β-Lactam antibiotic: A rudimentary review of the research timeline and types of drugs

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Abstract - Antibiotics are a large family of drugs that are taken as a therapeutic measure to kill harmful microbes causing diseases in host bodies. Centuries before its traditional medicinal use, antibiotics stayed an important part of human consumption. Bacteria with a long time of exposure generates antibiotic resistance. To deal with it, various new more effective antibiotic molecules are used. β Lactam antibiotics act in preventing bacterial cell wall formation and have a common β Lactam ring in them. To prevent this action, several bacteria generate β Lactamase enzyme that breaks down the β Lactam ring. But as time went by, more and more effective molecules are derived that act on antibiotic activity even against β Lactamase bacteria. In this review, a short history of β Lactam antibiotic is described with the molecular feature of more and more advanced antibiotics are mentioned.

Index Terms - Antibiotic, β Lactamase, Penicillin, Antibiotic resistance, Cephalosporin, Carbapenem, Monocyclic β-lactam (SDR)

I. Introduction: Overview and historical aspects

In 1893 Rudolf Emmerich and Oscar Low were the first persons to produce antibiotic drugs from the Pyocyanase which is a mixture of antibiotics having bacteriolytic ability and showing resistance against a large range of diseases like Cholera, Typhoid, Diphtheria, Antrax. This antibiotic was isolated from rod shaped bacteria Pseudomonas aeruginosa found in used bandages of patients.
Canadian physician Willam Osler published his book 'The principles and practice of medicine' in 1892 gave an introduction to antibiotic production. He used serum collected from manually infected horses with the isolated bacteria; and showed a proper treatment against Endocarditis
Paul Ehrlich introduced modern antimicrobial chemotherapy with the use of Ziehl Neelson TB that is toxic for various strains of bacteria. With the help of arsenic based chemotherapy Ehrlich introduced an effective treatment against Syphilis. In 1908 he received the Nobel prize for his contribution in immunology. He, along with Robert Koch and Emil von Behring improved the antitoxin of Diphtheria.

II. Short History of Penicillin: Researches associated with the antibiotic

In the year 1870, Sir John Scott Burdon-Sanderson discovered the action of a certain mould that is covering a bacterial culture is inhibiting growth of bacteria. Later it is estimated that the mould of his observation was *Penicillium glaucum.*
Next year 1871, English surgeon Joseph Lister discovered that the same mould is inhibiting bacterial growth in urine samples of humans.
During the year 1874, Welsh physician William Roberts confirmed the antibacterial effect of *Penicillium glaucum* in laboratory condition.
In 1875, John Tyndall demonstrated the antibacterial effect of *Penicillium glaucum* at the Royal Society.
French physician Ernest Duchesne at École du Service de Santé Militaire found the therapeutic use of *Penicillium glaucum* in the year 1897. He observed Arab saddle boys treating soares of saddles with moulds. He collected that mould and with the help of it he could cure typhoid of infected Guinea pigs.

In 1928, Scottish scientist Alexander Fleming discovered Penicillin at his lab. While working with Staphylococcal colonies one of his petri dishes was uncovered and got contaminated with mould spores. He observed that the bacterial colony around the mould was dying as it was clearing the agar gel. He saw this mould is highly effective towards the gram positive bacteria likely responsible for diseases like pneumonia, gonorrhea, meningitis, diphtheria, scarlet fever and many more. Alexander Fleming identified the potential of antibiotic Penicillin in therapeutic use against various diseases but he was unable to provide any purification processes of the antibiotic from the mixture of 'mould juice'. That is why he could not start any bulk production of the antibiotic in order to mass produce medicine.

Fleming could not provide a solution to mass produce or purify the necessary drug from mould, but a few years later Howard Florey and Ernst Chain published a paper on the techniques to purify Penicillin. In 1941 Howard Florey did the first trial of purified Penicillin to a policeman with cellulitis and during 1945 Penicillin was widely available for public use.

Now before going to the overview of β Lactamases a short understanding of the antibiotic supefamily β Lactam is needed.

III. BETA-LACTAM ANTIBIOTIC: AN OVERVIEW

β-Lactam antibiotics are the most available class of antibiotics and it comprises about 65% of all the prescribed antibiotics in the United States. This shows bactericidal activity by inhibiting covalent bond formation by binding to penicillin binding proteins. Following the nature of different β-lactam drugs are discussed.

Penicillins

Penicillins were the first noted antibiotics to be clinically used and still some members of it's family are used against a number of microbial diseases causing agents.

Penicillin G or benzylpenicillin was the first clinically applied β-lactam antibiotic. It was used to target streptococcal infections. But the emergence of penicillin-resistant penicillinase-producing streptococci, decreased the use of Penicillin G.

Penicillin V or phenoxymethylpenicillin is still used as an oral formula against mild streptococcal infections.

Methicillin, Oxacillin, Cloxacillin and Nafcillin are the penicillinase-stable β-lactams and were used in various staphylococcal infections, but with the rise of resistant species like MRSA(methicillin resistant Staphylococcus aureus) usage of these antibiotics were seized.

Carbenicillin was the first antipseudomonal penicillin but later its lesser potency opted out its usage.

Piperacillin or Ticarcillin were more potent against Carbenicillin. These were also used as an option for broad spectrum penicillin that can be used against penicillin susceptible staphylococci, enteric anaerobic bacterias, Pseudomonas species.

Mecillinam has a peculiar structure with a 6- β-amidino side chain. It only binds to a certain penicillin binding protein(PBP2) in enteric bacteria.

Temocillin, an analog of Temocillin: 6-α-methoxypenicillin is more stable than Triacillin as it shows higher resistance towards hydrolysis with serine β lactamases. But it has no effect towards gram positive bacterias. Even though this and Meicillinam was seized to be applied, currently it is being used in many enterobacter causing diseases with the help of Extended Spectrum Beta Lactamases(ESBL) actions.

On a concluding note, currently a very rare example of penicillin monotherapy is being seen. Some bacterial species that can not produce β-lactamases are still being treated with monotherapy of penicillin such as Ampicillin, Penicillin G and Penicillin V. In other cases for modern antibiotic therapy, penicillin is coupled with certain β-lactamases inhibitors to scale up the action of the antibiotic.

Cephalosporins

Cephalosporins opened a new path in antibiotic therapy. Several infections from pathogens like penicillinase producing Staphylococcus aureus could be treated with this new antibiotic. Other than different species of Staphylococcus, it is shown to be responsible in treating infections by β Lactamase producing enterobacteriaceae and Streptococcus bacterias. Cephalosporin C is the first of the family of Cephalosporin antibiotics to be discovered.

With the order of discovery, the Cephalosporin family can be classified into five generations.

Generation 1 cephalosporins: These are the early Cephalosporins to be discovered and it shows antibiotic activity against penicillinase containing Gram positive bacterias that shows susceptibility towards methicillin. It shows comparatively less activity against Gram negative bacterias. Cefazolin, Cephalexin are the primary first generation Cephalosporins and it is still used to treat benign respiratory tract and urinary tract infections.

Generation 2 cephalosporins: It shows higher activity towards Gram negative bacterias than first generation antibiotics but for gram positive bacterias, it shows less effects. Second generation cephalosporin, Cefuroxime can be dosed both parenteral and orally but esterification of the drug is needed to add proxetil group to get more efficacy. Other antibiotics for example Cefaclor, Cefoxitin are also used along with Cefuroxime in the treatment of soft tissue infections, upper respiratory infections and urinary tract infections.

Generation 3 cephalosporins: Though the activity of third generation cephalosporins against gram positive pathogens gets highly decreased, the activity is highly increased for Gram negative bacterias and shows an broad spectrum response as it shows a high rate of stability against hydrolysis treatment of β Lactamases but clinically it shows a high rate of bleeding of patients if treated. Because of its high activity towards gram negative pathogens, it is used to treat complicated urinary tract infections, osteomyelitis and meningitis caused by Gram negative bacterium.

Generation 4 cephalosporins: In the case of generation 4 cephalosporins, it shows a broad spectrum activity against Gram positive bacterias. Generation 4 cephalosporins are further divided into two sub groups according to their quaternary ammonium moiety; for group 1, it is C3 and for group 2 it is C7. Now the group 2 is again divided into two more sub groups where subgroup 1 has 2-amino-5-thiazolyl aryl group in their C7 and subgroup 2 has 5-amino-2-thiadiazole moieties at their C7. Examples of this generation-4 cephalosporins are Cefepime, Cefpirome, Cefozoprans. These can penetrate the outer membrane of Gram negative bacteria and show higher resistance against β-lactamases than third generation cephalosporins. For this reason it is used in critical infections caused by Gram negative bacterias like Meningitis. Antibiotics like Cefepime have a very low MIC value for enterobacter so it is used in broad spectrum treatments with higher efficacy. But usage of these broad spectrum antibiotics is also maximising the presence of ESBL pathogenic bodies that is hydrolysing a broad spectrum of β-lactam rings and the need of coupling Carbapenems with cephalosporins and penicillins getting more and more important.

Generation 5 cephalosporins: This generation of Cephalosporins is a very small spectrum but it shows a strong activity against Gram negative bacterias like Pseudomonas sp. and some Enterobactors. But for a large number of different classes of pathogens it is very less susceptible. Because of its narrow spectrum but high effectiveness, for very specific abdominal and urinary tract infections, these generations of cephalosporins are used. Ceftobiprole, Ceftaroline, Ceftolozanes are the prime examples of this group. For clinical use Ceftolozane is used, combined with tazobactam to treat critical urinary tract infections with high potency. In order to treat staphylococcal growth, Ceftaroline is highly more effective than Ceftobiprole, but for enterococcus growth, Ceftobiprole shows higher potency.

On a applictory point of view, Cephalosporin has a very low MIC value against MRSA and it binds to PBP2a which is a low affinity PBP that shows antibacterial activity of most β-lactams of MRSA.

Carbapenems

Modern day Carbapenem is a broad spectrum antibiotic showing response to a large range of Gram positive and Gram negative bacterias; but one of the first discovered Carbapenem, Thienamycin were very much insatiable in structure and more or less can not be used in any therapeutic needs alone. Carbapenem has the characterising Carbon present in 1 position rather than sulphur.

This unstable Thienamycin was made to stable and potent antibiotic Imipenem by adding N-formimidoyl group ro the 2-position. This antibiotic shows a vast range of bacterias especially those that can't produce carbamylase including several Gram positive, Gram negative, non-fermentative anaerobes.

In Escherichia coli, it is seen that Imipenem binds strongly with PBP2 and also can bind to PBP1a, PBP1b and PBP3. For this compatibility with several binding sites, Imipenem minimises the fast formation of new resistant traits.

No even for having such high effectiveness, Imipenem is hydrolysed with Human renal DHP9 (dehydropeptidase) making the drug inactivated. For this need Cilastatin, an DHP inhibitor is added. Imipenem is combined with Cilastatin and with or without Relebactam is used to treat mainly renal infections. Also this combination is shown to be effective towards Septicemia, Endocarditis, skin, bone, respiratory, urinary tract infections and in some cases a number of gynecologic infectious treatments.

But in later cases, the use of Cilastatin inhibitor was minimised as the Carbapenem altered with added β methyl group is shown to be stable around human DHP.

Several clinically used carbapenem antibiotics with functions:

Meropenem: This antibiotic can hinder cell wall synthesis by penetrating bacterial cell walls of bacterias like Pseudomonas aeruginosa that have no outer membrane porin protein. In 2017 Meropenem was introduced to the market combining with Vaborbactam in the market name of Vabomere to treat complicated urinary tract infections. Varying with the species, Meropenem has different affinity of PBP targets. It is seen to have affinity towards PBP1, PBP2, PBP3, PBP4 altogether. It is the only Carapenem to be used against bacterial meningitis caused by Staphylococci, Haemophilus influenzae and Neisseria meningitidis bacterias.

Doripenem: In characteristically and mechanism wise, Doripenem is a large way similar to Meropenem antibiotics. It is slightly more stable in gram negative bacterias than Meropenem or Imipenem. This is also used in critical infections caused mainly by gram negative bacterias. In 2007 Doripenem injections were introduced to treat complicated urinary tract infections (cUTIs). This is also seen to be used in treatment of ventilator associated pneumonia but later its use is very much controlled because of cases of lower clinical cure rates.

Ertapenem: Ertapenem is a carbapenem with a long half life and a high level of protein affinity. For this reason, Ertapenem is taken one a day while other carbapenem is taken twice or thrice a day. Unlike Imipenem, Meropenem, Doripenem, Ertapenem has little or none activity against Pseudomonas aeruginosa which is a major gap in coverage of it's vast spectrum of activity that includes reactions against methicillin resistance Staphylococcus aureus and other several Gram negative bacterias. Ertapenem is mainly used for treatment of Hospital acquired bacterial pneumonia(HABP) and Ventilator associated bacterial pneumonia(VABP) caused by Pseudomonas aeruginosa. For other several complicated infections such as intra abdominal infections caused by E. coli, Clostridium, Peptostreptococcus species; complicated skin infections like diabatic foot infections caused by Streptococcus specieses; acute pelvic infections, cUTIs post abortion initiated septic infections are also e treated with this antobiotic.

Japan only approves two types of carbapenem antibiotics named Biapenem and Tebipenem.

Biapenem: Biapenem(previously denoted as L-627) is about two to eight fold lower in MIC value than Imipenem and has 90% similarity in coverage like Imipenem. It is shown to be active against about 771 clinical bacterial isolates.Biapenem is also active against methicillin susceptible Staphylococcus species and as well as Listeria species.

Tebipenem: Tebipenem is a carbapenem antibiotic that is dosed in the form of pivoxil ester form, orally. Nitrogen of C3 heterocyclic side chain interacts with carboxylic acid group of C2 to form prodrug and is susceptible to take orally making it an important β-lactam antibiotic. Tebipenem has a broader spectrum than majority of the previously discussed β-lactam antibiotics thats shows activity against both Gram positive and Gram negative like MRSA, MRSE(methicillin resistant Staphylococcus aureus, methicillin resistant Staphylococcus epidermidis), Escherichia, Enterobacter and other colon residing bacteria that can cause internal infections. From 2009 it's use in children in Japan started with granule formula orally. Though they show stability to β-lactamases, they get hydrolysed by metallo carbapenemases. Also Biapenem shows stability towards metallo β-lactamases produced by IMP, VIM or NDM more than Tebipenem, Imipenem and Meropenem.

Monocyclic β-lactam

Monobactams or Monocyclic β-Lactams are β-Lactam antibiotics produced by bacterias which are relatively weak as other β-Lactam antibiotics in antibiotic activity but naturally occurring monocyclic β-Lactams has a high stability with bacterial β-Lactamases and that is why combining this with traditional antibiotics can give a new range of drugs with high efficacy and low MIC value.

This compound consists of only one β-Lactam ring and is not fused to any other rings. These are produced by majorly different species of Pseudomonas.

Here are some important monobactams and its significance:

Aztreonam: It is the first member discovered in the family of monobactams having a monocyclic β-Lactam ring with N1 Sulfonic acid residue. Aztreonam is the only monobactam with approved therapeutic use and used to treat Gram negative aerobic bacterias selectively as it is inactive against Gram positive bacteria. Thus at low MIC it shows activity against Enterobacter, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pneumoniae, Enterococcus faecalis etc. As Aztreonam has little to no effect on Gram-positive and anaerobes, it shows minimal effect of infections caused by indigenous fecal anaerobic bacterias. As the half life is low (~8 hours) Aztreonam is taken intravenously twice a day for severe urinary tract, lower respiratory tract, gynaecological, soft skin, tissue, bone or bile tract infections. It is also used in severe cases of infections in Gonorrhoea and septicaemia. This has high affinity towards PBP3 in gram-negative bacteria but weaker attraction towards PBP1a. Before the emergence of ESBL, Aztreonam was used as a monotherapeutic agent; but with multidrug resistance, it is seen that combining Aztreonam with β-Lactamase inhibitors it is useful to treat bacteria having SBL, and MBL resistance.

In most of the therapeutic needs, Aztreonam is applied coupled with other drugs to broaden it's activity spectrum.

BAL30072: This is one of the most modern examples of monobactam antibiotics having a large activity spectrum with comparison to previous monobactams. It is a novel monosulfactam having O-sulfate group in its N1 end. And 3-dihydropyridine siderophore and 4-gem-dimethyl substitution at the azetidinone ring. Unlike Aztreonam, which shows high binding affinity towards PBP3 only, BAL30072 shows inhibition of the binding with PBP1a and PBP1b. It has a higher penetration ability to Gram negative bacteria with iron uptake mechanism. For example, it shows up to more than 256 fold more activity against Acinerobacter and Burkholderia than traditional Imipenem. It accelerates it's activity while combining with proper β-Lactamase inhibitors or Meropenem and shows stability to hydrolysis by not only ESBL but also a large range of Carapenemases.

Other monobactam to be derived can include Sulfazecin, Isosulfazecin, Carumonam, Tigemonam, Pirazmonam etc. a lot of them have antipseudomonal activity and has more or less same drug activity profile as Aztreonam or BAL30072, but only Aztreonam is used in clinical usage as it's use is therapeutically safe and has the least side effects.

IV. CONCLUSIONS

Currently there are still a large amount of β Lactamase bacteria and more and more the resistance is increasing, more the need of new updated forms of antibiotics are needed. For that, a detailed study on protein ligand interaction in the drug delivery is required and only then a good formulation of drug can be developed.

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