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Need for Newer Antibiotics or Alternate Solution in ICU Management

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Introduction

The greatest threat to healthcare services is antibiotic resistance and evolution of multidrug resistant bacteria. Together they lead to infections, which cause extra burden on healthcare, thus leading to high morbidity, mortality, and expense. The estimated mortality due to sepsis from MDR is exponentially higher than the deaths caused by other infections.

Unfortunately, antibiotic-resistant pathogens have created a post-antibiotic era where new drugs are scarce and resistance develops faster. The twentieth century saw both – an era of development of newer antibiotics for human advantage, and at the same time leading to development of drug resistance. These have led to the never ending struggle to develop newer antibiotics for better cure and survival of humanity.

Further to this, a multi-factorial aetiology to sepsis leads to poorer outcomes and bigger challenge for critical care physicians. Developing newer antibiotics, which are economical, easier to administer, have a wide spectrum, and are least vulnerable to resistance is a greater challenge.

The last two decades have seen few antibacterial drugs being developed, which offer benefits over existing ones. It is unfortunate that out of these few drugs, five could reach the phase 3 clinical trials. Restriction of clinical use to few vulnerable diseases, short course of medical prescription, and limited medical fraternity prescribing it, makes antibiotics financially non profitable when compared to drugs used to treat non communicable diseases, i.e., hypertension, diabetes, etc. Financial loss to pharmaceutical firms becomes obvious and the race ends before it begins. A 2008 initiative named 10 x 20 Initiative was a challenge thrown by IDSA at USA and EU to develop ten new drugs over twenty years. Failure of this transatlantic initiative becomes quite apparent as no new drugs were developed over and above previous ones, except few with biosynthetic changes.

Recognition of metallo-beta-lactamases, extended spectrum beta lactamases (ESBLs), carbapenem-resistant Enteriobacteriaceae (CRE), *Klebsiella pneumonia* carbapenemases (KPCs), Vancomycin-resistant Enterococcus (VRE) and Methicillin-Resistant *Staphylococcus aureus* (MRSA) by microbiological laboratories needs to be much recognised and applauded in the ever-changing treatment of MDR infections.

Newer antibiotics

It is unfortunate that only two new classes of antibiotics were discovered over the last five decades. The last decade has seen even lesser numbers being brought into the market which is considerably lower than what was three decades age.

A dozen newer semi-synthetic salts are being tested and are in late clinical testing stage, but all appear to be modifications to pre-existing antibiotics. None from a new class has been on trial for the last decade. Their efficacy may get limited by the fact that many original salts showed resistance and their novo versions may just provide an extended window of time till further resistance is documented. Many strains of soil bacteria from different environments are already showing resistance to the new semi-synthetic antibiotics. This has been well documented with tigecycline which was introduced over a decade ago. In fact, resistance to many synthetic antimicrobials may already exist in nature. We all are aware that resistance is inevitable, and that primarily is due to the fact that organisms have been around for long and they know how to survive.

New antibiotics which have novel mechanisms of action against MDR organisms, with minimal side-effects, and are easier to administer (preferably by non intravenous route), and have specific effects on the microbiome, are the need of the hour.

Gram-positive organisms such as MRSA and VRE are stable or declining in frequency while Gram-negative ESBLs and CREs are increasing. It is important to remember and differentiate between carbapenemase-producing enterobacteriaceae (CPE) Gram-negative bacilli and carbapenem-resistant enterobacteriaceae (CRE) Gram-negative bacilli, the ones which have carbapenem resistance without producing a carbapenemase enzyme . A number of carbapenem-resistant Gram-negative bacilli are highly problematic and these are other than Enterobacteriaceae

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for, e.g., *Pseudomonas aeruginosa*, *Acinetobacter species* and *Stenotrophomonas maltophilia*. They are often implicated in infections within healthcare settings and survive within the milieu by using a combination of other resistance mechanisms. As the risk of transmission and dissemination is lower, it becomes important to identify them as coloniser versus source of infection to further isolate and/or initiate appropriate management.

Enterobacteriaceae family includes common pathogens such as *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae* and *Proteus species*. These are normal colonisers of the gut, but can lead to severe infections of the urinary tract, gastrointestinal tract, and the bloodstream. As human pathogens, they cause dissemination of infection, antimicrobial resistance, and cross-transmission of genes; this is further exaggerated by easy spread of cross-resistance between different species and strains within the Enterobacteriaceae family. Carbapenemase-producing Enterobacteriaceae (CPE) produce the enzyme carbapenemase, which inactivates all the common members of the carbapenem antimicrobial class. Other carbapenemase enzymes commonly identified are IMP, NDM, VIM, KPC, OXA-48 and this is an ever-expanding family. Compounding to the above it has been documented that they almost always have resistance to other important antibiotic classes, i.e., beta-lactams, beta-lactamase inhibitors, quinolones and aminoglycosides.

Newer antibiotics: The last two decades of the new millennia

Oxazolidinones

Linezolid, an oxazolidinone, was introduced more than two decades ago and inhibits bacterial protein synthesis at the initiation/elongation step. It has sensitivity against Gram-positive bacteria, especially methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE) and *Streptococcus pneumoniae* and *Mycobacterium tuberculosis*. Radezolid (RX-1741), Torezolid (TR-700), and a research molecule RWJ-416457 are under clinical trials.

Glycopeptides

Vancomycin, the first drug of this group has come a long way. Oritavancin, Telavancin, Dalbavancin are few of the new phenyl glycopeptides. They inhibit peptidoglycan biosynthesis by inhibiting transglycosylation and transpeptidation. They all have activity against vancomycin-intermediate isolates of *S. aureus* (VISA), vancomycin resistant staphylococci and *Enterococcus faecium* (VRE), MRSA. Oritavancin is not as potent against vancomycin intermediate *S. aureus* (VISA).

Ketolides

Elithromycin, a ketolide has Carbonyl group at C3 position in a fourteen-membered ring macrolide thus conferring sensitivity to macrolide resistant strains. Cethromycin and Telithromycin are the other few drugs made available and they all inhibit protein synthesis in *S. pneumoniae*.

Glycylcyclines

A tetracycline class of antibacterial drugs Tigecycline was approved in 2005, which shows efficacy against both non resistant and resistant isolates especially enterococci and streptococci. It also acts against carbapenamase producing *Acinetobacter* and enterobacteriaceae. PTK0796 an oral aminomethylcycline is under development.

Carbapenems

Carbapenems are β-lactam penicillins (penam) and cephalosporine (cephem). They differ from the penams by the replacement of carbon for sulphur at position 1 and unsaturation in the 5-membered ring. Doripenem, was approved in 2007 for urinary and intra-abdominal sepsis.

Non-fermentative MDR GNB especially *Pseudomonas, Acinetobacter spp*. and *Burkholderia cepacia* are highly susceptible to its antibacterial activity. Razupenem (PZ-601) is under trial for multi drug-resistant Gram-positive and Gram-negative (ESBL producers) bacteria.

Lipopeptides

Daptomycin is a cyclic lipopeptide, derived from *Streptomyces roseosporus*. This is the first drug in a new class of antimicrobials. Its unique mechanism of action of inserting a lipophilic tail into the cell membrane without entering the cytoplasm, makes it a promising drug for future research also. An adverse life-threatening complication of eosinophilic pneumonia has been reported in literature.

Cephalosporin

Ceftobiprole and ceftaroline are the newer cephalosporins. Ceftobiprole, binds strongly to PBP2a (or PBP2′) of MRSA and shows action against penicillin-resistant streptococci also. Being a broad spectrum antibiotic, it is effective against *P. aeruginosa* and *Enterococci* also.

Ceftaroline fosamil is a prodrug of ceftaroline, developed by modification of fourth generation cephalosporin cefozopran. Phosphatise enzyme-induced activation converts prodrug into active form once injected in blood.

Pleuromutilin

Retapamulin, the first approved drug in this new class is

used as a topical preparation for infections caused by *S. pyogenes* and *S. aureus* in the skin or soft tissue.

Dihydrofolate reductase inhibitors

Iclaprim, a synthetic diaminopyrimidine, selectively inhibits enzyme dihydrofolate reductase. It is quite similar to trimethoprim in action, but does not require to be combined with other sulphonamides. Though it has shown high synergistic activity with sulfamethoxazole and sulfadiazine as well, it is being used as single agent against Trimethoprim-resistant isolates.

Others

Nitazoxanide, a nitro-thiazolide, exhibits broad spectrum activity against anaerobic bacteria and against anaerobic intestinal parasites. Nitazoxanide is FDA approved for the treatment of *Giardia intestinalis* and *Cryptosporidium parvum, Clostridium difficile*. It has also demonstrated antiviral activity against rotavirus and hepatitis C.

NXL103 (XRP2868) is a mixture of modified forms of quinupristin/dalfopristin streptogramins making it more water-soluble and permitting oral administration.

Fidaxomicin (OPT-80) is a novel macrocycle antibiotic, which is non-absorbed systemically and has potency against anaerobes such as *C. difficile*.

Sulopenem is an orally active penem in current clinical development and is potent against multi-drug resistant pathogens including penicillin-resistant *S. pneumoniae* and ESBL producing Enterobactericeae.

Others under research

BAL30376	Combination of monobactam
BAL19764	Class C β-lactamase inhibitor
BAL29880	Clavulanic acid
NXL104	Serine β-lactamases
BLI-489	Bicyclic penem inhibitor,
JNJ-Q2	Fluoroquinolone type II topoisomerase inhibitors
Finafloxacin 8-cyano fluoroquinolone	
LED209 Quorum-sensing blockers	
PC190723	
Rx100472	
Fab I inhibitors	
Lipid II binding compounds	
Bacterial efflux pump inhibitors	
Bacterial 2 - component signal transduction inhibitors	

Developing next generation antimicrobials, alternate solutions and newer technology for the ICU: the way forward

Targeting bactericidal functions of bacteria, by inhibiting proteins and fat synthesis is one of the ways to counter bacteriostatic pathways of inhibition and drug resistance presently being encountered. For e.g., essential enoyl-ACP reductase FabI required for fatty acid biosynthesis is being researched for bactericidal effects. Multi-drug resistant pathogenic fungi can be similarly targeted by blocking nuclear receptor pathways required for multi-drug resistant efflux development. A new therapeutic approach is needed to counter the previous mechanisms of resistance.

Newer pathways being targeted

Bacterial proteins: Inhibiting beta-ketoacyl carrier protein synthase I/II enzyme required for the fatty acid biosynthesis.

Virulence factors: Virulence inhibitors targeting toxin function.

Inhibiting bacterial systems type II or III secretion

Gene regulation of gene expression and adhesion

Inhibition of the formation of pili by pilicides.

Modulating host response pathways: Toll like receptor activators and modulator for adaptive immune response.

Therapeutic bacteriophages: Small, acid soluble protein (SASPs) genes which bind and inactivate bacterial DNA.

Combination of antibiotics with bioenhancers: Bioenhancers agents are capable of increasing availability and efficacy of drug when co administered with another drug, but do not have any pharmacological activity themselves, e.g., cow urine distillate (CUD) combined with rifampicin increased the activity of drug manifold[1]. (*Escherichia coli* 5 - 7 times, Gram-positive bacteria 3 - 11 times).

Herbal drugs

Herbs with antibacterial potential

Common name	(Botanical name)	Spectrum of activity
Chakvad	(*Cassia tora*)	*S. Aureus*
Pot marigold	(*Calendula officinalis*)	*B. subtilis, P. aeruginosa*
Karela	(*Momordica charantia*)	*E. coli*
Peppermint	(Mentha piperita)	*E. coli*
St. John's wort	(*Hypericum perforatum*)	MRSA
Honey		*S. aureus, E. coli, S. faecalis, P. aeruginosa, P. mirabilis, Salmonella typhi*
Cow urine distillate		(CUD) *Klebsiella pneumonia, B. subtilis, P. aeruginosa, Salmonella typhi*

The rise of the superbugs and role of biotechnology

CRISPR

CRISPR (clustered regularly interspaced short palindromic repeats) is dependent on immune system of bacteria where-in a single protein for binding and cleavage is used for RNA to detect DNA followed by Cas enzyme for nucleic acid destruction[2]. A molecular tool devised on similar basis helps as an antimicrobial, killing bacteria and also immunising them against resistant plasmids. This selectively removes in a programmed manner the specific microorganisms.

Nanotechnology to combat resistant and MDR bacteria

Nanotechnology for the synthesis of newer and older antibiotics is new technological development, for both drug delivery and tackling antibiotic resistance. Nanometric size synthesis of antibiotics improves absorption, penetration, bioavailability, thus causing enhanced mucoadhesion and intracellular drug delivery with concentration[3]. A controlled release mechanism by encapsulated delivery system enhances the activity of adsorbed drugs. Metal specific nanoparticles, e.g., silver, has been used along with antibiotics for inhibition, alteration of cell wall synthesis and its lysis. Nano particle technology has a great potential as infectious pathogens can be targeted at inaccessible locations.

Polymeric nanoparticles and nanocrystals

Polymeric nanocapsules for antibiotics and drug nano crystals which are specific and stable components of delivery have been developed. Polylactide-co-glycolide (PLGA) along with encapsulated gentamicin sulfate/ zirconium is being used for drug delivery system. It is a revolutionary drug delivery system of the future.

Lipid nanoparticles (liposomes) containing rifabutin (RFB) for pulmonary tuberculosis and nanoceramics in orthopedic surgeries for local antibiotic administration have been developed and are being used[4]. Studies have documented formation on nanoparticle-pathogen complex in the microenvironment of release.

Metallic nanoparticles

Metallic nanoparticles or nanoparticulate metals, metal oxides, metal halides, and bimetallic materials have revealed antimicrobial activity especially when Ag, Au, Zn, Cu, Ti, and Mg have been used[5].

Nanocages

Hollow nanocages synthesized from metals proteins, polymers are being utililsed for antibiotic delivery especially in cases of MDR. Nanocages technology has led to improved adhesion, retention, and activity of antibiotics at the site of action. Gold nanocages, apoferritin-based nanocages, silica and silver naocages are being used for various therapies[6].

Bacteriophages

Bacteriophages-viruses targeting the bacterial cells – the natural predators of bacteria, have been the earliest discovery of science. With more than a thousand types known for nearly a century, their use in fighting antibacterial resistance has been advocated and researched over the last two decades. Their unique ability of specific receptor adhesion to bacteria and ability to kill them is the mainstay in combating and killing drug-resistant bacteria. Few clinical trials have been performed and accepted by FDA and EMA (European Medicines Agency).

Identification of specific bacteria involved in infection and its subsequent enveloping with the lytic bacteriophage is the pre-requisite for this therapy. Accumulation at high concentrations at host site is due to the bacteriophages site-specific exponential growth and this leads to bacterial death by cell wall lysis. Bacteriophage tailoring with new technology has improved upon:-

1. Penetrating capability into bacterial biofilms;
2. Polymicrobial phage typing;
3. Improving phage efficacy by making it more specific, stable, and highly lytic.

Microbiome manipulation

Ever-evolving mechanisms are being developed to control infections, and one such model is the microbiome. Currently, faecal transplants for *C. difficile* are the only approach to microbiome manipulation proven to work. Future microbiome manipulations could lead to decolonisation of MDR in gut.

Is it always the way forwards: Learning from the past, for strategies of the future

Preventing spread of resistance

1. Prevention, preparing, and planning to curtail infections in the hospital environment.

a) Patient screening on arrival from other healthcare facilities and identifying patients at risk.

b) Cleaning and disinfection of high-risk areas of the healthcare facility.

c) Microbiology laboratories to culture for infection spread and timely notification.

d) The five moments protocol of hand hygiene and strong implementation of it.

e) Patients and visitors education about hand hygiene.

2. Antimicrobial stewardship programme for appropriate use and prescription of antibiotics within healthcare facility.

   a) Monitor the use of antibiotics

   b) Audit system in place to identify and control inappropriate antibiotic use.

   c) Recent therapeutic guidelines should be followed.

   d) Monitoring antimicrobial resistance.

3. Screening and surveillance

   Strict screening and surveillance of patients who have had prolonged hospitalisation, undergone surgery in a facility outside the premises of present healthcare or overseas, multiple or recent exposures to antibiotics (e.g., cephalosporins, fluoroquinolones and carbapenems), post-ventilation or ET support, indwelling medical devices, post-organ or stem cell transplant patients.

4. Outbreak management

   Regular surveillance of data and notification or alert in healthcare facility of sudden increase of a particular infection should guide further management of the outbreak. All hospitals should have an outbreak management team with partners from all the facilities in the hospital.

5. Rotation of antibiotics

   Studies have shown that rotation of antibiotics decreased microbiologically documented infections significantly and a trend towards lower incidence of potentially antibiotic-resistant infections. The susceptibilities of potentially antibiotic-resistant bacteria to antibiotic regimens significantly increases. Increased antibiotic duration increases the incidence of colonization with MDR, especially nosocomial strains, and this was documented with facilities having higher rates of antibiotics prescription. The necessary time span to alter this bacterial ecology after antibiotic withdrawal or rotation is not known. Gram-positive infections are more difficult to treat with cyclic use as the number of effective antibiotics is limited.

Alternate source for new antibiotics

Penicillium notatum came from a mould in 1920, and since then soil-dwelling microorganisms are the source of antibiotics.

Genomic sequencing of bacteria and identification of their survival genes helps in the searchof an inhibitory chemical which subsequently is used to develop antibiotics. Isolating DNA directly from the soil and growing bacteria from lichens, seaweed, seawater, sea mud, fungi, helps in furthering the search of antibiotics with extended spectrum. Screening for antibiotic production in lab by this DNA sequencing strategy is called metagenomics.

Antimicrobial peptide called plectasin has been isolated from a fungus that acts against MRSA (presently under clinical trials), and this has been developed by genomic sequencing.

Preserving antibiotics for the future

British Columbia initiative "Do all bugs needs drug" targeted healthcare providers, children, teachers and seniors, and brought awareness about antibiotic misuse which led to 13% decrease in antibiotic prescription between 2005 - 2018. Cohesive interaction between medical associations, government and social groups can bring down antibiotic use and abuse by spreading awareness.

What we need to do as community contributors

- Promote appropriate antibiotic use.
- Share knowledge, skills, and training.
- Continue investing in research and surveillance.

Conclusion

Newer and innovative methods need to be developed for recognition and initiation of treatment for these infections. Antibiotic resistance has brought new challenges, but along with it came the opportunities to recognise and develop better ways to overcome them.

Inappropriate use of antibiotics needs to be curtailed. Defensive prescription and using broad spectrum antibiotics should be discouraged. Over-the-counter dispensing, self medication, and unwarranted indication have contributed in many ways to this resistance pattern. Overuse of antibiotics both in outpatient, and inpatients needs to be controlled

and guided by strict policies of hospital dispensing. Rampant misuse in developing countries and their use in veterinary practice have contributed to the continuing emergence of resistance and its spread. Rapid tests to diagnose infections will break the barriers to treat infections effectively and will alongside reduce unnecessary usage. Both of these will go a long way in implementing the guidelines.

These new, innovative technologies need to be mastered over a period of time before being put to therapeutic use. Till then we need to control and judiciously use the currently available antibiotics.

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