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ANTIBIOTICS – QUO VADIS?

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ABSTRACT. Antibiotics are one of the most frequently prescribed medications in modern medicine. Antibiotics are useful in a wide variety of infections but it is important to realize that antibiotics only threat bacterial infections. Used properly, antibiotics can save lives by killing bacteria or keeping them from reproducing. Inappropriate antibiotic treatment and overuse of antibiotics, incorrect use in combination therapy with other antibiotics, excessive use of prophylactic antibiotic, incorrect or sub-optimal antibiotic prescribed in some cases may facilitate the development of bacterial populations with antibiotic resistance, or/and increase risk of side effects. Antibiotics must be used judiciously and indicated when systemic signs of involvement are evident at high enough doses and frequencies to archive adequate blood level and prevent resistance and potential complications as life-threatening infections with low toxicity.

Keywords: antibiotics, antibiotic resistance, antibiogram, side effects, life-threatening infections

INTRODUCTION

The word antibiotic comes from the Greek *anti* meaning 'against' and *bios* meaning 'life' (Davey PG, 2000). Originally known as *antibiosis* (term introduced by the French bacteriologist Vuillemin) these drugs were later renamed antibiotics by Selman Waksman in 1942.

Antibiotics are also known as antibacterials, and they are drugs used to treat infections caused by bacteria. Antibiotics are a group of chemicals derived from the metabolism of living cells, most of them obtained through synthesis or semi-synthesis, substances which, in very diluted solutions, have the property of stopping the multiplication or even destroy certain microorganisms (Cionga et.al.1978).

After the discovery of the first antibiotic (penicillin) by Alexander Fleming in 1928, subsequent researches have led to the discovery/isolation of a great number of antibiotics, of which several tens were introduced in therapeutic practice.

There are several different types of modern antibiotics commonly classified based on their mechanism of action, chemical structure or spectrum of activity. According to the classical structure we have the following classes of antibiotics: aminoglycosides, ansamycins (anti-tumoral antibiotics), β-lactamases (penicillines, cephalosporins, penem, carbapenem, monobactam), fluoroquinolones, glycopeptides, imidazoles, lincosamides, cyclic lipopeptides, macrolides, oxazolidinones, polypeptides, sulfonamides, tetracyclines, glycylcyclines (derived from tetracycline), and other groups.

Most antibiotics (β-lactamases, tetracyclines, macrolides, aminoglycosides) are derived from natural sources, being subsequently modified in order to grant better properties to the medicine. Other classes of antibiotics (sulfonamides, fluoroquinolones, oxazolidinones) are totally synthetic.

Most antibiotics target bacterial functions or growth processes. Antibiotics which target the bacterial cell wall (β-lactamases, glycopeptides), or cell membrane (polymyxins), or interfere with DNA replication (quinolones), or metabolic processes (sulfonamides) are usually

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bactericidal in nature. Those which target protein synthesis, such as aminoglycosides, macrolides, oxazolidinones and tetracyclines, are usually bacteriostatic (Wikipendia).

Each class of antibiotics includes a wide variety of representatives. Each representative is unique in its way. This uniqueness determines the selective action on the different types of microbial germs, with positive effect in the treatment of infections that these generate. Except for the cases in which the microorganism which causes a pathological manifestation is precisely known, it is necessary to isolate the germ that produces it, and to determine its sensitivity. Performing the antibiogram is mandatory in order to institute a rational treatment, so as to avoid the risk of administering a product with no efficiency (but with possible toxic effects on the body), and especially in order to avoid the loss of time, which can be sometimes fatal.

When establishing the sensitivity of a germ one needs to take into consideration the resistance towards antibiotics that some types of germs manifest. The phenomenon of resistance has become obvious a few years after the mass use of antibiotics, and constitutes one of the main directions of research in this field. In the last few years three new classes of antibiotics have been brought into clinical use. These new antibiotics are of the following three classes: cyclic lipopeptides (daptomycin), glycylcyclines (tigecycline), and oxazolidinones (linezolid). Tigecycline is a broad-spectrum antibiotic, while the two others are used for Gram-positive infections (Wikipendia). FAb1 inhibitors and GyrB and Par E inhibitors are new classes of antibiotics in development. (Drug Developement technology, 2010). These developments show promise as a method of counteracting bacterial resistance to existing antibiotics.

The optimal efficiency of the antibiogram depends not only of the microbial sensitivity and the concentration of the antibiotic in the blood or tissues, but also of the intact function of the immune system. Normally, the body has the capacity to defend itself against microbial germs through mechanisms of local defense, cellular and humoral. Even if symptoms do occur, our immune system can usually fight off the infection. When this capacity of defense is overcome, then the time is right for antibiotics to intervene. In patients with severe infections that endanger the patient`s life, antibiotics have a minor impact on their rate of survival. This can be explained through the fact that the immune system and other defense mechanisms are the main factor preventing infection, while antibiotics offer only supplementary help. “It is the internal environment (not de external world) that provides the physical needs for life” –Claude Bernard.

Even if they offer only assistance to the defense mechanisms of the body, their important role in fighting against bacterial infection cannot be contested. They are strong medicines which, if administered appropriately, can save lives. They can be administered orally, in injections, or topically.

SIDE EFFECTS

Even though, generally, they are considered safe and well-tolerated, they have been associated with a wide variety of side effects. These side effects represent a problem not only because they produce lesions upon the body, but also because they determine the interruption and complication of therapy with using some alternative, more expensive, medication, which can solve the emergency and which determines the apparition of resistant organisms. Side effects attributed to antibiotics are frequently determined through three mechanisms: exaggerated response to known pharmacological effects of the drug, immunologic reaction to the drug or to his products of metabolism, and toxic effect of its components or its products of metabolism. Some side effects are determined by the antibiotic dose administered when it is not in accordance with patient’s weight and overdosing occurs.

Some antibiotic-induced adverse reactions occur rarely and appear to be unique to the compound administered. Chloramphenicol-induced aplastic anemia and sulfonamide-

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induced toxic epidermal necrolysis or Stevens-Johnson syndrome are two such examples. In addition to the direct influence of the antibiotic, however, numerous host factors (genetic constitution, integrity of drug elimination mechanisms, concomitant medical disorders) can affect the frequency and severity of antibiotic-related adverse events. A prime example is the HIV-infected patient. There are numerous reports of oxacillin-induced hepatitis and cutaneous reactions occurring in HIV-infected patients who have received trimethoprim-sulfamethoxazole or aminopenicillins. Moreover, trimethoprim-sulfamethoxazole causes more non-dose-related gastrointestinal intolerance, fever and altered liver function in patients with AIDS, than in non-HIV-infected patients.

The penicillin family of drugs are usually well tolerated, but they have been associated with a wide range of hypersensitivity reactions, including fever, rash (maculopapular and urticarial), anaphylaxis, exfoliative dermatitis, multiform erythema, serum sickness, and hemolytic anemia. When administered intravenously in high doses, particularly to patients with renal impairment, they have the potential to cause central nervous system toxicity, manifested by myoclonic jerks, seizures or coma. Specific members of the penicillin family have been identified with particular adverse reactions: ampicillin, amoxicillin, and amoxicillin/clavulanate with diarrhea and C. *difficile* colitis, as well as rash when prescribed to the patient with chronic lymphocytic leukemia; nafcillin-induced neutropenia; carbenicillin and ticarcillin (with/without clavulanic acid) with hypokalemia, platelet dysfunction, and fluid overload; and methicillin and ampicillin with interstitial nephritis. Platelet-mediated bleeding caused by ticarcillin and piperacillin

is duration-related and can be serious, and it is additive with other risk factors, including chemotherapy, thrombocytopenia and renal insufficiency. Of interest is the observation that the administration of ticarcillin/clavulanate is statistically less frequently associated with C. *difficile*-related disease than that attributed to the third-generation cephalosporins.

The cephalosporins have proven to be very safe compounds and this is one explanation for their wide appeal. Untoward events attributed to the cephalosporins have included diarrhea, pseudo-membranous colitis, and rarely, hypersensitivity reactions including drug fever, rash, interstitial nephritis or immediate life-threatening events. Specific members of the cephalosporin family of compounds have been identified with particular adverse reactions: ceftriaxone, cefixime, ceftibuten, cefdinir, and cefoperazone with diarrhea; ceftriaxone with reversible biliary sludge; cefoperazone, cefotetan, moxalactam, and cefamandole with hypoprothrombinemic bleeding; ceftazidime with abnormal liver function; cefoperazone, cefonicid, and cefamandole with disulfiram-like reactions following the ingestion of alcohol; and cefazolin-induced seizures in patients with renal failure who have received high doses. Imipenem, cilastatin and aztreonam have caused phlebitis, gastrointestinal untoward events, and rash. A particular concern is the development of seizures attributed to imipenem and cilastatin. This adverse event usually occurs in the setting of an elderly patient, particularly when renal impairment or underlying central nervous system (CNS) disease exists.

The most notorious side effect of clindamycin is diarrhea and C. *difficile*-related colitis. This drug has rarely caused drug fever, rash, blood dyscrasias, and hepatotoxicity.

Doxycycline has been associated with diarrhea and, infrequently, photosensitivity; rash; hepatitis; and, particularly in elderly patients, esophageal ulcerations or strictures.

Infrequent untoward events attributed to vancomycin include rash, fever, nephrotoxicity, ototoxicity, and reversible, transient hematopoietic toxicity. The most dramatic side effect is the red man syndrome, a non-immunologically mediated reaction consisting of pruritus and erythema with or without hypotension, which appears to be

dependent on dose, frequency of administration, and rate of infusion. The pronounced erythema has a predilection for the face, neck, upper body, and upper extremities. Concerns regarding administration of the aminoglycosides include nephrotoxicity, specifically nonoliguric acute renal failure, ototoxicity, both the auditory and vestibular components, and neuromuscular blockade, a rare event that has developed in patients with myasthenia gravis, renal disease, hypocalcemia, or hypermagnesemia. Factors contributing to nephrotoxicity include duration of therapy, older age, liver disease, shock and the coadministration of drugs that have the potential to cause nephrotoxicity, such as amphotericin B, cisplatinum, cyclosporine, and ethacrynic acid. Factors contributing to ototoxicity include hypovolemia, total dose administered, renal impairment, liver dysfunction, elevated serum trough concentrations, cisplatinum, furosemide, and ethacrynic acid.

Rash, fever, and gastrointestinal adverse reactions are the most common side effects precipitated by trimethoprim and sulfamethoxazole. Additional rare untoward events include nephrotoxicity, hyperkalemia, hematologic derangements (neutropenia, thrombocytopenia, agranulocytosis, aplastic anemia, and megaloblastic anemia), hepatitis, pancreatitis, pseudomembranous colitis, and adverse CNS events (headache, insomnia, vertigo, ataxia, and aseptic meningitis).

Adverse events attributed to the macrolides have included nausea, vomiting, abdominal pain, diarrhea, and, rarely, antibiotic-associated colitis, pancreatitis, cholestatic jaundice, acute hepatitis, abnormal taste (clarithromycin), and reversible ototoxicity. Clarithromycin and azithromycin cause fewer gastrointestinal adverse events than does erythromycin.

The most common adverse events attributed to the fluoroquinolones are gastrointestinal symptoms, nervous system complaints (headache, dizziness, insomnia, agitation, and hallucinations), and allergic reactions (rash and pruritus). Rare adverse effects include seizures, elevations of liver enzymes, and tendinopathy (Gleckman et al, 2000).

Immunoglobulin E (IgE)-medicated hypersensitivity reactions are the most feared adverse events attributed to the penicillins, imipenem and cilastatin, and cephalosporins. These reactions are manifested by urticaria, pruritis, hypotension, bronchospasm, and laryngeal edema. Of note is the association between an increased risk and severity of an allergic drug reaction to penicillin when ß-blockers are used concomitantly. Severe cutaneous reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, and small vessel vasculitis compose "late" or delayed hypersensitivity reactions.

Classically sulfonamides have been associated with these dermatologic reactions, but penicillins, cephalosporins, fluoroquinolones and vancomycin have been implicated as well (Gleckman et al, 2000).

The multitude of adverse reactions that can occur, their complexity and gravity make us think that sometimes “our arsenals for fighting off bacteria are so powerful…that we’re in more danger from them than from the invaders” - Lewis Thomas.

CLINICAL CASES

Case 1

42 years old patient, with left genian tumefaction, attends the emergency service, where we observed the presence of suppuration and in local anesthesia incision and drainage of the purulent collection is performed. Since from the anamnesis resulted that the patient is allergic to amoxicillin, 600 mg of clindamycin were administered every 8 hours, in association with 100 mg of ketonal every 12 hours. The symptoms receded and the patient was recommended admission into the hospital for surgical intervention – cystectomy – since the X-ray exam showed the presence of a left maxillary cyst. Amoxicillin was administered postoperatively for the prophylaxis of postoperative infection. Immediately the patient’s status worsens. Erythematous areas appear on the thorax and

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limbs, respiratory disorders, and the patient enters into anaphylactic shock. Injection of antibiotic is interrupted and corticosteroids are administered. The evolution is favorable, with recovery of all vital functions.

Case 2

9 years old patient, with painful left submandibular tumefaction, attended his family doctor who establishes the diagnosis of submandibular abscess and recommends antibiotic treatment with ampicillin, 500 mgs every 6 hours, and nurofen. The patient follows the treatment for 10 days with no improvement in symptoms. He attends the emergency department of the maxilla-facial clinic, where incision and drainage of abscess are practiced, followed by antibiotic therapy with ampicillin, 1 g. every 12 hours, and 100 mg Ketonal every 12 hours. Evolution is favorable with remission of symptoms, the patient is discharged as healed, after removal of causative factor (extraction of the tooth 3.6 and alveolar curettage).

Case 3

3 years old patient, with dental-alveolar contusion (teeth 6.1, 6.2) following an accidental fall one week ago, develops a left genian tumefaction, accompanied by pain. He sees the doctor, who recommends treatment with ampicillin, 100 mg/kg/day and gentamicin, 1.5 g/kg, every 8 hours, intravenously. Symptoms do not improve and the patient attends the emergency service. Examining shows genian tumefaction and also the presence of a purulent collection with a diameter of approx. 1 cm on the vestibular side, at the level of the teeth 6.1 and 6.2. Incision and drainage of abscess is performed and ampicillin is administered, 500 mg each 12 hours. In 48 hours the symptoms recede.

Case 4

18 years old patient, attends the emergency service with a massive cervico-facial edema (temporal and genian region, bilaterally, with bilateral latero-cervical extension) and headache. From anamnesis it results that the patient presented a vesicular lesion localized on the vestibular side, at the level of 6.3, for which she followed treatment with ampicillin 500 mg every 6 hours and Ketonal 100 mg every 12 hours. After administering the antibiotic the patient noticed a bilateral genian tumefaction appeared which extended itself gradually at the level of the frontal region and cervico-facial region, bilaterally. The tumefaction appearing after administering the antibiotic suggested an allergic reaction (Quincke edema). The antibiotic was interrupted and corticotherapy was instituted. Since at the moment of seeing the doctor there was no initial lesion, supplementary investigations were performed in order to identify the primary infection and to confirm diagnosis. The following investigations were performed: SAF, which showed blurring of maxillary sinuses, bilaterally; panoramic X-ray which shows inclusion of upper left canine; and blood exam which shows leukocytosis with neutrophilia. Following these results, inter-disciplinary exams were performed: ENT (with sinus endoscopy) and allergological. Both examinations showed the same diagnosis: Quincke edema and corticotherapy was recommended. Since symptoms did not recede and the headache did not yield to regular analgesics, a neurological exam was performed. Following this exam, the diagnosis of thrombophlebitis of anterior longitudinal sinus, and the patient was transferred to the neurology department.

Case 5

56 years old patient, with left lateral mandibular fracture. Osteosynthesis was performed exobuccally, and cephazone was administered postoperatively every 12 hours in association with gentamicin 80 mg every 8 hours for prophylaxis of the postoperative infection. Though the patient was under antibiotic protection, suppuration appeared in the postoperative wound, 48 hours after surgery.

Case 6

43 years old patient, attended the emergency service of the clinic with the following symptoms: right submandibular

tumefaction, with extension behind the mandibular angle and below the chin, wooden consistency, painful spontaneously and on palpation, local warmth. Intra buccaly we have a congestioned oral floor, dental caries with massive crown destruction and involvement of the pulp chamber at the level of 4.6, vestibular mucosa at the level of the tooth is tumefied, congestioned, painful on palpation, deficient hygiene. The patient presents fever, acute pain and respiratory disorders, halitosis. The onset was as a right submandibular tumefaction. The patient took ampicillin treatment, 500 mg every 6 hours, self-medicated. Diagnosis on admission was phlegmon of oral floor, odontogenic, 4.6. Repeated incisions were performed, through which the submandibular areas were opened, bilaterally, submental and right latero-pharyngeal, antiseptic washing and antiseptic dressing 4-5 times per day, antibiotic therapy with cefozone, gentamicin, metronidazole, analgesics and anti-inflammatory drugs, and aerosols. The patient`s state worsens, complicates with productive cough, thoracic pains and finally mediastinitis. After that bacteriological exam and an antibiogram are performed, showing multi-drug resistant bacteria; also, histopathological exam of a fragment of the pulmonary parenchyma is performed (histological diagnosis – left pulmonary emphysema). The patient is admitted in a worsened state, through inter-hospital transfer, in the department of thoracic surgery with the diagnosis on discharge: odontogenic phlegmon of the oral floor, 4.6; acute mediastinitis; malaise, fever with chills, dysphagia, acute pain, indisposition and fatigue. Pacient dies despite of all medical efforts.

DISCUSSION

Development of infection localized or extended locally, at distance or affects the general state, depends on the result of interaction between the invading microbes and the host defense mechanisms. The complex process of the host-microbe interaction can be schematized as an equation in which the risk of infection is directly proportional with the number of microbial factors and reverse proportionally with the presence and integrity of the various defense mechanisms (Dunn,2008).

The immune system and the mechanisms of local defense are key elements which work together to prevent microbial development. When one of these mechanisms is compromised, the risk of infection increases. Diet, nutrition, hydration and local hygiene influence significantly the individual risk. Medication also plays an important role: immunomodulating agents and immunosuppressing agents affect the immune function (Brush et al, 2009).

A precise characterization and quantification of each factor individually is rarely possible. This is why, the complete history, examination of the patient, identification of risk factors, and using and interpreting accordingly the diagnosis tests are critical in determining the opportunity of surgical treatment, antibiotic treatment, or both.

Except for antibiotic therapy with no questioning the patient in regard to previous use of the antibiotic and the reactions to its administering, as well as non-testing the antibiotic in case of it not being used previously can cause allergic reactions that can vary from fever, hives, multiform erythema, hemolytic anemia, to anaphylactic shock or cardiorespiratory arrest. In the case when the allergic reactions are produced in the hospital (see case 1), emergency treatment can be instituted and the patient can be saved. In the case when the allergic reaction is produced at the patient's home and is severe, their chances of survival are considerably reduced.

Each antibiotic is addressed to a smaller or greater number of microbial species. This microbial spectrum determines the indications of the antibiotic. Oxacillin and gentamicin, frequently used in dental and cervico-facial infections (see case 3), have a targeted microbial spectrum (Table 2) different from the one targeted in these infections mentioned (Table 1), and as a consequence their use in these infections not only does not have any

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efficiency, but also influences the ecological balance of the normal microbial flora and favors the occurrence of resistance to antibiotics. Also, antibiotics in the group of penicillin cause the "in vitro" inactivation of gentamicin, and as a result, their administration in the same intravenous infusion is not recommended.

Administration of antibiotic therapy for a longer period of time, without performing incision and drainage of the purulent collection, is not only inefficient (see case 2), but the ecological imbalance of the saprophyte microbial flora can be caused, together with developing antibiotic-resistant germs. This is all the more severe considering we are speaking about a child who is growing and whose development can be influenced in a negative manner.The facial edema and the headache after administering the antibiotic is associated with the allergic reaction to the respective antibiotic. Interruption of administrating the antibiotic and instituting corticosteroid treatment is the correct attitude. Sometimes corticotherapy is inefficient (see case 4) and supplementary investigations are required, following which one can detect the presence of severe conditions or complications. Administration of antibiotic therapy by the patient, with no previous consulting the doctor and receiving indications from them can determine masking the symptoms or some severe conditions which endanger the patient`s life if they are not diagnosed in due time.

Prophylactic administration of bactericidal antibiotics with wide spectrum, of the $2^{nd}/3^{rd}$ generation, singularly or in association with other bactericidal antibiotics, does not always prevent infection. Sometimes this can even favor its occurrence (see case 5). This can be explained by the fact that these strong antibiotics produce the imbalance of the saprophyte microbial flora, favoring the development of pathogenic germs and the occurrence of infection.

Changing the antibiotic used in the treatment of an infection when it is observed to be inefficient, without performing the antibiogram previously, can have the same inefficiency, as the germs responsible for the infection could not be sensitive to the respective antibiotic, even if it is bactericidal and with wide spectrum. All the more, the use of such strong antibiotics in multiple associations, without antibiogram, can disturb the balance of the bacterial flora, favoring the development of germs resistant to antibiotics, the presence of fungal associated infections (which are an explanation of the persistent fever) (Marino P.L., 2007) and certain complications which lead eventually to the patient's death (see case 6).

CONCLUSIONS

We can conclude that recommendation of antibiotic treatment without considering the principles of using antibiotherapy can have severe consequences not only on the evolution of the respective condition, but also on the patient's state of health due to the adverse reactions that can occur and the complications that can endanger patient's life, leading sometimes to their death. 'The danger with germ-killing drugs is that they may kill the patient as well as the germ'- J.B. Haldane.

Table 1

Patogens of dental and cervico-facial infections (Bartlett, 2009)

	Pathogens
Dental infections	*Streptoccocus mutans* *Pigmented Bacteroides* *(poephinomonas & prevotela)* *Streptococus milleri* *Actinonices viscosus* *Peptostreptococus*
	Bacteroides species

Cervico-facial infections	*Prevotella spp.* *Fusobacterium nucleatum* *Peptostreptococus* *Streptococcus species* including *S. milleri* *Fusobacterium necrophorum* *S. aureus* including MRSA

Table 2

Detailed Spectrum of activity (Pham, 2009)

Oxacilin	Aerobic gram-pozitive cocci *Staphylococcus aureus* (methicillin- sensitive) *Staphylococcus epidermidis*
Gentamicin	Aerobic gram-negative bacilli *Aeromonas hydrophila* *Alcaligenes xylosoxidans* *Campylobacter fetus* *Campylobacter jejuni* *Citrobacter diversus* *Citrobacter freundii* *Edwardsiella tarda* *Enterobacter aerogenes* *Enterobacter cloacae* *Erwinia (Pantoea or Enterobacter) agglomerans* *Francisella (Pasteurella) tularensis* *Hafnia alvei* *Klebsiella oxytoca* *Klebsiella pneumoniae* *Morganella morganii* *Proteus mirabilis* *Proteus vulgaris* *Pseudomonas aeruginosa* *Pseudomonas putida or fluorescens* *Yersinia enterocolitica* *Yersinia pestis* *Yersinia pseudotuberculosis* Aerobic gram-positive bacilli *Bacillus species* (not anthracis or cereus) Aerobic gram-positive cocci Leuconostoc species Miscellaneous *Bartonella quintana* *Bartonella species*

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	Parasite *Babesia microti*

REFERENCES

Antibiotic classes. in Wikipendia,the free encyclopedia. 18 Apr 2010 <http:/en.wikipendia.org>

Bruch JM, Treister NS, Oral infections. in Clinical Oral Medicine and Pathology, Humana Press, 2009, 20 Apr 2010 <http://www.springerlink.com>

Bartlett JG. Cervical facial (perimandibular) space infectious in Bartlett JG, Auwaerter PG, Pham PA, The Johns Hopkins ABX Guide: Diagnosis & Treatment of Infectious Diseases, 07/13/2009, 11/03/2010 <http://hopkins-abxgiude.org>

Cionga E, Avram LC: Antibiotice in Medicamente chimioterapice. Editura Dacia, Cluj-Napoca,1978.

Davey PG.: Antimicrobial chemotherapy. in Ledingham JGG, Warrell DA.: Concise Oxford Textbook of Medicine. Oxford University Press, Oxford, pp. 1475, 2000

Dunn DL, Diagnosis and Treatment of Infections. in Norton JA, Barie PS, Bollinger RR, Chang AA, Lowry SF, Mulvihill SJ, Pass HI, Thompson RW, Surgery: Basics Science and Clinical Evidence, Springer, second edition 2008, 20 Apr 2010 <http://www.springerlink.com>

Gleckman RA, Czachor JS, Antibiotic side effects. 01 Jan 2010. 05 Apr 2010 <http://www.medscape.com/viewarticle/410873_2 - 4 >

Marino PL, ICU Book, The, 3rd Edition, Lippincott Williams & Wilkins, 2007

Marinopoulos S. Dental infections in Bartlett JG, Auwaerter PG, Pham PA, The Johns Hopkins ABX Guide: Diagnosis & Treatment of Infectious Diseases, 10/31/2008, 11/03/2010 <http://hopkins-abxgiude.org>

New classes of antibiotics in development. 22 Apr 2010 <http://www.drugdevelopement-technology.com/projects/tybacil2.btml >.

Pham PA, Bartlett JG, Oxacilin. in Bartlett JG, Auwaerter PG, Pham PA, The Johns Hopkins ABX Guide: Diagnosis & Treatment of Infectious Diseases, 08/07/2009, 11/03/2010 <http://hopkins-abxgiude.org>

Pham PA, Bartlett JG, Gentamicin. in Bartlett JG, Auwaerter PG, Pham PA, The Johns Hopkins ABX Guide: Diagnosis & Treatment of Infectious Diseases, 08/07/2009, 15/03/2010 http://hopkins-abxgiude.org>.