REVIEW ARTICLE

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Cephalosporins: A Review on Imperative Class of Antibiotics

Devansh Mehta[1*], Anuj Kumar Sharma[1]

Abstract: Antibiotics are an important class among the series of researched and developed molecules and used as treatment therapeutics, thus have revolutionized the medical as well as pharmaceutical industry. Since the time penicillin's have been discovered, it has become an important tool to deal with infections, affecting the people and community we live with. With ever growing complexicity involved in dealing with infections effectively, there is need to improve the present available treatment options for the medical community. The two driving factors for development and advancement of the present antibiotic treatments are, 1. Increasing resistance against the available molecules to deal with infections, 2. High-end research driven activities to discover and develop newer classes of antibiotics which are not prone to resistance development. With new FDA guidelines, which are now highly stringent, it has raised "tensions and burden" on the research and development communities. The present review focuses on very important class of antibiotics available to us, the cephalosporins. Like penicillin's even cephalosporins have become equally important therapeutics to deal with the growing nature of infections in our present world. The review focuses on the older and newer discoveries in cephalosporins, in molecular terms, thus important for understanding of its nature for the drug industry and the healthcare practitioners as a whole.

INTRODUCTION

Antibiotics term was first termed by S. A. Waksman in the year 1942, these are class of medicines which are anti-bacterials or anti-microbials which could be used to treat and prevent bacterial infections. Antibiotics are produced from several fungi and bacteria thus they are natural in origin. Antibiotics or antibacterial's work on two major principles which are mainly, 1. Killing the infective micro-organism, or 2. Inhibiting the growth of microbials which result in restricting their advancement and spread in the body, thus restricting the growth of infection in the infected body. Thus resulting in restricting their growth of severity. Though antibiotics are known to kill micro-organisms, they are not effective against the viruses. This is often misunderstood by some in the medical and patient community. Thus the difference between antibiotics and antivirals are distant terms which shall not be confused as same as described earlier. In the year 1928, when Alexander Fleming, identified, penicillin, the first chemical compound with antibiotic potency, it revolutionized treatment goals to deal with infection. [1] Since then the whole history of treatment potential of drugs changed completely, which signifies the importance of the discovery and is often known as the biggest discovery by the mankind, to deal with diseases affecting the man. Another revolution in the history of antibiotics came in the year 1932 with the discovery of sulfonamides, which have been proved to be more effective in dealing with infections bestowed upon the mankind. Sulfonamides being effective drug, have shown tremendous positive results against many strains of bacteria's, like in Urinary tract infections (known as UTI's), *Shigellosis and Pneumococcal pneumonia*. To add more Sulfonamides have been effective in treatment to the infections caused by *Cornybacterium diphtheria* and *Treponema palladium*. Another antibiotic, Streptomycin's have been effective against *Gram negative* aerobic bacterial strains and *Mycobacterium tuberculosis*. [2]

The data on important discoveries of antibiotics was lost some years later, which resulted in two new phenomena's: 1) New bacterial agents were discovered that were not affected with penicillin or streptomycin. Typical representatives of such agents were *Mycoplasmata*, *Chlamydiae* or *Rickettsiae*. 2) Development of resistance. Resistance was the roadblocks in the goal of treatment. The first resistance were reported by *Staphylococci* described in 1946, 16 years after the discovery of penicillin's', not only this, the resistance spread across the world in 1950's. This came out to be greatest challenge in the history of development of antibiotics. The other microbes followed up in this way. Development of resistance revolutionized the development of newer class of antibiotics against whom the resistance was not yet developed or resistance development became tough for the microbials'. The present status of antibiotic treatment came not with easiness, as the earlier discovered newer antibiotics were too toxic like Neomycin and Colimycin which were poorly purified, thus their age soon came to an end. A new step in progress of antibiotic treatment was taken in the year 1960's, when first of semisynthetic antibiotics were prepared from the penicillin molecule, 1). Methicillin and 2). Ampicillin. These two drugs were active against *Staphylococci* and common *Gram-negative* bacteria's like *E. coli*, *H. influenzae* or *S. enterica* (including *S. typhi abdominalis*). The war between US and Vietnam pressed upon focus towards development of even more advanced form of antibiotics, which were both effective and efficient, to deal with the then infections due to injuries (It was the time of advancement and expansion of intensive care). The injured soldiers were able to survive acute phase of trauma but died due to complicated infections. These infections in critically ill patients were caused by microbes of little virulence, but were not yet known to medical community at that time. These new pathogens were recruited from the hospital environment, like, *Pseudomonas* sp., *Serratia* sp., *Acinetobacter* species, which were resistant to then available antibiotics or disinfecting substances. The treatment of these infections – that were typically of nosocomial origin - was very difficult and led to extensive

[1]Kharvel Subharti College of Pharmacy, Swami Vivekanand Subharti University, Subhartipuram, NH-58, Meerut-250110, Uttar Pradesh, India.
E-mail: devanshmehta.pharma@gmail.com
*Corresponding author

Table 1: Classification of Antibiotics [4]

Antibiotic Classification	Examples	Mode of Action
Beta-Lactams	*Penicillins such as Amoxicillin and Flucloxacillins; Cephalosporins such as Cefalexin*	Inhibit bacterial cell wall biosynthesis. Thus if cell wall is not biosynthesized it will lead to death of this microbe.
Aminoglycosides	*Streptomycin, Neomycin, Kanamycin, Paromycin*	Inhibit the synthesis of proteins by bacteria, leading to cell death. So hitting the protein development is another treatment goal to develop antibiotics
Chloramphenicol	*Pentamycetin, Chloromycetin*	Inhibit synthesis of proteins, preventing growth
Glycopeptides	*Vancomycin, Telcoplanin*	Inhibit bacterial cell wall bio-synthesis
Ansamycins	*Geldanamycin, Rifamycin, Naphthomycin*	Inhibit the synthesis of RNA by bacteria, leading to cell death. Apart from restricting the protein biosynthesis, microbes could be targeted by hitting their RNA synthesis. Thus restricting their growth. Thus controlling infection growth.
Streptogramins	*Pristinamycin IIA, Pristinamycin IA*	Inhibit the synthesis of proteins by bacteria, leading to cell death
Sulfonamides	*Prontosil, Sulfanilamide, Sulfadiazine, Sulfisoxazole*	Donot kill bacteria but inhibit their growth and multiplication. Cause allergic reactions in some patients
Tetracyclines	*Tetracycline, Doxycycline, Limecycline, Oxytetracycline*	Inhibit synthesis of proteins by bacteria, preventing growth
Macrolides	*Erythromycin, Clarithromycin, Azithromycin*	Inhibit protein synthesis by bacteria, occasionally leading to cell death
Oxazolidinones	*Linezolid, Posizolid, Tedizolid, Cycloserine*	Inhibit synthesis of protein by bacteria, preventing growth
Quinolones	*Ciprofloxacin, Levofloxacin, Trovafloxacin*	Interfere with bacteria DNA replication and transcription
Lipopeptides	*Deptomycin, Surfactin*	Disrupt multiple cell membrane functions, leading to cell death

research. Thus the new age of antibiotics started with the development of modern aminoglycosides, anti-pseudomonadal penicillins and other beta-lactams. It was during this age that newer class of antibiotics were developed which were focused upon the then discovered pathogens or the known microbes to the researchers. Still the patients whose immunity was diminished and had broken natural immunity barriers due to multiple invasive procedures and use of devices, their skin were flooded with colonization of even advanced form of microbes, like, coagulase-negative staphylococci, enterococci, *Candidae*. Despite some new discoveries like, teicoplanin, triazol antimycotics, the account of anti-infective drugs in this field were unsatisfactory. Many new antibiotics with high level of compatibility for patients were introduced for treatment of community infections as well. This resulted in development of oral cephalosporin's, new macrolides, doxycyclin and fluoroquinolones. These antibiotics which were known for their easiness to be taken by the patients and effective treatment, resulted in over usage of these antibiotics, which resulted in development of resistance to even these advanced antibiotics. Thus the challenges for researcher never came to end if we go down the lane in the history of antibiotics. A few type of resistance could be dealt with development of new drugs, but, unfortunately, micro-organisms became even smarter, thus making it challenging for researchers in their goal to come up with better treatment options for the patients and community as a whole. The challenge was this time the resistance were not revertible. To deal with this menace, only sensitization the population and community for not over using the antibiotics could be of some help to the researchers, who were pressed upon even more due to rising over usage and advancement of newer class of microbes which were resistant and smarter for medical community to deal with. The common mistake by the healthcare practitioners was prescribing the latest antibacterial's for the mild or not so severe infections. This rather than treating the major goal, resulted in resistance class of microbes which resulted in threat to the existence of community as a whole. No doubt medical research community had been working day and night to develop better treatment for the mankind. But, it is equally important as an alert healthcare practitioner and community to understand the greater complexity of these microbes and the way they work. If we are not alert keeping these guidelines in our mindset, the advancement in treatment options will be of no help and treatment goal will be back to square one. Thus though antibiotics are the more advanced form of tool in the hands of skilled healthcare practitioners, there is equally important to be alert while prescribing these class of medicines for the betterment of community as a whole. [3] This review focuses upon the important class of antibiotics called Cephalosporins which have come to an advancement of fifth generation antibiotics which are having even more broad spectrum to deal with the growing pressure of infections and their complexity.

CLASSIFICATION OF ANTIBIOTICS

During secondary research, here I have enlisted the complete classification of antibiotics in Table 1, the tools which are present to the healthcare practitioners and medical community as a whole.

MAJOR TARGETS OF ANTIBIOTIC ACTIVITIES ON BACTERIAL CELL WALL

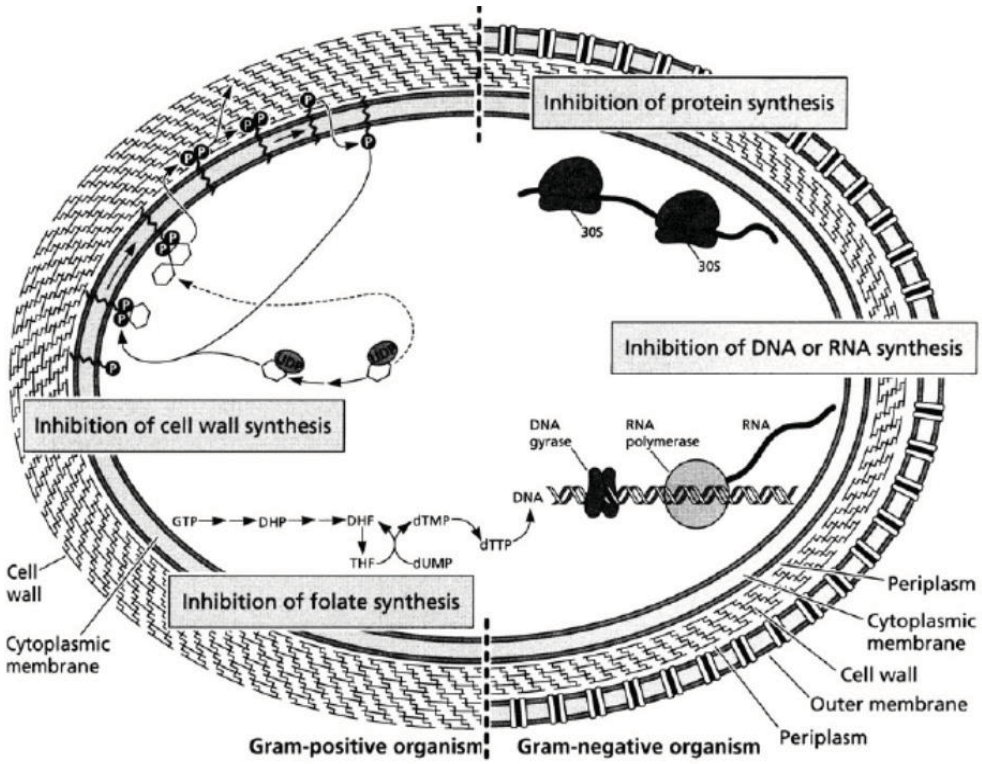

Figure 1: Major targets for antibacterial infection [5]

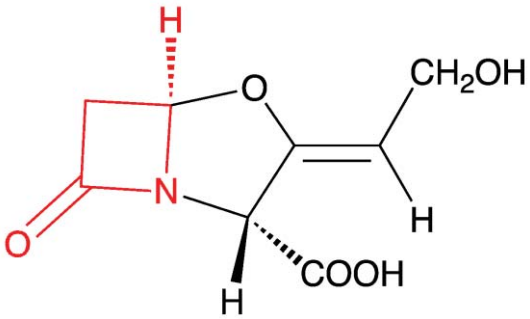

Figure 2: Beta-lactam Ring [7]

As a researcher, it is very important to know the behavior of microbes and finding out way to restrict their growth and damage to the infecting person or community. The medical research community have come up with following major targets to deal with growing complexity and severity of the microbes. Thus, the major targets of antibiotic activity on bacteria can be summarized into four major areas:

1. Inhibition of protein synthesis
2. Inhibition of DNA or RNA synthesis
3. Inhibition of folate synthesis
4. Inhibition of Cell wall synthesis

These are further described in Figure 1. [5]

CEPHALOSPORINS

Cephalosporin's were previously known as Cephalosporium, was discovered in the year 1945, thus they are part of research for many generations. Cephalosporin's belong to one of the most important class of antibiotics known as Beta-lactam antibiotics or are also read as β-lactam. They are called β-lactam antibiotics because all antibiotics which belong to this class of antibiotics have β-lactam ring in their molecular structure. As described earlier that antibiotics are natural in origin, thus, even cephalosporin's are natural in origin and are derived from fungi, *Acremonium.* Since they have been in research for many generations and even they have history of developing resistance, thus, as more and more research which have been done in this class of antibiotics, they have been classified as, First Generation, Second Generation, Third Generation, Fourth Generation and the latest are Fifth Generation, which are classified and described later in this review. First generation of Cephalosporins is active predominantly against *Gram-positive* bacteria and successive generations have increased activity against *Gram-negative* bacteria. [6] These include penicillin's, cephalosporins, monobactums and carbapenems. β-lactam antibiotics work by inhibiting cell wall biosynthesis in the bacteria and are most used anti-bacterial's. The most widespread cause of resistance of β-lactam antibiotics is the production of enzyme β-lactamases. β-lactamases are a family of enzymes produced by many *Gram positive* and

Table 2: Gram-positive and Gram-negative Bacteria's [9-10]

Gram-positive	Gram-negative
Gram-positive bacteria's are bacteria's which give positive result in the gram stain test.	Gram-negative bacteria's are group or class of bacteria's which donot retain the crystal violet stain used in gram stain test.
Gram-positive bacteria's have thicker peptidoglycan layer in their cell wall, thus, they retain the crystal vioilet color in their gram stain test.	Gram-negative bacteria's have thinner peptidoglycan layer in their cell wall structure because of which they are not able to retain the crystal violet color during the gram-stain test.
Periplasm is less in volume.	Periplasm is more in volume.

Table 3: Classification of Cephalosporin's [12]

Generation	Dose	Route
1st Generation (Narrow spectrum)		
Cefazolin	1-2 gm	IV/IM
Cephalothin	1-2 gm	IV/IM
Cephapirin	0.5-1 gm	IV/IM
Cephalexin	200-500 mg	PO
Cefadroxil	500 mg	PO
Cephradine	250-500 mg	PO
2nd Generation(Intermediate spectrum)		
Cefamandole	1-2 gm	IV/IM
Cefuroxime	0.75-1.5 gm	IV/IM
Cefoxitin	1-2 gm	IV/IM
Cefotetan	1-2 gm	IV/IM
Cefmetazole	2 gm	IV
Cefaclor	250-500 mg	PO
Cefprozil	250-500 mg	PO
Cefpodoxime	200-400 mg	PO
Loracarbef	200-400 mg	PO
3rd Generation (Broad Spectrum)		
Cefotaxime	1-2 gm	IV/IM
Ceftriaxone	1-2 gm	IV/IM
Ceftizoxime	1-2 gm	IV/IM
Ceftazidime	1-2gm	IV/IM
Cefoperazone	1-2gm	IV/IM
Cefixime	400 mg	PO
4th Generation (Broad Spectrum)		
Cefipime	2 gm	IV
5th Generation (Extended Spectrum)		
Ceftaroline	600 mg	IV
Ceftobiprole	600 mg	IV

IV - Intravenous, IM - Intra-muscular, PO - Post-operative, mg - milli gram, gm - gram

Gram-negative bacteria that inactivate β-lactam antibiotics by opening the β-lactam ring. So even the microbe's function the way researchers work in coming up with new strategies to accomplish their goal. [8]

Difference between Gram-negative and Gram-positive Bacteria's

Differences between gram-negative and gram-positive bacteria's is shown in Table 2.

Mechanism of Action of β-lactam Antibiotics

β-lactam antibiotics work by restricting the growth of cell wall of infected bacteria's, thus leading to restricting their growth and spread and cell death. If we go deeper, we see that through microscope view cell wall of bacteria consist of peptidoglycan which is unique in nature to the respective bacteria's. The cell wall envelops the cytoplasmic membrain and gives shape to cell structure. Cell wall consists of cross link polymer of polysaccharides and polypeptides. The polysaccharides are formed via alternating amino sugars, N-acetyl glucosamine and N-acetyl muramic acids. These terminate into D-alanyl-D-alanine structures. During growth the penicillin-binding-proteins removes the terminal alanine structure to form cross link with nearby peptides. β-lactam antibiotics works by restricting the cross linking via inhibiting the final transpeptidation forming covalent bond with penicillin-binding-proteins. The final bactericidal action is the inactivation of an inhibitor of autolytic enzymes in the cell wall, which leads to the lysis of the bacteria. [11]

The mechanism of action of Cephalosporin drugs is similar to that of penicillin, they inhibit the enzymes that are necessary for the synthesis of cell wall of bacteria by combining with penicillin binding proteins (PBP). [12]

CLASSIFICATION OF CEPHALOSPORINS

Cephalosporin's can be classified by different ways such as, Spectrum, Generation, Chemical structure, Resistance to β-lactamases and Clinical pharmacology. [12] Most renowned is classification based on Generation.

First Generation Cephalosporin's

First generation cephalosporin have relatively narrow spectrum of activity focused mainly on the gram-positive cocci. They work against gram-postive bacteria's like *Streptococci, Staphylococci, Enterococci*. Since they have narrow spectrum of activity, they are not effective against the Methicillin-resistant bacteria's like *Staphilococcus aureus*. Penicillin-resistant Strep. pneumoniae. Among the Gram-postive bacteria's, they are effective against, *Escherichia coli, Proteus mirabilis* and *Klebsiella pneumoniae*, though susceptibilities may vary. Not effective against, poor activity against *Moraxella catarrhalis* and *Hemophilus influenzae*. Effective against most *Penicillin-susceptible* anaerobes except Bacterioides fragilis groups.

First generation cephalosporins can be used in case of uncomplicated skin and soft tissue infections, against *Strepticoccal pharyngitis* and mild surgical prophylaxis. It is a good alternative to Anti *Staphylococcal penicillins*. But is not indicated in case of Otitis media. First generation cephalosporins are safer as they don't penetrate into cerebral spinal fluid. Though they are not recommended for central nervous system infections, as they are narrow spectrum antibiotics. Cefazolin is one of the better molecule among the first generation cephalosporins.

Second Generation Cephalosporin's

The second generation cephalosporins are another class of cephalosporins which have advantage over first generation cephalosporins in terms of the activity spectrum they have to deal with infections. Second generation cephalosporins have greater spectrum of activity against the *Gram negative* bacteria's with exception to anaerobes. They are also more resistant to beta-lactamase. Second-generation cephalosporins are effective against *Hemophilus influenza, Moraxella catarrhalis*, *Proteus mirabilis*, *E. Coli*, *Klebsiella, Neisseria gonorrheae. Cephamycins*among the class of second generation cephalosporins have a 7-alpha-methoxy group that gives resistance to beta-lactamases and makes them different from other cephalosporins *cephamycins* (cefotetan, cefoxitin and cefmetazole) have activity against anaerobic bacteroides. No efficacy against Pseudomonas, enterococci.

Second Generation Cephalosporins Uses: The 2nd Generation cephalosporins are effective against the upper and lower respiratory tract infections, acute sinusitis and Otitis media unlike 1st Generation cephalosporins which were not effective against otitis media. Among the class of 2nd Generation Cephalosporins, Cephamycins are effective against mixed aerobic and anaerobic infections of skin and soft tissue, intra-abdominal and Gynecological infections. They are also effective in surgical prophylaxis, they are not toxic but are not effective against the Central nervous system infections as they cannot cross the blood-brain barrier. Cyphamycin is the drug of choice among the 2nd generation class of Cephalosporins.

Third Generation Cephalosporins

The 3rd Generation Cephalosporins are marked by their effectiveness against most of *Gram*-negative bacteria's. In terms of effectiveness, efficiency, the 3rd generation cephalosporins are superior in nature, as they have higher β-lactamase stability and can penetrate the cell wall of Gram-negative bacteria's thus killing them and preventing them in creating infections which could be harmful for the patients. 3rd-generation cephalosporins are notorious for inducing resistance among Gram-negative bacilli. In terms of spectrum they are effective against the Gram-positive bacterial infections, have limited activity against Gram-negative bacteria's. Among the 3rd generation cephalosporins, cefotaxime, ceftriaxone and ceftizoxime have better *Gram-positive* coverage. They are effective against methicillin resistant strains unlike 1st generation and 2nd generation class of Cephalosporins. The 3rd Generation Cephalosporins are effective in curing, *Gram-negative* bacillary meningitis, serious infections of Entero-bacteriaceae, Upper Respiratory tract infections, otitis media, pyelonephritis with added advantage against, skin and soft-tissue infections. Ceftriaxone, Cefotaxime, ceftazidime, ceftriaxone, ceftizoxime and moxalactam are drug of choice among the 3rd generation Cephalosporins. Caution: *Enterobacter* species have a tendency to become resistant during cephalosporin therapy and thus cephalosporins are not the drugs of choice for Enterobacter infections.

Ceftazidime and Ceforperazone are two of the 3rd generation cephalosporins which are also known as Anti-Pseudomonal Cephalosporins. They are effective against *Pseudomonas aeruginosa*.

Fourth-Generation Cephalosporin's

Fourth generation cephalosporins have the broadest spectrum of activity, with similar activity against gram-positive organisms as first generation cephalosporins. They also have a greater resistance to beta-lactamases than the third generation cephalosporins. Cefepime and cefpirome are highly active against many resistant organisms that traditionally have been difficult to treat. They are effective against *Gram-positive* cocci, *Streptococcus pneumoniae*. Effective against Entero-bacteriaceae and *Pseudomonas aeruginosa* strains. As they have broad spectrum of activity to deal with infections they are effective against CNS infections and can be used for treating meningitis unlike the above mentioned generations of cephalosporins.

Fifth-Generation Cephalosporin's

The drug of choice in the latest 5th generation cephalosporins, the Ceftaroline is unique in its activity against multidrug-resistant *Staphylococcus aureus*, including MRSA, VRSA and VISA. Ceftaroline is the ONLY beta-lactam with MRSA activity. It is also active against *Enterococcus*. Another drug of choice among the 5th generation cephalosporins, is the Ceftobiprole which is a very broad-spectrum cephalosporin with activity against gram-positive cocci, including MRSA and methicillin-resistant *Staphylococcus epidermidis* (MRSE), penicillin-resistant *Streptococcus pneumoniae*, *Enterococcus faecalis* and many gram-negative bacilli including AmpC producing *E. coli* and *Pseudomonas aeruginosa*. It is

investigated in the treatment of complicated skin and skin structure infections. Ceftobiprole still awaits FDA. But I am sure it will soon hit market soon. [13]

CONCLUSION

With the advancement in technology, the major area of concern in antibiotic resistance still haunts the medical fraternity. With coming up of fifth generation cephalosporins, it has provided with even more wider weapon to deal with infections, but, their use shall be highly restricted as, if the bacteria's develop resistance against the fifth-generation cephalosporin's, the management of infections would be as difficult as it is with Cancer and AIDS. So, my recommendation is the use of fifth generation cephalosporins shall be used with great cautions.

REFERENCES

1. Wikipedia [Online]. 2015 November 27 [cited 2015 Dec 6]; Available from: URL: https://en.wikipedia.org/wiki/Antibiotics.
2. Ethesis [Online]. [cited 2015 Dec 6]; Available from: URL: http://ethesis.nitrkl.ac.in/3153/1/Rejitha_thesis-_full.pdf.
3. Review of antibiotics [Online]. [cited 2015 Dec 6]; Available from: URL: http://old.lf3.cuni.cz/studium/materialy/infekce/en_atb.pdf.
4. Different classes of antibiotics- An overview [Online]. 2014 [cited 2015 Dec 6]; Available from: URL: http://www.rsc.org/learnchemistry/resource/download/res00001884/cmp00005916/pdf.
5. Antibiotics overview [Online]. [cited 2015 Dec 6]; Available from: URL: http://faculty.smu.edu/jbuynak/medicinal_outline_11_4_04.pdf.
6. Cephalosporins [Online]. 2015 November 20 [2015 December 7]; Available from: URL: https://en.wikipedia.org/wiki/Cephalosporin
7. Structure of β-lactam antibiotics [Online]. 2015 [2015 December 7]; Available from: URL: https://www.google.co.in/search?q=structure+of+beta+lactam+antibiotics&espv=2&biw=1366&bih=633&source=lnms&tbm=isch&sa=X&ved=0ahUKEwiO3InGo8jJAhXIC44KHXD8BhEQ_AUIBigB#q=structure+of+beta+lactam+antibiotics&tbm=isch&tbs=isz:l&imgrc=0RCu_bJ6Aq7OOM%3A.
8. Laxmi R. Role of Beta lactamases in antibiotic resistance: A Review. Int Res J Pharm, 5(2):37-40, 2014.
9. Gram-positive bacteria's [Online]. 2015 December 7[cited 2015 December 8]; Available from URL: https://en.wikipedia.org/wiki/Gram-positive_bacteria.
10. Gram-negative bacteria's [Online]. 2015 November 12[cited 2015 December 08]; Available from: URL: https://en.wikipedia.org/wiki/Gram-negative_bacteria
11. Rang H P, Dale M M, Ritter J M, Flower R J. Drugs used in the treatment of infections and cancer and antibacterial drugs. Textbook of pharmacology 6th edition. Churchhill Living Stone, 650-65, 2006.
12. Classification of Cephalosporin antibiotics [Online]. 2013 May 20 [cited 2015 December 7]; Available from: URL: http://medimoon.com/2013/05/classification-of-cephalosporin-antibiotics.
13. Cephalosporins (Cephems)[Online]. 2013 November 02[cited 2015 December 07]; Available from: URL: http://www.emedexpert.com/compare/cephalosporins.shtml

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