D., Hutson, R., De Zoysa, A., Engler, K. H. & Collins, M. D. (1997a). *Corynebacterium imitans* sp.nov. isolated from patients with suspected diphtheria. *J Clin Microbiol*. 35 (8): 1978-83.

Funke, G., Englert, R., Frodl, R., Bernard, K. A. & Stenqer S. (2010). *Corynebacterium canis* sp. nov., isolated from a wound infection caused by a dog bite. *Int J Syst Evol Microbiol*. 60 (11): 2544-7.

Funke, G., Punter, V. & von Graevenitz, A. (1996). Antimicrobial susceptibility patterns of some recently established coryneform bacteria. *Antimicrob Agents Chemother*. 40 (12): 2874-8.

Funke, G., von Graevenitz, A., Clarridge III, J. E. & Bernard, K. A. (1997b). Clinical Microbiology of coryneform bacteria. *Clin Micrbiol Rev*.10 (1): 125-159.

Garcia-Bravo, M., Aguado, J. M., Morale, J. M. & Norwega, A. R. (1996). Influence of external factors in resistance of *Corynebacterium urealyticum* to antimicrobial agents. *Antimicrob. Agents Chemother*. 40 (2): 497-499

Gomes, D. L, Martins, C. A, Faria, L. M, Santos, L. S, Santos, C. S, Sabbadini, P. S, Souza, M. C, Alves, G. B, Rosa, A. C, Nagao, P. E, Pereira, G. A, Hirata, R. Jr, & Mattos-Guaraldi, A. L. (2009). *Corynebacterium diphtheriae* as an emerging pathogen in nephrostomy catheter-related infection: evaluation of traits associated with bacterial virulence. *J Med Microbiol*. 58 (11): 1419-27.

Gomez-Garces, J-L., Alos, J-I. & Tamayo, J. (2007). *In vitro* activity of linezolid and 12 other antimicrobials against coryneform bacteria, *Int J Antimicro Agents*. 29 (6): 688-692.

Hall, R. M., Collis, C. M., Kim, M. J., Partridge, S. R., Recchia, G. D. & Stokes, H. W. (1999). Mobile gene cassettes and integrons in evolution. *Ann N Y Acad Sci.* 18 *(*870): 68-80.

Hodgson, A.L., Krywult, J. & Radford, A. J. (1990). Nucleotide sequence of the erythromycin resistance gene from the *Corynebacterium* plasmid pNG2. *Nucleic Acods Res*. 18 (7): 1891.

Ifantidou, A. M, Diamantidis, M. D, Tseliki, G., Angelou, A. S., Christidou, P., Papa, A. & Pentilas, D. (2010). *Corynebacterium jeikeium* bacteremia in a hemodialyzed patient. *Int J Infect Dis*. 14 (3): 265-8.

Johnson, A. P., Mushtaq, S., Warner, M. & Livermore, D. M. (2004).Activity of daptomycin against multi-resistant Gram-positive bacteria including enterococci and *Staphylococcus aureus* resistant to linezolid. *Int J Antimicrob Agents*. 24 (4): 315-319.

Katsumata, R., Ozaki, A., Oka, T. & Furuya, A. (1984). Protoplast transformation of glutamate-producting bacteria with plazmid DNA. *J Bacteriol*. 159 (1): 306-311.

Kono, M., Sasatsu, M. & Aoki, T. (1983). R plasmids in *Corynebacterium xerosis* strains. *Antimicrob Agents Chemother*. 23 (3): 506-508.

Lagrou, J., Verhaegen, M., Janssens, G., Wauters, G. & Verbist, L. (1998). Prospective study of catalase-positive coryneform organisms in clinical specimens: identification, clinical relevance, and antibiotic susceptibility. *Diagn Microbiol Infect Dis*. 30 (1): 7-15.

Leclercq, R. (2002). Mechanisms of resistance to macrolides and lincosamides: nature of the resistance elements and their clinical implications. *Clin Infect Dis*. 34 (4): 482–92.

López-Medrano, F., García-Bravo, M., Morales, J. M., Andrés, A., San Juan, R., Lizasoain, M. & Aguado, J. M. (2008). Urinary tract infection due to *Corynebacterium urealyticum* in kidney transplant recipients: an underdiagnosed etiology for obstructive uropathy and graft dysfunction-results of a prospective cohort study. *Clin Infect Dis*. 46 (6): 825-30.

Luna, V.A., Coates, P., Eady, A., Cove, J. H., Nguyen, T. T. H. & Roberts, M. C. (1999). A variety of Gram-positive bacteria carry mobile mef genes. *J Antimicrob Chemother*. 44 (1): 19-25.

Łętowska, I. and Olender, A. (2010). Rekomendacje doboru testów do oznaczania wrażliwości bakterii na antybiotyki i chemioterapeutyki 2010. Oznaczanie wrażliwości pałeczek Gram-dodatnich z rodzaju *Corynebacterium* spp. Krajowy Ośrodek ds. Lekowrażliwości KORLD. www.korld.edu.pl

Martinez-Martinez, L., Suarez, A. I., Winstanley, J., Ortega, M. C. & Bernard, K. (1995). Phenotypic characteristics of 31 strains of *Corynebacterium striatum* isolated from clinical sample. *J Clin Microbiol*. 33 (9): 2458-2461.

Nieto, N. C, Foley, J. E, MacLachlan, N. J, Yuan, T. & Spier, S. J. (2009). Evaluation of hepatic disease in mice following intradermal inoculation with *Corynebacterium pseudotuberculosis*. *Am J Vet Res*. 70 (2): 257-62.

Ojo, K. K., Striplin, M. J., Ulep, C. C., Close, N. S., Zittle, J., Luis, H., Bernardo, M., Leitao, J. & Roberts, M. C. (2006). *Staphylococcus* efflux *msr*(A) gene characterized in *Streptococcus*, *Enterococcus*, *Corynebacterium*, and *Pseudomonas* isolates. *Antimicrob Agents Chemother*. 50 (3): 1089-1091.

Olender, A. and Niemcewicz, M. (2010). Macrolide, lincosamide, and streptogramin B-constitutive tract resistance in *Corynebacterium pseudodiphtheriticum* isolated from upper respiratory tract specimens. *Microb Drug Resist*. 16 (2): 119-22.

Otsuka, Y., Kawamura, Y., Koyama, T., Iihara, H., Ohkusu, K. & Azeki, T. (2005). *Corynebacterium resistens* sp.nov., a new multi-resistant coryneform bacterium isolated from human infection. *J Clin Microbiol*. 43 (8): 3713- 17.

Otsuka, Y., Ohkusu, K.,Kawamura, Y., Baba, S., Azeki, T. & Kiura, S. (2006). Emergence of multidrug-resistant *Corynebacterium striatum* as a nosocomial pathogen in long-term hospitalized patients with underlying diseases. *Diagn Microbiol Infect Dis*. 54 (2): 109-14.

Perrin-Guyomard, A., Soumet, C., Leclercq, R., Doucet-Populair, R. & Sanders, P. (2005). Antibiotic susceptibility of bacteria isolated from pasteurized milk and characterization of macrolide-lincosamide-streptogramin resistance genes. *J Food Prot.* 68 (2): 347-352.

Pitcher, D., Johnson, A., Allerberger, F., Woodford, N. & George, R. (1990). An investigation of nosocomial infection with *Corynebacterium jeikeium* in surgical patients using a ribosomal RNA gene probe. *Eur J Clin Microbiol Infect Dis*. 9 (9): 643-648.

Power, E. G., Abdullah, Y. H., Talsania, H. G., Spice, W., Aathithan, S. & French, G. L. (1995) VanA genes in vancomycin-resistant clinical isolates of *Oerskovia turbata* and *Arcanobacterium (Corynebacterium) haemolyticum*. *J Antimicrob Chemother*. 36 (4): 595-606.

Riegel, P., Ruimy, R., Renard, F. N. R., Freney, J., Prevost, G., Jehl, F., Christen, R. & Monteil, H. (1997). *Corynebacterium singulare* sp. nov., new species for urease-positive strains related to *Corynebacterium minutissimum*. *Int J Syst Bacteriol*. 36 (4): 1092-1096.

Roberts, M. C., Leonard, R. B., Briselden, A., Schoenknecht, F. D., & Coyle, M. B. (1992). Characterization of antibiotic-resistant *Corynebacterium striatum* strains. *J Antimicrob Chemother*. 30 (4): 463-474.

Roberts, M. C., Sutcliffe, J., Courvalin, P., Jensen, L. B., Rood, J. & Seppala, H. (1999). Nomenclature for macrolide and macrolide-lincosamide-streptogramin B resitance determinants. *Antimicrob Agents Chemother*. 43 (12): 2823-30.

Rosato, A. E., Lee, B. S. & Nash, K. A. (2001). Inducible macrolide resistance in *Corunebacterium jeikeium. Antimicrob Agents Chemother*. 45 (7): 1982-89.

Ross, J. I., Eady, A. A., Carnegle, E. & Cove, J. H. (2002). Detection of transposon Tn5432 - mediated macrolide- lincosamide-streptogramin B (MLSB) resistance in cutaneus propionibacterie from six European cities. *J Antimicrob Chemiother*. 49 (1): 165-168.

Serwold-Davis, T. M. and Groman, N. B. (1986). Mapping and cloning of *Corynebacterium diphtheriae* plasmid pNG2 and characterization of ist relatedness to plasmids from skin corynefrms. *Antimicrob Agents Chemother*. 30 (1): 69-72.

Serwold-Davis, T. M., Groman, N. B. & Kao, C. C. (1990). Localization of an orgin of replication in *Corynebacterium diphtheriae* broad host range plasmid pNG2 that also functions in Escherichia coli. *FEMS Microbiol Lett.* 54 (1-3): 119-23.

Serwold-Davis, T. M., Groman, N. & Rabin M. (1987). Transformaction of *Corynebacterium diphtheriae*, *Corynebacterium ulcerans*, *Corynebacterium glutamicum* and *Escherichia coli* with the *C.diphtheriae* plasmid pNG2. *Poc Natl Acad Sci USA*. 84 (14): 4964-68.

Shah, M. and Murillo, J. L. (2005). Successful treatment of *Corynebacterium striatum* endocarditis with daptomycin plus rifampin. *Ann Pharmacother*. 39 (10): 1741-4.

Sierra, J. M., Martinez-Martinez, L., Vazquez, F., Giralt, E. & Vila, J. (2005). Relationship between mutations in the *gyr*A gene and quinolone resistance in clinical isolates of *Corynebacterium striatum* and *Corynebacterium amycolatum*, *Antimicrob Agents Chemother*. 49 (5): 1714-9.

Suzuki, E., Mochida, K. & Nakagawa, M. (1988). Naturally occurring subclinical *Corynebacterium kutscheri* infection in laboratory rats: strain and age related antibody response. *Lab Anim Sci.* 38 (1): 42-5.

Takahashi, T., Tsuji, M., Kikuchi, N., Ishihara, C., Osanai, T., Kasai, N., Yanagawa, R. & Hiramune, T. (1995). Assignment of the bacterial agent of urinary calculus in young

rats by the comparative sequence analysis of the 16s rRNA genes corynebacteria. *J Vet Sci*. 57 (3): 515-7.

Tauch, A., Kassing, F., Kalinowski, J. & Pühler, A. (1995). The *Corynebacterium xerosis* composite transposon Tn*5432* consists of two identical insertion sequences, designated IS*1249*, flanking the erythromycin resistance gene ermcx. *Plasmid*. 34 (2): 119-31.

Tauch, A., Kassing, F., Kalinowski, J. & Pühler, A. (1995). The erythromycin resistance gene of the *Corynebacterium xerosis* R-plasmid pTP10 also carrying chloramphenicol, kanamycin and tetracycline resistance is capable of transposition in *Corynebacterium glutamicum*. *Plasmid*. 33 (3): 168-79.

Tauch, A., Krieft, S., Kalinowski, J. & Pühler, A. (2000). The 51,409-bp R-plasmid pTP10 from the multiresistant clinical isolate *Corynebacterium striatum* M82B is composed of DNA segments initially identified in soil bacteria and in plant, animal, and human pathogens. *Mol Gen Genet*. 263 (1): 1-11.

Tauch, A., Krieft, S., Pühler, A. & Kalinowski, J. (1999). The *tetAB* of the *Corynebacterium striatum* R-lasmid pTP10 encode an ABC transporter and confer tetracycline, oxytetracycline and oxacillin resistance in *Corynebacterium glutamicum*. *FEMS Microbiol Lett*. 173 (1): 203-9.

Tauch, A., Zheng, Z., Pühler, A. & Kalinowski, J. (1998). *Corynebacterium striatum* chloramphenicol resistance transposon Tn5564: genetic organization and transposition in *Corynebacterium glutamicum*. *Plasmid*. 40 (2): 126-39.

Troxler, R., Funke, G., von Graevenitz, A. & Stock, I. (2001). Natural antibiotic susceptibility of recently established coryneform bacteria, *Eur J Clin Microbiol Infect Dis*. 20 (5): 315-23.

Wagner, K. S, White, J. M, Neal, S., Crowcroft, N. S, Kuprevičiene, N., Paberza, R., Lucenko, I., Jõks, U., Akbaş, E., Alexandrou-Athanassoulis, H., Detcheva, A., Vuopio, J., von Hunolstein, C., Murphy, P. G., Andrews, N., Members of the Diphtheria Surveillance Network & Efstratiou, A. (2011). Screening for *Corynebacterium diphtheriae* and *Corynebacterium ulcerans* in patients with upper respiratory tract infections 2007-2008: a multicentre European study. *Clin Microbiol Infect*. 17 (4): 519-25.

Weiss, K., Laverdiere, M. & Rivest, R. (1996). Comparison of antimicrobial susceptibilities of *Corynebacterium* species by broth microdilution and disc diffusion methods. *Antimicrob Agents Chemother*. 40 (4): 930-3.

Wendisch, V. F., Bott, M., Kalinowski, J., Oldiges, M. & Wiechert, W. (2006). Emerging *Corynebacterium glutamicum* systems biology, *J Biotechnol*. 124 (1): 74-92.

Williams, D. Y., Selepak, S. T., Gill, V. J. (1993). Identification of clinical isolates of nondiphterial *Corynebacterium* species and their antibiotic susceptibility patterns. *Diagn Microbiol Infect Dis*. 17 (1): 23-8.

Wilson, A. P. R. (1995). Treatment of infections caused by toxigenic and non-toxigenic strains of *Corynebacterium diphtheriae*. *J Antimicrob Chemother*. 35 (6): 717-20.

Valbuena, N., Letek, M., Ordonez, E., Atala, J., Daniel, R. A., Gil, J. A. & Mateos, L. M. (2007). Characterization of HMW-PBPs from the rod-shaped actinomecete *Corynebacterium glutamicum*: peptydoglycan synthesis in cells lacking actin-like cytoskeletal structures. *Mol Microbiol*. 66 (3): 643-57.

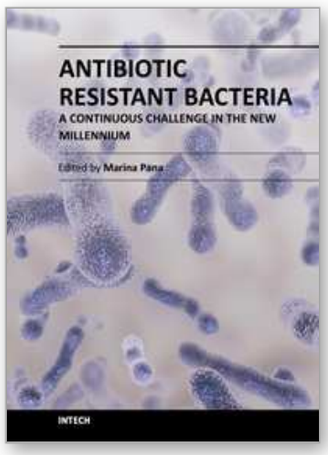
Vertes, A. A., Inui, M. & Yukawa, H. (2005). Manipulating Corynebacteria, from individual genes to chromosomes. *Appl Environ Microbiol*. 71 (12): 7633-42.

Von Hunolstein, C., Scopetti, F., Efstratiou, A. & Engler, K. (2002). Penicillin tolerance amongst non-toxigenic *Corynebacterium diphtheriae* isolated from cases of pharyngitis. *J. Antimicrob Chemother*. 50 (1): 125-8.

Yague Guirao, G., Mora Peris, B., Martinez-Toldos, M. C., Rodriguez Gonzalez, T., Valero Guillen, P.L. & Segovia Hernandez, M. (2005). Implication of *erm*X genes in macrolide- and telithromycin-resistance in *Corynebacterium jeikeium* and *Corynebacterium amycolatum. Rev Esp Quimioterap.* 18 (3): 136-242.

Yassin, A. F. and Siering, C. (2008). *Corynebacterium sputi* sp. nov., isolated from the sputum of the a patient with pneumonia. *Int J Syst Evol Microbiol*. 58 (12): 2876-9.

Yoon, S., Kim, H., Lee, Y. & Kim, S. (2011). Bacteremia caused by Corynebacterium amycolatum with a novel mutation in gyrA gene that confers high-level quinolone resistance. *Korean J Lab Med*. 31(1): 47-8.



Antibiotic Resistant Bacteria - A Continuous Challenge in the New Millennium

Edited by Dr. Marina Pana

ISBN 978-953-51-0472-8
Hard cover, 576 pages
Publisher InTech
Published online 04, April, 2012
Published in print edition April, 2012

Antibiotic-resistant bacterial strains remain a major global threat, despite the prevention, diagnosis and antibiotherapy, which have improved considerably. In this thematic issue, the scientists present their results of accomplished studies, in order to provide an updated overview of scientific information and also, to exchange views on new strategies for interventions in antibiotic-resistant bacterial strains cases and outbreaks. As a consequence, the recently developed techniques in this field will contribute to a considerable progress in medical research.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Alina Olender (2012). Mechanisms of Antibiotic Resistance in Corynebacterium spp. Causing Infections in People, Antibiotic Resistant Bacteria - A Continuous Challenge in the New Millennium, Dr. Marina Pana (Ed.), ISBN: 978-953-51-0472-8, InTech, Available from: http://www.intechopen.com/books/antibiotic-resistant-bacteria-a-continuous-challenge-in-the-new-millennium/mechanisms-of-antibiotic-resistance-in-corynebacterium-spp-causing-infections-in-people

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen