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Research Article

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Efficacy of old antibiotics against commonly isolated bacterial isolates in a tertiary care hospital

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ABSTRACT

Centers for Disease Control and Prevention (CDC) and FDA each affirmed that antibiotic-resistant infections and the lack of new drugs to treat them pose a significant public health threat. Increased isolation of MRSA/MR-CoNS infections in both community and hospital setups, followed by emergence of pan-resistance (PDR) and extreme drug resistance (XDR) among Gram negative bacteria has lead to serious concerns among clinicians worldwide. Drastic decrease in the development of new antibiotics in the recent years by nearly 75% aggravates the situation. The global scientific community in search for an alternative solution found that the evaluation and use of Old Antibiotic compounds is the easiest and promising option. Low use of old antibiotic compounds has helped them to remain active against a large number of prevalent bacterial isolates. Compounds like amino glycosides, chloramphenicol, nitrofurantoin, polymixins, trimethoprime-sulphamethoxazole are re-emerging as potential means to combat infections. A total of 8,344 bacterial cultures were isolated from Feb 2013 till June 2014. MIC of colistin, vancomycin, trimethoprime-sulphamethoxazole, tetracycline, gentamicin, amikacin, tobramycin, chloramphenicol, linezolid, clindamycin and nitrofurantoin was tested against 2,314 Gram Positive and 6,030 Gram Negative isolates. MIC values prove that the old antibiotics are an excellent option to treat multi-drug resistance. In order to avoid entering the Post-Antibiotic era use of old antibiotics has to gain momentum in the years to come. The availability of novel molecular modification methods helps to reduce the toxicity and efficacy drawbacks of some of the old antibiotic compounds. More laboratory and clinical studies will lead to revival of many of the old antibiotic compounds.

Key words: Old Antibiotics, MIC, Drug Resistance

INTRODUCTION

Microbial drug resistance is a global problem. It has become nearly impossible to treat infections due to emergence of completely drug resistant micro organisms. Despite the constantly increasing need for new antimicrobial agents, antibiotic drug discovery and development seem to have greatly decelerated in recent years. Presented with the significant problem of advancing antimicrobial resistance, the global scientific community has attempted to find alternative solutions; one of the most promising ones is the evaluation and use of old antibiotic compounds. Due to the low-level use of many of the old antibiotic compounds, these have remained active against a large number of currently prevalent bacterial isolates [1] A number of old antibiotic compounds, such as polymyxins, cotrimoxazole, aminoglycosides and chloramphenicol, are re-emerging as valuable alternatives to treat multi drug resistant strains. In a tertiary care hospital like ours we have also noticed a similar trend. Older antibiotics are more active against MDR, XDR and PDR strains, due to their low level use.

Colistin is a decades-old drug that fell out of favor due to its nephro-toxicity. It remains one of the last-resort antibiotics for multidrug-resistant *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Acinetobacter* spp [2].NDM-1 metallo-β-lactamase multidrug-resistant Enterobacteriaceae have also shown susceptibility to Colistin.

[3]. Regarding MRSA, clindamycin and trimethoprim-sulfamethoxazole (TMP-SMX) are still the oral drugs of choice, even though each drug has its shortcomings. In addition, vancomycin remains the preferred intravenous (IV) antibiotic for serious MRSA infections. Oral amoxicillin and IV ampicillin have emerged as the preferred agents for routine community-acquired pneumonia, as outline by the recent clinical practice guidelines released by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. For the treatment of UTI's a second or third-generation cephalosporin can lead to successful symptom resolution in about 95-98% of children. This is because resistance to ampicillin is between 40% and 50% and resistance to TMP-SMX is reportedly between 20% and 30%. As per the AAP Guidelines published October 1st, other antibiotics, including TMP-SMX, and first generation cephalosporins, may also provide effective therapy. For prophylaxis of UTI, antibiotics that are not used to treat systemic infections, such as nitrofurantoin are the drug of choice. Nitrofurantoin has been used successfully for a long time for the prophylaxis and treatment of acute lower urinary tract infections in adults, children and pregnant women, but the increased emergence of antibiotic resistance has made nitrofurantoin a suitable candidate for the treatment of infections caused by multidrug-resistant pathogens. [4]

The study was carried out over a period of one and a half year to monitor and access the efficacy of a panel of old antibiotic compounds against prevalent micro-organisms in a tertiary care hospital setup.

Table: 1 Antibiotics, their spectrum of activity, mechanism of action and route of administration and toxicities

Antibiotic	Year of Introduction to clinical practice	Spectrum of activity	Mechanism of action	Route of Administration	Toxicities
Amikacin (Aminoglycoside)	1976 by the Bristol-Banyu research institute in Japan.	Most often used for treating severe, hospital-acquired infections with multidrug-resistant Gram-negative bacteria such as *Pseudomonas aeruginosa*, *Acinetobacter*, and *Enterobacter*. *Serratia marcescens* and *Providencia stuartii* are also included in the spectrum. Amikacin can also be used to treat non-tubercular mycobacterial infections and tuberculosis (if caused by sensitive strains) when first-line drugs fail to control the infection.[5-7]	Works by binding to the bacterial 30S ribosomal subunit, leading to misreading of mRNA and leaving the bacterium unable to synthesize proteins vital to its growth.[5-7]	Intravenous Intramuscular Nebulization [6]	Nephrotoxicity Hearing Loss Hypokalemia
Clindamycin (Lincosamide)	By BJ Magerlein, RD Birkenmeyer, and F Kagan on the fifth Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in 1966	It is most effective against infections involving the following types of organisms: Aerobic Gram-positive cocci, including some members of the *Staphylococcus* and *Streptococcus* (e.g. pneumococcus) genera, but **not** *Enterococci*. . Anaerobic, Gram-negative rod-shaped bacteria, including some *Bacteroides*, *Fusobacterium*, and *Prevotella*, although resistance is increasing in *Bacteroides fragilis*.[8,9]	It is a bacterial protein synthesis inhibitor by inhibiting ribosomal translocation,[36] in a similar way to macrolides. It does so by binding to the 50S rRNA of the large bacterial ribosome subunit[8,9]	Oral Capsules Oral suspensions Tropical creams and gels	Diarrhea, pseudomembranous colitis, Nausea, vomiting, abdominal pain or cramps and/or rash. High doses (both intravenous and oral) may cause a metallic taste.
Colistin (Polymyxin E)	Colistin was derived from a flask of fermenting bacteria by a Japanese researcher in 1949	*Acinetobacter* species ($MIC_{90} \leq 2$ mg/L) *P. aeruginosa* ($MIC_{90} \leq 4$ mg/L) *K. pneumoniae* ($MIC_{90} \leq 1$ mg/L) *E. coli* ($MIC_{90} \leq 2$ mg/L) *Enterobacter* spp ($MIC_{50} \leq 1$ mg/L) It also may be active against	Directed against the bacterial cell membrane.	Intravenous Intramuscular Intrathecal	Neurotoxicity Nephrotoxicity[10]

		Salmonella spp ($MIC_{90} \leq$ 1 mg/L), *Shigella* spp ($MIC_{90} \leq$ 0.5 mg/L), *Citrobacter* spp ($MIC_{90} \leq$ 1 mg/L) [10,11]			
Nitrofurantoin	1953	Nitrofurantoin has been shown to have good activity against the following organisms: *E. coli*, *Staph. saprophyticus*, Coagulase negative staphylococci, *Enterococcus faecalis*, *Staphylococcus aureus*, *Streptococcus agalactiae*, *Citrobacter* species, *Klebsiella* species,[12-14]	The drug works by damaging bacterial DNA, since its reduced form is highly reactive. This is made possible by the rapid reduction of nitrofurantoin inside the bacterial cell by flavoproteins (nitrofuran reductase) to multiple reactive intermediates that attack ribosomal proteins, DNA, respiration, pyruvate metabolism and other macromolecules within the cell.[12-14]	Oral	Gastrointestinal: Diarrhea, dyspepsia,abdomial pain, constipation, emesis;Neurologic: Dizziness,drowsiness, amblyopia; Respiratory: Acute pulmonary hypersensitivity reaction; Allergic: Pruritus, urticaria; Dermatologic: Alopecia; Miscellaneous: Fever, chills, malaise
Trimethoprime-sulphamethoxazole	In UK since 1969	Used in the treatment of a variety of bacterial, fungal and protozoal infections[15,16]	Trimethoprim (TMP) selectively inhibits microbial reductases, but its effectiveness is strikingly enhanced when the synthesis of FAH_2 is simultaneously blocked by sulfamethoxazole (SMZ).[15]	Oral	Fever, Nausea, Vomiting, Diarrhea, Weight loss, Rash, Muscle aches, Joint pain, Itch Sore, Hyperkalaemia, Thrombocytopenia [17]
Tetracycline	Discovered as natural products by Benjamin Minge Duggar in 1945 and first prescribed in 1948.	*Escherichia coli:* 1 µg/ml - >128 µg/ml[9,19] *Shigella spp.:* 1 µg/ml - 128 µg/ml[9] Tetracyclines have a broad spectrum of antibiotic action.[18]	Tetracycline binds to the 30S subunit of microbial ribosomes. It inhibits protein synthesis by blocking the attachment of charged aminoacyl-tRNA to the A site on the ribosome. Thus, it prevents introduction of new amino acids to the nascent peptide chain[18]	Oral Intravenous Intramuscular	Dis-colouration of Teeth Fatty Liver Anaphylactic shock Lupus Hepatitis Skin Photosensitivity [18]
Tobramycin	1975 by doctors at Children's Hospital and Medical Center in Seattle, in conjunction with PathoGenesis Corporation	*Pseudomonas aeruginosa* - <0.25 µg/mL - 92 µg/mL *Pseudomonas aeruginosa* (non-mucoid) - 0.5 µg/mL - >512 µg/mL *Pseudomonas aeruginosa* (ATCC 27853) - 0.5 µg/mL - 2 µg/mL[9]	Tobramycin works by binding to a site on the bacterial 30S and 50S ribosome, preventing formation of the 70S complex. As a result, mRNA cannot be translated into protein and cell death ensues.[20]	Intravenous Intramuscular	Nephro-toxicity Ototoxic Loss of equilibrium[21]

Table: 2 MIC Breakpoints of Antibiotics

Antibiotic	(µ/mL)	***S.aureus* ATCC 29213**	***E. faecalis* ATCC 29212**	***E.coli* ATCC25922**	***Kleb. pneumonia* ATCC 700603**	***P. aeruginosa* ATCC 27853**
Amikacin	2-32	0.5->1	0.5-2	<=0.5-4	<=8-16	1-4
Colistin	0.5-4	-	-	-	<=2	<=0.5-1
Nitrofurantoin	16-64	<=16-32	<=16	<=8-16	<=64	-
Trimethoprime-sulphamethoxazole	1/19-4/76	<=0.5/9.5	<=0.5/9.5	<=0.5/9.5	-	8/152->16/304
Tetracycline	0.5-2	<=0.5-1	<=0.5-1	-	-	-
Tobramycin	1-4	<=1	-	0.25-1	<=2-4	0.25-1

EXPERIMENTAL SECTION

Study Design: 8,344 bacterial isolates were collected from cases of clinical infections from a period from Feb 2013 till June 2014. The isolates were recovered from clinical specimens (blood, pus, other body fluid, etc.) at NH Health City, Bangalore, India. Duplicate isolates from clinical samples were excluded.

Antimicrobial Susceptibility Testing

MIC of colistin, vancomycin, trimethoprime-sulphamethoxazole, gentamicin, amikacin, tobramycin, chloramphenicol, linezolid, clindamycin and nitrofurantoin was tested against 2,314 Gram Positive and 6,030 Gram Negative isolates using BD Phoenix 100 system. The MIC breakpoints were determined as per CLSI 2013-2014 guidelines [10][Table 2]

RESULTS

Among the 6,030 Gram negative isolates tested, 2291 isolates were *E.coli* and they showed 100% susceptibility to nitrofurantoin, and 98% susceptibility to gentamicin. Non fermenters like, 546 isolates of *Acinetobacter spp* and 1028 isolates of *Pseudomonas spp* showed 100% susceptibility to colistin. Among 2,314 Gram positive isolates tested all were susceptible to vancomycin. 1666 isolates of *Staphylococcus* spp and 301 isolates of *Enterococci spp* were all susceptible to linezolid. Trimethoprime-sulphamethoxazole was found to be sensitive against 80% of the isolates. We did not report any cases of VRE during the study period. Inducible clindamicin resistance was detected in 40% of *Staphylococcus aureus* strains.

DISCUSSION

The data obtained from our study and other studies worldwide has proved that antibiotics that have been off patients for quite some years are proving effective to tackle emerging drug resistance. Studies have shown that nitrofurantoin is a good antibiotic for the treatment of acute uncomplicated urinary tract infections, with good acceptable tolerability in adults [22].

On the other hand the efficacy of gentamicin lies in the optimal dosage as it has a narrow therapeutic index. Improved guidelines for gentamicin usage can lead to better patient outcomes in treating Gram negative sepsis, including potentially reduced mortality. Reduced, need to escalate to broader spectrum antibiotics, thereby preserving their utility for more complex infective cases. Aminoglycosides are still the treatment of choice for diseases such as brucellosis and plague. Toxicity, along with the discovery of equally potent and less toxic antibiotics, has shelved aminoglycosides the past 30 years. However, this has largely saved them from resistance development. Apart from retaining efficacy, strategies to overcome toxicity, especially once daily administration, has made aminoglycosides a safer choice. Further, plazomicin is a very promising synthetic aminoglycoside that escapes all clinically significant aminoglycoside-modifying enzymes and has completed a clinical Phase II trial. [5-7,23]

Colistin, an antibiotic approved in the late 1950s for the treatment of acute and chronic infections caused by certain sensitive strains of Gram-negative bacteria, is one of these older antibiotics that have regained its efficacy. Our study showed 100% sensitivity to colistin by Gram negative bacteria like *E.coli, Klebsiella* spp, *Pseudomonas aeruginosa* and *Acinetobacter* spp. Studies showed renal function affects colistin levels in the body. This is because the human renal system effectively clears foreign chemicals, such as colistin. Therefore depending upon a patient's renal function the daily dosage of colistin should be adjusted in order to maintain ideal drug concentration [2,10,11].

Co-trimoxazole and ampicillin are both effective in treatment of non-severe pneumonia in children. In 2006, WHO reinforced this suggestion in a guideline document recommending cotrimoxazole prophylaxis for all infants exposed to HIV infection and all children and adults with CD4 cell counts less than 200cells/mm [24]. People who develop severe allergic reactions to cotrimoxazole appear to be at increased risk of rapid disease progression, for reasons that remain unclear [17,24]. Gradually introducing the drug to the body, through dose escalation reduces the chance of an allergic reaction. These desensitization regimens are designed to enable people who are allergic to cotrimoxazole to continue to take the drug without problems.

Meta-analysis studies on the efficacy of linezolid in comparison with glycopeptides (vancomycin and teicoplanin) for the treatment of *Staphylococcus aureus* infections shows that Linezolid was slightly more effective than glycopeptides in the intent-to-treat population (odds ratio [OR], 1.05; 95% confidence interval [CI], 1.01–1.10), was more effective in clinically assessed patients (OR 95% CI: 1.38, 1.17–1.64) and in all microbiologically assessed patients (OR 95% CI: 1.38, 1.15–1.65). However, when physicians choose to use linezolid, risk of hematological and gastrointestinal events should be taken into account according to the characteristics of the specific patient populations. [25]

Clindamycin may be assuming a more significant role in pediatric infectious disease therapy, as it maintains relatively good activity toward several important pathogens, such as *Streptococcus pneumoniae* and *Staphylococcus aureus*. It is important for clinicians to assess the potential for community-acquired MRSA to express inducible resistance to clindamycin. This may occur in strains resistant to erythromycin, expressing a gene (erythromycin resistance methylase gene) that allows resistance to clindamycin to be induced during therapy.[8,9] The Alexander Project evaluated antibiotic susceptibilities to more than 8,000 *S. pneumoniae* isolates cultured from adults worldwide with community-acquired respiratory tract infections in 1998-2000. Rates of resistance displayed included 18.2% for penicillin, 0.6% for ceftriaxone, 21.9% for cefdinir, 24.4% for azithromycin and 13.9% for clindamycin. [26]

CONCLUSION

Optimised clinical use of off-patent antibiotics, along with adapting breakpoints, enriching treatment guidelines, and implications for regulatory issues, specially indications and dosage regimens, play a key contribution to preserving the efficacy of these essential drugs in an era of escalating multi-drug resistance.

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