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NEWER ANTIMICROBIALS: FUTURE PROSPECTIVES

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ABSTRACT

Antimicrobials have posed a challenge due to resistance emerging leading to increased length in the hospital stay and increased health care cost. This review aims to highlight newer antimicrobials (Antibiotics, antivirals, antifungals etc) with new targets and some still awaiting clearance by food and drug administration.

KEYWORDS: Newer Antimicrobials, resistance

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INTRODUCTION

Antimicrobials are the class of drugs to treat bacterial, viral, fungal and protozoal infections. They have been known since ancient times. Large number of drugs are there to treat various infections in humans. Due to resistance emerging due to misuse of the antimicrobials, treatment of the microbes pose a challenge, leading to longer hospitalization and increased health care cost. These drugs are used to treat the notorious organisms which are posing a risk in the hospitals and leading to higher mortality especially in septicaemic and immunocompromised patients.[1] Many of the newer drugs like zosurabalpin and lariocidin utilize novel mechanisms that bypass resistance mechanisms developed by bacteria.

NEWER ANTIBIOTICS

Antibiotics are the class of drug to treat or prevent bacterial infections. In ancient times natural substances like honey, moldy bread and plant extracts were used in ancient Egypt, Greece and India for wound care. Traditional Chinese and Ayurveda used herbal preparations for antimicrobial properties. In 1676 Antonie van Leeuwenhoek observed bacteria through microscope. They act by various mechanism i.e. prevent cell wall synthesis, inhibit protein synthesis by acting on 30S and 50 S ribosome or act by inhibiting DNA gyrase enzyme.

Newer antibiotics designed to treat resistant or emerging infections especially Multi Drug Resistant (MDR) organisms

1. **CEFIDEROCOL** – It is a fifth generation cephalosporin. Act as novel cephalosporin antibiotic with a unique "Trojan horse Mechanism". It binds to ferric iron, which it then uses to enter bacterial cell through iron transporter channels. It inhibits cell wall synthesis by binding to penicillin binding protein. This unique mechanism of action enables it to overcome resistance mechanisms like point mutation and efflux mechanisms and increased stability to beta lactamase enzyme. Approved in September 2020. It inhibits gram negative bacteria like E.Coli, K.pneumoniae, Ps. Aeruginosa and Acinetobacter baumanii. Used to treat complicated urinary tract infections, hospital acquired bacterial pneumonia and ventilator associated bacteria pneumonia in

adults.[2] It is given in a dose of two gram intravenously. Dose reduction is needed in patients of kidney impairment. Side effect reported are diarrohea, rash, pyrexia and increased levels of alanine and aspartate amino tranferase and creatine phosphokinase.

2. **DELAFLOXACIN** – It is a fourth-generation fluoroquinolone(FQ) antibiotic. Approved in June 2017. Acts against gram positive and negative pathogen. Inhibits bacterial DNA gyrase and topoisomerase IV essential for DNA replication, repair and transcription. Used to treat acute bacterial skin and skin structure infections (ABSSI) and community acquired bacterial pneumonia (CABP). Effective against Methicillin resistant staphylococcal aureus (MRSA) and broad spectrum antibiotic effective against gram positive, gram negative and anaerobes.[3] In contrast to older FQs effective against MRSA, active in acidic environment and less risk of QT prolongation. Causes nausea, diarrhoea, headache, tendonitis, peripheral neuropathy, CNS effects seizures and confusion and raised serum liver enzymes.

3. ERAVACYCLINE- It is a newer tetracycline used to treat complicated intraabdominal infections. It inhibits bacterial protein synthesis by binding to 30S ribosomal. It is effective against multi drug resistant (MDR) organisms including gram positive and negative organisms ie MRSA, VRE(vancomycin resistant enterococci), ie extended spectrum beta lactamase (ESBL) producing and carbapenem -resistant Enterobacteriaceae and anaerobic pathogens eg. Bacteroides. It was FDA approved in August 2018. It has a half-life of 20 hrs with protein binding of 80%. It is given intravenously for complicated intra-abdominal infections.[4]

4. **DALBAVANCIN and ORITAVANCIN** – They are semisynthetic lipoglycopeptide derived from teicoplanin effective against gram positive skin infections and MRSA approved in May 2014. It acts by inhibiting cell wall synthesis. It has a long half-life permitting it to be given single or weekly dosing.[5,6]

5. **OMADACYCLINE**: It is a tetracycline antibiotic belonging to the subclass Aminomethylcycline. Approved in October 2018. Active against resistant gram-positive pathogens ie MRSA, penicillin resistant and multidrug rest Streptococcus pneumoniae, streptococcus pyogenes and vancomycin resistant enterococcus. Used in community acquired bacterial pneumonia (CABP), in acute bacterial skin and soft tissue infections.[7]

6. **TEDIZOLID**: It is a second generation oxazolidinone. It acts by inhibiting protein synthesis. Used in acute bacterial skin infection caused by gram positive bacteria staphylococci, enterococci, streptococci including methicillin resistant staphylococcus aureus and vancomycin resistant enterococci. Given once a day and cause less bone marrow suppression than linezolid and nausea being the common side effect.[8]

7. RELEBACTAM: It is a beta lactamase inhibitor that works by blocking the enzymes that break down the antibiotic. Inhibits beta lactamase enzyme which deactivate beta lactam antibiotic ie imipenem. Approved in 2019. Imipenem-Cilastatin-Relebactam – Imipenem is hydrolysed by dehydropeptidase enzyme. Cilastatin is dehydro-peptidase inhibitor. Relebactam is a beta lactamase inhibitor and reestablishes the activity of imipenem. Thus, the combination is used for MDR gram negative infections – for pseudomonas. Used in urinary tract infections (UTIs), chronic intra-abdominal infections, hospital and ventilator acquired bacterial pneumonia.

8. VABORBACTAM – It is a beta lactamase inhibitor. Used in Complicated UTIs and pyelonephritis caused by Klebsiella. It was approved by US FDA in 2017 along with Meropenem

9. LEFAMULIN –Belong to class of Pleuromutilin antibiotic. It was approved by US FDA in August 2019 but not in India. Used in community acquired bacterial pneumonia. Effective against streptococcus pneumoniae, MRSA, streptococcus pneumoniae. It acts by inhibiting protein synthesis by binding to 50S ribosome, thus preventing the binding of transfer RNA thus inhibiting the formation of peptide bond and halting protein production.

10. DAPTOMYCIN - Daptomycin is a lipopeptide antibiotic obtained from Streptomyes Roseosporus. Acts by binding to bacterial membrane and causes depolarization leading to loss of membrane potential and killing of bacteria. Used for Gram positive bacteria especially resistant strains.ie MRSA, MSSA, VRE and streptoccus spp. Used in complicated skin and soft tissue infections, in bacteraemia and endocarditis due to MRSA and VRE

and endocarditis. It is highly bound to plasma protein and has serum half-life of 8-9 hrs. It causes myopathy, eosinophilic pneumonia, GI upset, rash and headache.[9]

11. NAFITHROMYCIN- It is a novel lactone ketolide antibiotic for community acquired bacterial pneumonia. It is ten times more effective than azithromycin offering three-day treatment regimen

12. ZOSURABALPIN- It is a macrocyclic peptide which targets a complex in the inner membrane which block lipopolysaccharide transport leading to accumulation of endotoxin in the cell and death of bacteria especially carbapenem resistant Acinetobacter baumannii.[10]

NEWER ANTIVIRALS – Viruses cause toxicity to host cell. Clinical and laboratory diagnosis is difficult. Viruses undergo structural change. Thus, leading to development of resistance. Latent virus i.e. nonreplicating virus are not affected. Clinical symptoms appear after rapid multiplication where antivirals are more effective. Therefore, therapy has to be started in the incubation period i.e. has to be prophylactic or preemptive.

1. REMDESIVIR: It is a nucleotide analog. Inhibits RNA dependent RNA polymerase. It was the first drug FDA approved in 2020. Used in severe acute respiratory syndrome coronavirus 2 infections (the causative pathogen of the disease COVID-19). The side effects reported with the drug are back pain, chest tightness, cough, chills, fever.[11]
2. MOLNUPIRAVIR – oral antiviral for COVID-19 (mild to moderate). It was approved for emergency use in 2021. Acts by inducing viral RNA mutagenesis.
3. ENSITRELVIR – It is a protease inhibitor. Used in SARS- CoV2 infection approved in Japan in 2022. Used for mild to moderate COVID infection.
4. NIRMATRELVIR/RITONAVIR – Protease inhibitor boosted with ritonavir. Acts by inhibiting protease enzyme. For COVID-19 treatment especially in high-risk patients.
5. BULEVIRTIDE: It is a entry inhibitor. Inhibits NTCP (sodium taurocholate cotransport polypeptide) receptor (prevents HBV/HDV entry into hepatocytes). Approved in 2020 for chronic Hepatitis D virus infection. The side effects reported are headache, pruritic, fatigue, eosinophilia, arthralgia and asthenia. [12]
6. LENECAPAVIR: It was approved in 2022 for multidrug resistant HIV. It is a capsid inhibitor and targets HIV-1 capsid protein. Given once every 6 months as is long acting and given parenterally.
7. MARIBAVIR- It was approved in 2021 for post transplant cytomegaloviral (CMV) infection. Inhibits CMV replication.

NEWER ANTIFUNGALS: These agents are used to treat rising antifungal resistance and limited treatment options for invasive fungal infections. But they have high cost and limited availability.

1. IBREXAFUNGERP – It is a triterpenoid antifungal and inhibits β-1,3 D- glucan synthesis essential for fungal cell wall synthesis. It is highly bioavailable, undergoes high Plasma protein binding, extensive tissue distribution and less CYP drug interactions Used in vulvovaginal and invasive candidiasis, Aspergillus and Pneumocystis infection.[13] It causes mild gastrointestinal symptoms.
2. REZAFUNGIN – ECHINOCANDIN. Inhibits β-1,3 D- glucan synthesis that is chemically related with anidulafungin. Used in vulvovaginal and invasive candidiasis. Being evaluated for patients undergoing bone marrow transplant. It has a long half-life of 130 hours, better tissue penetration and good safety profile. Thus, given once weekly intravenously. Approved in 2023.
3. OLOROFIM- Is in phase3 clinical trial for aspergillus and resistant mold infection. Inhibits dihydroorotate dehydrogenase which is essential for fungal pyrimidine synthesis. It is given orally and intravenous administration
4. FOSMANOGEPIX- It is in clinical trials for Candida, Aspergillus and Fusarium species.[14] Impairs cell wall synthesis. It is a prodrug of manogepix, an inhibitor of the fungal enzyme. It cause reduction in cell wall linked mannoproteins which are required for cell wall integrity, adhesion, pathogenicity an devading the host immune response.
5. OTESECONAZOLE - It is an azole derivative. It inhibits fungal CYP51 required for ergosterol synthesis. Long half-life of 150 days. Less effect on human CYP450 enzymes. Used in vulvovaginal candidiasis.

NEWER APPROACHES

1. PHAGE THERAPY – Use viruses(bacteriophages) that infect and kill bacteria. Effective against multidrug resistant infections. Has been used since ancient times and due to emergence of resistant strains their reuse

is being considered. Used for chronic wound infections and infections in various systems ie bone and joint, respiratory, urinary tract and gastrointestinal infections.

2. MONOCLONAL ANTIBODIES – Bezlotoxumab is the monoclonal antibody for CL. DIFFICILE infection given by intravenous route.
3. ANTIMICROBIAL PEPTIDES – These are short naturally occurring peptides that disrupt microbial membranes. Broad spectrum activity with less resistance potential. They inhibit bacteria, viruses, fungi and parasites. [15]
4. CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) BASED ANTIMICROBIALS – Use gene editing tools to kill bacteria by targeting resistance genes. It is a promising alternative to traditional antibiotics especially in the case of rising antimicrobial resistance. It is a DNA sequence in bacteria that together with Cas (CRISPR-associated) proteins defends against invading viruses by cutting their DNA. They target and cut specific DNA sequences in invading bacteria. The materials used are bacteriophages, plasmids and nanoparticles or liposomes. They are highly specific (targets resistant/pathogenic strains), prevents resistance spread and preserve microbiota.[16]
5. NANOPARTICLE BASED DRUG DELIVERY – Targeted delivery reduces toxicity and improved efficacy. Liposomes, polymeric nanoparticles and silver/gold nanoparticles.
6. MICROBIOME MODULATION - Gut microbiota plays a central role in the regulation of health and disease. Polymicrobial interaction between bacteria (bacteriome) and fungus (mycobiome) present in the gut have gained focus as therapies. Probiotics, Prebiotics and fecal microbiota transplantation are used to restore healthy microbiota. They rebalance the gut microbiome, increase gut epithelium barrier function and enhance cytokine production. They Inhibit clostidium difficile infections and resist colonization by pathogens.[171]
7. HOST DIRECTED THERAPY- Modulates the host immune response. Reduce the pathogen survival and replication. They include monoclonal antibodies, cytokines, cellular therapy, recombinant proteins and micronutrients. They are used in Tuberculosis and viral infections.[18]

CONCLUSION

Due to widespread use of antimicrobials, ineffectiveness in patients has posed a challenge. Various efforts have been made to overcome the resistance so that new drugs can be discovered to treat the emerging pathogens. These antimicrobials will be available in the market after clearance by the government agencies in various countries and adverse drug reaction monitoring will be done for these antimicrobials in real life situation. Hope, these antimicrobials may combat the resistance emerging and cure the patients from the drugs available in the market.

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