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Comparing The Antimicrobial Activity of Rocephin and Augmentin for The Management of Septicemia

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ABSTRACT

The current situation of 30 million episodes and 6 million deaths per year comes from an organized review that anticipated from published national or local population estimates to the global population. The aim of this investigation was to compare the anti-microbial activity of Rocephin and Augmentin for the management of Septicemia. Microbial infections are the main cause for millions of deaths every year worldwide. Bacteria may become resistant to antibiotic inactivation, target modification, efflux pump, and plasmidic efflux. The second name of Rocephin is Ceftriaxone that acts by inhibition of bacterial cell wall synthesis. Ceftriaxone is more active in the presence of some beta-lactamases, both penicillinase and cephalosporinase, of gram-negative and gram-positive bacteria. Amoxicillin impedes penicillin binding protein 1 and other high molecular weight penicillin-binding protein. Penicillin bind proteins are the main cause for glycosyltransferase and trans peptide reactions that results in cross-linking of D-alanine and D-aspartic acid in bacterial cell wall. Without the function of penicillin binding proteins, bacteria upregulate autolytic enzymes and are ineffectual to build and repairing the cell wall, resulting in bacterial action. Septicemia is mainly caused when the toxins from the bacterial infection. mostly on the lungs or skin, enters your bloodstream and unfurl to your entire body. due to an infection that takes place in another part of the body that speedily enters your bloodstream. Staphylococcus aureus, and Streptococcus pneumoniae and E.coli are the main causative agent of septicemia. Bacterial septicemia can be cured by the use of antimicrobials like ceftriaxone (Rocephin) and the combination of amoxicillin/ Clavulanic acid (Augmentin).

INTRODUCTION:

Antimicrobial Activity

Antimicrobial activity are the agents that inhibit the growth of bacteria, prevent the formation of microbial colonies, and may destroy microorganisms. [1]

Anti-microbial agents are categorized according to their mechanism of action, i.e. interference with cell wall synthesis, DNA and RNA synthesis, lysis of the bacterial membrane, inhibition of protein synthesis, inhibition of metabolic pathway etc.

There are four major mechanisms that mediate bacterial resistance to drugs

1. Bacteria fabricate enzymes that inactivate the drug eg. B-lactamases can inactivate penicillin and cephalosporins by splitting the B-lactam ring of the drug.

2. Bacteria synthesize changed targets against which the drug has no effect eg. a mutant protein in the 30S ribosomal subunit can result in resistance to streptomycin and a methylated 23S rRNA can result in resistance to erythromycin.

3. Bacteria lessen their permeability such that a productive intracellular concentration of the drug is not attained eg. changes in porins can decrease the amount of penicillin entering the bacterium.

4. Bacteria activity exports drugs utilizing a ‘multi-drug resistance pump’ (MDR) pump. The MDR pump imports protons and, in interchange type reaction, exports a variety of foreign molecules certain antibiotics such as quinolones. [2]

Mechanism of drug resistance

Sr.No	Mechanism	Important example	Drug commonly affected
1	Inactivate drug	Cleavage by B-lactamases	B-lactam drugs such as penicillins, cephalosporins
2	Modified drug target in bacteria	Mutation in penicillin-binding protein	Penicillin
		Mutation in protein in 30S ribosomal unit	Aminoglycosides such as streptomycin
		Replace alanine with lactate in peptidoglycan	Vancomycin
		Mutation in DNA gyrase	Quinolones
		Mutation in RNA polymerase	Rifampin
		Mutation in catalase peroxidase	Isoniazid
3	Reduce permeability of drug	Mutation in porin protein	Penicillins, aminoglycosides and others
4	Export of drug from bacteria	Multi-drug resistance pump	Tetracyclines, sulfonamides

Bacterial septicemia

Sepsis is a severe organ dysfunction which takes place as a result of a body's response to infection causes. Sepsis occurs in 31.5 million people, and the number of deaths reaches 5.3 million per year.

Blood stream infections (BSIs) are responsible of morbidity and mortality. These infections are the major leading cause of death in the United States, and the ageadjusted death rate has increased by 78% over the past 2 decades. [3]Based on a study of nosocomial bloodstream infections in US hospitals, it shows that the quantity of nosocomial BSIs traceable to antibiotic-resistant organisms is raising. Among 24,179 cases of BSIs over a 7-year period, 65% were caused by gram-positive organisms and 25% by gram-negative organisms. The most common gram-positive organisms causing BSIs were coagulase-negative staphylococcus (30%), Staphylococcus aureus (21%), and Enterococcus sp (9%), and gram-negative organisms were E coli species and Klebsiella. [4]

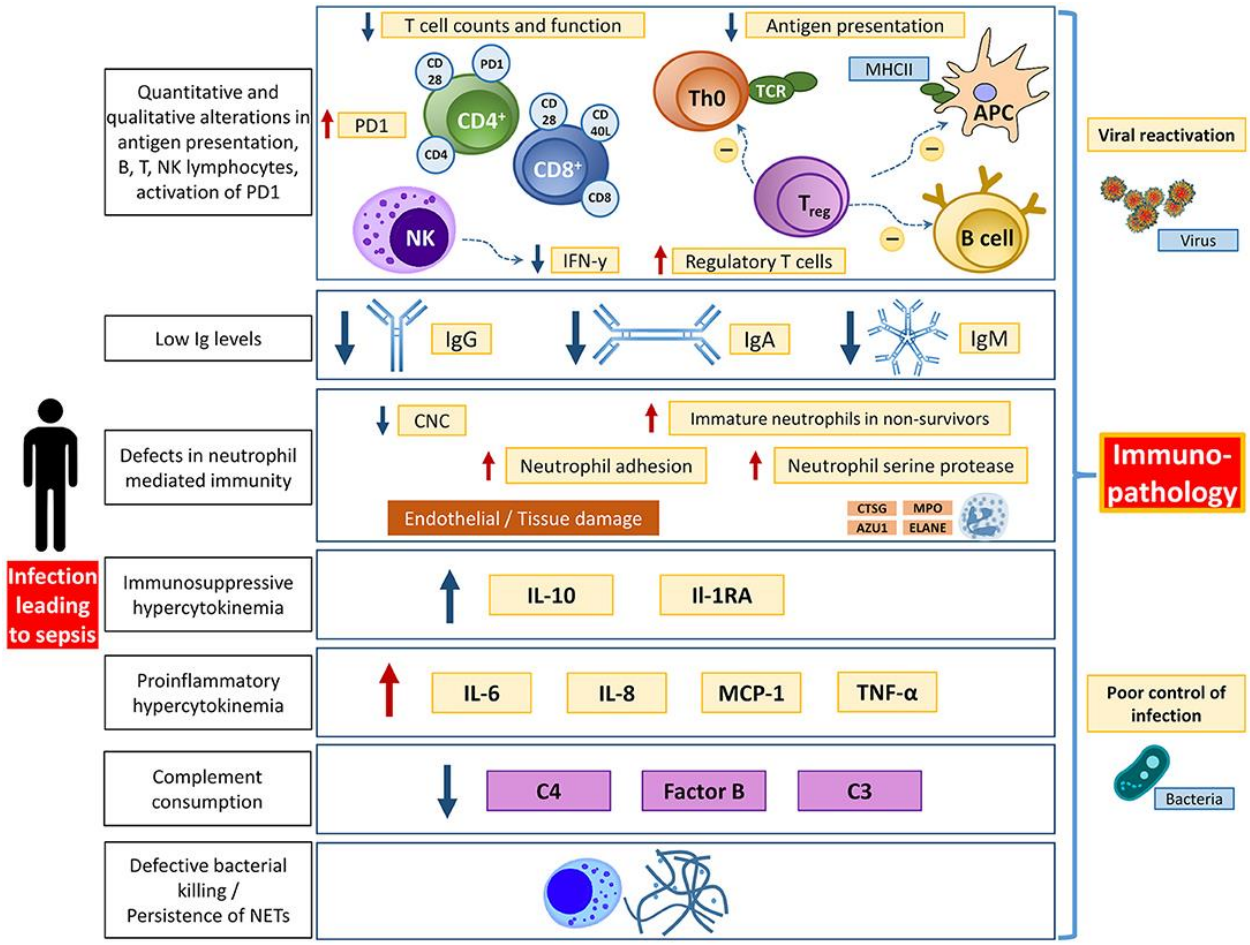

Fig no. 1: Pathogenesis of Sepsis[5]

Mechanism of Sepsis

1. In the early stages of sepsis, the consumption of B and T lymphocytes can be noticed in addition to the high apoptosis rate of stromal cells and APCs [6]. The sepsis may be caused by increased migration into the tissue, raised apoptosis, and lessened production since in extremity hematopoiesis the production of neutrophils and monocytes is given priority using the cytodiff flow cytometric system can provide information for the discrimination of sepsis severity and prediction of outcome in sepsis patients.

2. The determination of lymphopenia, and the reduction of immunoglobulin levels during sepsis, are connected with increased mortality, B lymphocytes also release cytokines, act as APCs, and modify the innate immune response [7]. Through interaction with dendritic cells, macrophages, T and other B lymphocytes, clonal expansion is persuaded, which ultimately leads to the synthesis of highly specific antibodies. After differentiation into high-affinity,

antibody-secreting plasma cells, B lymphocytes contribute remarkably to efficacious host protection by generating antibodies [8].

3. At the onset of sepsis, B cells can be activated by pathogens by interaction with pathogen recognition receptors (PRRs), which leads to an initial immune response by innate-like B cells. In septic shock, non-survivors have freshly been observed to have marked functional deterioration of B lymphocytes, resulting in declined IgM production following stimulation and an overall decreased level of IgM [9].

4. The ratios of different peripheral B cell subgroups (immature/transitional B cells, naive B cells, tissue-like memory B cells, resting memory B cells, and activated memory B cells) in septic shock differ notably from those of healthy control patients.

5. Sepsis survivors also have a notably large number of circulating B lymphocytes than non-survivors, mainly in the first 24 h after the onset of sepsis. This effect can be assigned to the production of IgM, a natural antibody that is extremely chief in the fight against Gram-negative bacteria.

6. The hypothesis of B lymphocyte protection by secreted IgM is reinforced by the determination that in survivors of sepsis or septic shock increased levels of circulating IgM antibodies have been observed in comparison to non-survivors just in the first 24 hours of the disease [10].

7. Apart from sepsis-induced lymphopenia, a higher rate of apoptosis of APCs and monocytes is a normal determination during sepsis, which is also correlated with a remarkable decrease of pro-inflammatory cytokines[11]. At the same time, there is reduced expression of human leukocyte antigen DR (HLA-DR) on the surface of the remaining monocytes and dendritic cells, resulting in pathogen recognition impairment and a decrease of opsonization with T cell receptor proteins. This leads to disruption of the Th1- and Th2-response as a main component of the adaptive immune response.

8. The inability of monocytes to reinstitute normal levels of HLA-DR expression during the course of the disease has been observed to be a negative predictor for the outcome of sepsis, as well as endotoxin tolerance in the early stages of sepsis [12].

9. In addition to the loss of pro-inflammatory cytokine production due to the decrease of APCs and monocytes, acute infection leads to notable raised granulopoiesis, whereby

immature myeloid cells migrate into the peripheral blood and become functionally active. These myeloid-derived suppressor cells (MDSCs) generate anti-inflammatory cytokines. In the context of malignant diseases, the immunosuppressive properties of MDSCs are the center of considerable research.

10. In sepsis, the expression of inhibitory immune checkpoint molecules such as programmed death protein 1 (PD-1) is raised on the surface of T cells, APCs and peripheral tissue epithelial cells, which binds to the inhibitory programmed death protein 1-receptor (PD1-R) expressed on B and T lymphocytes [13]. Binding to PD1-R suppresses leukocyte function and leads to apoptosis of immune cells, which gives to the further decrease of T and B cells, APC dysfunction, and expansion of regulatory T cells (T_{reg}) (). Although controlled apoptosis of cells of innate and adaptive immunity is advantageous for the host, the concurrent downregulation of the inflammatory response in sepsis leads to the extensive loss of immune cells and the inability of the host to continue to defend itself against invading pathogens.

11. The acquired immunosuppression in sepsis is investigated by epigenetic and metabolic mechanisms resulting in reprogramming of immune cells. After activation of pro-inflammatory genes in early sepsis, histone-mediated modification lead to the conversion of euchromatin to silent heterochromatin [14]. These epigenetic processes are connected to metabolic pathways, such as glycolysis or oxidative phosphorylation, which can lead to the accumulation of metabolic products such as acetyl-coenzyme A (Acetyl-CoA) and nicotinamide adenine dinucleotide (NAD) during the course of sepsis. Acetyl-CoA as well as NAD act as cofactors for the epigenetic enzyme's histone acetyltransferase and histone deacetylases sirtuin-1which negatively affect gene transcription [15].

Staphylococcus aureus is the second most common bloodstream isolate. Bacteremia from S. aureus still confers astonishing high mortality, ranging up to 60% in some investigation, although anti-staphylococcal antibiotics have been accessible for more than 40 years. Likewise, bacteremia from Enterococcus species continues to be very strenuous to treat, given the intrinsic resistance of enterococci to b-lactam antibiotics.[16]

Remarkably, there are some clinical trials that have the focal point on the use of combination therapy for gram-positive bacteremia and sepsis. Even, the use of initial low-dose gentamicin in the management of suspected S aureus endocarditis is found on in vitro data showing that synergistic doses of aminoglycosides, in combination with anti-staphylococcal penicillin or vancomycin, leads in quick bactericidal activity against S aureus, and on in vivo data from a

rabbit model of endocarditis demonstrating more rapid eradication of S aureus from cardiac vegetations. Likewise, the use of combination therapy for Enterococcus species is focus on a study that demonstrate bactericidal synergism between penicillin G and streptomycin, showed by in vitro time-kill techniques. [17]

Rocephin

Rocephin (ceftriaxone sodium) Ceftriaxone is a new 'third generation' semisynthetic cephalosporin with a long half-life. It has a broad spectrum of activity against gram-positive and gram-negative aerobic and some anaerobic bacteria. [18]

Table no.1: Properties of Rocephin[19]

Nomenclature	(6R,7R)-7-[2-(2- Amino-4-thiazolyl)glyoxylamido]-8-oxo-3-[[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-astriazin-3-yl)thio]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 72 -(Z)- (O-methyloxime), disodium salt, sesquaterhydrate.
Chemical formulae	C18H16N8Na2O7S3•3.5H2O
Appearance	White to yellowish-orange crystalline powder
Solubility	Readily soluble in water, sparingly soluble in methanol and very slightly soluble in ethanol.
pH	The pH of a 1% aqueous solution is approximately 6.7

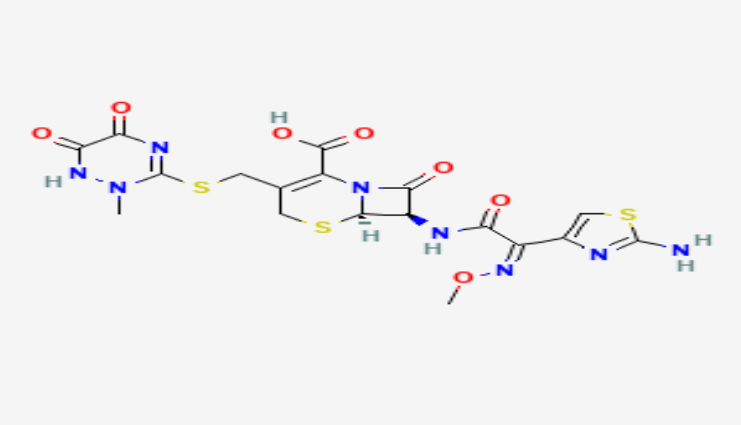

Fig no. 2 Chemical structure of Rocephin

It is within the β-lactam family of antibiotics. Ceftriaxone discriminatory and inevitably inhibits bacterial cell wall synthesis by binding to transpeptidases, also known as transamidases, which are penicillin-binding proteins (PBPs) that catalyze the cross-linking of the peptidoglycan polymers generating the bacterial cell wall. [20]. The peptidoglycan cell wall is built by the pentapeptide units connected to a polysaccharide backbone with altering units of N-acetylglucosamine and N-acetylmuramic acid. It is a β-lactam structurally related to the penicillin and have the potential to inactivate a wide variety of β-lactamases by blocking the active sites of these enzymes. Clavulanic acid is especially active against the clinically important plasmid-mediated β-lactamases often responsible for transferred drug resistance to penicillin and cephalosporins. PBPs act on a terminal D-alanyl-D-alanine moiety on a pentapeptide unit and catalyze the formation of a peptide bond between the penultimate D-alanine and a Glycine unit on an adjacent peptidoglycan strand, releasing the terminal D-alanine unit in the process. [21]The structure of ceftriaxone imitates the D-alanine-D-alanine moiety, and the PBP attacks the β-lactam ring in ceftriaxone as if it were its normal D-alanyl-D-alanine substrate. The peptidoglycan cross-linking activity of PBP attack is a construction and repair mechanism that normally helps to maintain bacterial cell wall integrity, so the inhibition of PBPs leads to damage and destruction of the cell wall and eventually to cell lysis.

Augmentin

Augmentin is an oral antibacterial combination comprising of the semisynthetic antibiotic amoxicillin and beta-lactamase inhibitor, clavulanate potassium (the potassium salt of clavulanate acid) Amoxicillin is a cognate of ampicillin, obtained from the basic penicillin nucleus, 6-aminopenicillinis acid.

Amoxicillin

Table no.2: Properties of Amoxicillin[21]

Nomenclature	(2S,5R,6R)-6-[(R)-(-)-2-Amino-2-(phydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate
Chemical formula	C16H19N3O5S•3H2O
Molecular weight	419.46

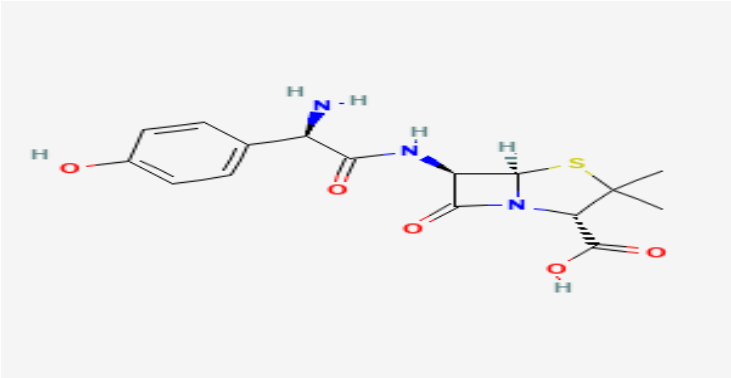

Fig no.3 Chemical structure of Amoxicillin[21]

Amoxicillin is a penicillin derivative and has same activity against gram-positive and gram-negative bacteria, containing *Enterococcus species, Listeria monocytogenes, Streptococcus species, Haemophilus influenza, Moraxella pneumoniae, Salmonella spp, Shigella spp and Borrelia species.* [22] Amoxicillin is a broad-spectrum beta-lactam antimicrobial originally obtained from penicillin. It is a bactericidal agent that targets and kills bacteria by inhibiting the biosynthesis of the peptidoglycan layer of the bacterial cell wall. [23]This layer builds the outermost portion of the cell wall and is responsible for the structural integrity of the cell. Peptidoglycan synthesis involves the facilitation of DD-transpeptidases, which are a type of penicillin-binding protein (PBP). Amoxicillin acts by binding to these PBPs and inhibiting peptidoglycan synthesis, which interrupts the generation of the cell wall and finally leads to the destruction, or lysis, of the bacteria. [24]

Clavulanic acid

Clavulanic acid is released by the fermentation of Streptomyces clavuligerus. It is β-lactam structurally connected to penicillin and have the ability to inactivate a wide variety of β-lactamases by blocking the active sites of these enzymes. The spectrum is raised to contain all β-lactamase-generating strains of the early mentioned organisms and broadening the coverage to contain methicillin-sensitive *Staphylococcus aureus (MSSA), Neisseria species, Proteus species, Pasteurella multocida and Capnocytophaga canimorsus*, among others [25].

Clavulanic acid is a beta-lactamase inhibitor often used in concurrence with amoxicillin to widen its spectrum and combat resistance. These enzymes target and hydrolyze the beta-lactam ring, which is required for penicillin-like antimicrobials to function. Clavulanic acid stops this degradation by binding and deactivating the beta-lactamases, thus replacing the antimicrobial effects of amoxicillin. [26]

Table no.3: Properties of Clavulanic acid[27]

Nomenclature	(Z)-(2R,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]-heptane-2-carboxylate
Chemical formula	C8H8KNO5,
Molecular weight	237.25

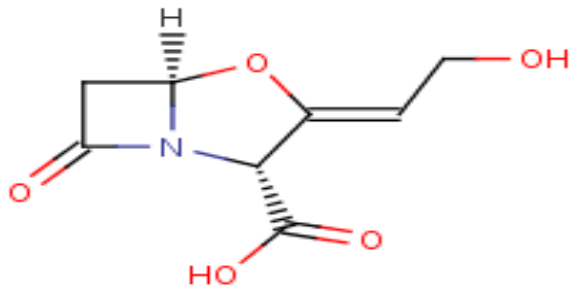

Fig no.4: Chemical structure of Clavulanic acid28

Discussion

The host response is thus possibly potentially the right way to supplement initial sepsis system for curing and treating sepsis. The chief instructions include white blood cells counts, C-reactive protein, and procalcitonin. Today, the keystone in therapy of sepsis and septic shock still contains early focus control, properly administration of anti-infective drugs and hemodynamic stabilization through fluids and vasopressors. Clinical perception is regularly developing toward an immunological responsive. Early discernment of infection in the tissues and collection of suitable antibacterial medication in sufficient doses is of chief importance. Inhibition of the release of bacterial antioxidant enzymes (catalase, superoxide dismutase, glutathione peroxidase) may raise the efficacy of phagocytosis in the tissues and oxycytosis in the bloodstream. Inactivation of bacterial hemolysins may stop bacterial pe through erythrocyte membranes and producing of infection reservoir inside erythrocytes. Antimicrobial drugs are effective against the bacterial septicemia like Rocephin, Augmentin etc. Amoxicillin acts by binding to these PBPs and inhibiting peptidoglycan synthesis, which interrupts the generation of the cell wall and finally leads to the destruction, or lysis, of the bacteria. Clavulanic acid is a beta-lactamase inhibitor often used in concurrence with amoxicillin to broaden its spectrum and combat resistance. These enzymes target and hydrolyze the beta-lactam ring, which is required for penicillin-like antimicrobials to function. This investigation showed that the antimicrobials like amoxicillin, Rocephin, clavulanic acid can be recommended for the destruction of bacteria against septicemia.

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Conflict of interest

No

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