RESUSCITATING AND REPURPOSING OLDER ANTIBIOTICS FOR COMBATING INFECTIONS OF MDR BACTERIA

Abstract

The increased occurrence of community and nosocomial infections caused by multiple drug-resistant bacteria has become a serious challenge for effective chemotherapy. Moreover, this alarming state of drug resistance evolution has not been compensated by the development of novel antibacterial agents. The emergence of resistance in newer antibiotics is an issue of grave concern. In this context, old antibiotics are being revisited or revived and their rational usage can make them an alternative remedy in combating the infections of MDR bacteria. The therapeutic armamentarium of antibiotics would also be optimized by preserving novel antibacterial drugs for future application. Furthermore, at the time of these drug approval pharmacokinetic and pharmacodynamic data were unknown and there was difficulty in dosing recommendations and dose-finding for their optimal usage in health care settings. In this chapter, an attempt has been made to provide a brief overview of the methodology of resistance prediction as well as the challenges associated with rejuvenating the older antibiotics, the need for resuscitating older antibiotics for hospital and community-acquired infections, and the strategies to redevelop these drugs including the involvement of standard methods, incorporating knowledge into regulatory frameworks, dose justification and optimization and filling the knowledge gaps from the research bench to bedside.

Authors

Shirjeel Ahmad Siddiqui
Department of Agricultural Microbiology
Faculty of Agricultural Sciences
Aligarh Muslim University
Aligarh, Uttar Pradesh, India

Samreen
Department of Agricultural Microbiology
Faculty of Agricultural Sciences
Aligarh Muslim University
Aligarh, Uttar Pradesh, India
samreenfatima7860@gmail.com

Meenu Maheshwari
Department of Agricultural Microbiology
Faculty of Agricultural Sciences
Aligarh Muslim University
Aligarh, Uttar Pradesh, India

Asghar Ali
Department of Agricultural Microbiology
Faculty of Agricultural Sciences
Aligarh Muslim University
Aligarh, Uttar Pradesh, India

Iqbal Ahmad
Department of Agricultural Microbiology
Faculty of Agricultural Sciences
Aligarh Muslim University
Aligarh, Uttar Pradesh, India

I. INTRODUCTION

The infections caused by multi-drug resistant (MDR) bacterial pathogens have become a serious threat globally in terms of public health perspective challenging our armamentarium of antibiotics. The development of newer antibiotics is getting difficult due to various constraints both in academia and in the industries (Zorzet, 2014; Laterre and Francois, 2015; Anand et al; 2022). Therefore, novel approaches targeting resistance mechanisms are urgently needed for combating MDR problems (2008; Hughes and Karlen, 2014). For the search of effective antimicrobials *denovo* drug discovery and repurposing or reviving of drugs both have been used. Although the problem of antibiotic resistance is a global threat, its solution is difficult and varies regionally. Reviving the older or forgotten antibiotics being cheaper and broad spectrum could be beneficial over the newly discovered costly antibiotics which should be preserved for the near future (Theuretzbacher et al., 2015). It has been observed that the pathogenic bacteria are going to be resistant to newly developed antibiotics probably due to the pre-existence of resistance genes in the bacterial population. Therefore, the antimicrobial resistance at present time is increasing at an alarming rate whereas the rate of antibiotic development is being decreased (Le and Rakonjac., 2021; Ahmad et al., 2022). This ongoing challenge can be tackled by using multifaceted approaches like improved surveillance of resistance rates and antibiotic consumption, retardation of healthcare-associated infections their transmission and environmental dissemination, reducing the veterinary and clinical mis usage of antibiotics, and rapid diagnosis (Ahmad et al., 2008; Pulcini et al., 2012). Based on their spectrum of coverage the older antibiotics when compared with today's commonly used antibiotics sparse data on dose regimens for various types of infections are obtained and considered less effective in practice guidelines. Therefore, their safety and efficacy must be evaluated for optimizing their usage in chemotherapy.

II. WHY THERE IS NEED OF OLD ANTIBIOTICS TO BE REDEVELOPED / REVIVED?

The niche for early antibiotics covers both the community and hospitals. Currently and in the upcoming future three kinds of infections caused by MDR or XDR pathogens will be difficult to treat). These are:

1. Community acquired infections by ESßL producing Enterobacteria
2. Hospital-acquired infections by ESßL producing Enterobacteria
3. Severe-hospital-acquired infections by carbapenem resistant gram negative bacilli (Theuretzbacher et al., 2015)

The two most common ESßL producing enterobacterial species Escherichia coli and Klebsiella pneumonia are the causative agents of community acquired urinary tract infections (UTIs). In order to avoid broad spectrum Beta lactams and increased hospitalization for intravenous antibiotic administrations the old antibiottics that are predominantly being used for the treatment of UTIs are fosfomycine or mecillinam and nitrofurontoin are considered as relevant options at present time (Tasbakan et al., 2013; Giske et al., 2015). The mortality associated with carbapenem resistant gram negative bacteria (CR-GNB) is about 30-40% worldwide (Martin et al., 2018). Although the new antibiotics for such infections are being

approving or in pipeline. A 60 year old antibiotic, polymyxin has been considered as last line of treatment to such infections over the last decades. Their spectrum of action is not only limited to carbapenemase producing or non carbapenemase producing gram negative bacilli but also towards carbapenem resistant Pseudomonas and Acinetobacter spp. In high antibiotic consumption hospitals carbapenem resistant Acinetobacter spp have been found susceptible towards cephalosporins and minocyclline that spare the polymyxin treatment and thus delaying the emergence of resistance towards it. Various factors responsible for the safe and effective use of polymyxins ,knowledge gap and set of key objectives for the future priority research associated to this drug have been developed (Nation et al., 2015; Giacobbe et al., 2015).

Reviving of old antibiotics is considered as a immediate solution to the newly developing costly antibiotics that should reserved for the near future. For the international availability of most important and relevant antibiotic candidates must be prioritized.

III. RESISTANCE PREDICTION TOWARDS OLD AND NEW ANTIBIOTICS

Evolution of bacteria towards resistance in response to prolonged exposure of drugs is unstoppable consequently the problem of drug resistance follows the introduction of new antibiotics that ultimately leads to emergence of multi drug , pan drug or extensively drug resistant pathogens. There is urgent need to identify druggable targets by means of experimental methods and strategies having potential for inhibiting evolution of resistance (Mehta et al., 2018). Emergence can result either from mutation in housekeeping regulatory or structural genes or through acquiring foreign genetic elements. Dissemination of resistance genes can occur at bacterial own level either clonal spread , plasmid or through replicative transposes. The spread of resistance is closely associated with extensive application of drugs emphasizing the prudent use of these drugs. However based on deeper understanding of physiology of bacterial resistance towards antibiotics much more progress has to be needed in methods and techniques for in vitro elucidation and detection of resistance. The progress in resistance prediction in turn will be helpful in delaying the onsets of resistance i.e dissemination.

During the drug development process of new antibacterial or revival of old antibiotics both the pharmaceuticals and academic researchers have major concern for the prediction of the risk of resistance. The development of risk assessment methods and also mutational resistance at a low rate in vitro are being increasing for the new hits and leads (Ling et al., 2015). The first method for the prediction of mutational resistance in the laboratory is serial passage experiments in which the increasing concentrations of antibiotics determines the appearance of resistant mutants and also predict that how high level of resistance they have. Second method is the mutant prevention concentration that determines at which increasing dose of antibiotics plates with plated same of amount of cells (usually 1010) have no resistant mutants appearance. Both of the above methods are used to predict mutation rates but they actually give a qualitative idea based on serial passage or mutant prevention concentration (threshold values. Another method for the determination of mutation rates is Luria-Delbruck Fluctuation assay where different independent cultures are fully grown and the bacterial cells are plated on increasing concentration of antibiotics to determine the appearance of mutation rates. The advantage of this method is that it is based on the

population size of the bacteria and also calculated probability of resistance emergence and fixation of resistant mutants per cell per generation (Dong et al., 1999; Drlica et al., 2003).

Although the in vitro measurements of mutational resistance have certain limitations since one of the major resistance mechanism seen in MDR pathogens is the transfer of resistance genes through horizontal gene transfer (HGT) (Sommer et al., 2017). These resistance genes are the part of resistome (collection of all resistance genes including the precursor genes) of bacteria encode certain proteins that can target the drug or antimicrobial and are able to transferred in readymade form to other bacteria (Perry et al., 2014). For example the transfer of plasmid encoded qnrA gene from Shewanella algae to the members of Enterobacteriaceae, likewise the widespread and problematic group of genes i.e CTX-M are imported in different species of Kluyvera of environmental origin (Humeniuk et al., 2001; Poirel et al., 2005). Another relevant example is the occurrence of tetX gene in the bacteria Bacteroides fraglis is found to be proginator of the tetX gene. A study from Sierra Leone hospital revealed the occurrence of tetX gene in 21% of Gram-negative pathogens indicating the transmission of resistance genes into human pathogens from the bacteria of other origin (Leski et al., 2013). Therefore, resistance prediction will provide useful information to use antibiotics as specific purpose or recommended for common infection control.

IV. CHALLENGES FOR THE REVIVAL OF OLD ANTIBIOTICS

From a long time antibiotics have easy access in most of the countries of the world, dosing regimens were not optimized through indication and their registration did not require any relevant efficacy in comparative studies as well. Lack of regulatory approval to redevelop or restructure the drugs, no incentives to the companies as they are exiting from antibacterial space, no information about dose finding process or dose justification and poor communication between academia and industry are some of the challenges for reviving older antibiotics. In 1995 different antibiotics were approved by national approving authorities generating divergent product knowledge across the Europe (Podolsky ., 2010). As a result of signing of Kefauver-Harris amendments in to a law, FDA was required that newly synthesized drugs are to be passed through adequate and well controlled clinical investigations by the trained and experienced scientific expertise to evaluate the safety and efficacy of newly involved drug (Theuretzbacher et al., 2014). Since 1995 there was continuous evaluation of national referrals and centrally authorized drugs for their consistency across the European medicine member states by European agencies, actually it was limited to the newly synthesizing drugs not to previously approved. From a long ago antibiotics are considered well therapeutic agent in combating infections but, in addition to increased understanding of the relationships between dosing regimens, exposure and response. This is mainly the case of old antibiotics that have been revolutionalized because of the development of resistance and the consequent the need for potentially active chemotherapeutic agents. Since the registration of older antibiotics approx six to seven decades ago, no new information have been updated and sometimes their original information becomes unjustified in many cases. Although the new formulations have been developed from them generating the significant pharmacokinetic (PK) profiles without providing any updated product information (Kotwani et al., 2012; Murni et al., 2015). Some of the challenges in rejuvenating the older drugs to come in existence are listed here.

1. **Pharmacokinetic and Pharmacodyanamic relationships (PK/PD):** Now a day's both national and international regulatory agencies have been accumulating the requirements to represent he increased demands for antibiotics that are potentially active against problematic species of multi drug resistant bacteria. The guidance from these authorities provides recommendations for the dose rationales on the basis of PK/PD studies, since they provide a universal framework for the exposure-outcome relationships including the measurement toxicity or safety efficacy and emergence of resistance (Mouton et al., 2012). For determining optimal dosage or suitability for a particular indication, various factors of the exposure-outcome relationship should be considered like-

   - The MIC distribution of organism of interest\
   - The PK profiling with different doses among various population
   - PD target and what actually exposure-response relationship

   Most commonly the PD properties are studied in different species like in dogs or the rodents (Ambrose et al., 2010). Then phase I studies are carried out in humans on the basis of relevant dosage and its outcome to the particular effect. Further phase 2 and phase 3 trial studies are carried out for the evidence of effective and safe exposure response relationship. In general PK/PD knowledge gaps are considered in current research (Sime et al., 2015; Muller etal., 2015). At present time colistin is gaining attention, its dosing recommendation varied in different countries of the world and adequate studies were not done. In one case it was observer that 3-6 million international units9MIU0 colistimethate per day did not have sufficient colistin levels. In addition, the time needed to reach the steady state was also not in acceptable range suggesting the requirement for a loading dose strategy in severely compromised patients (Plachourus et al., 2009). In another case contradictory results were obtained with much higher compared to the expected levels of colistinmathanesulphonate dosing with quick access to the steady state further challenging the requirement for loading dose (Gregoire et al., 2014). Such huge and unexplained variations for the colistin concentration suggesting the need for its therapeutic drug monitoring (TDM) among the patients. Patients that are taking renal replacement therapy through the means of continuous haemodialysis, the high extent removal needs the larger doses as compared to patients having the normal renal functions (EMA., 2014). To standardise the use of colistin worldwide, the studies carried in the last decades resulted in formal changes in dose recommendations.

   Again, much more advancement have been done with colistin recommendations. Recent reports suggest that there is no significant difference in low(4 MIU/day) than high (9MIU/day) colistin doses in terms of mortality (Benattar et al., 2016). Therefore the dosing assessment for most older antibiotics are vastly missing and inadequate. Similar kind of advancements are needed in terms of PK/PD studies of other existing older antibiotics.

2. **Lack of knowledge in manifesting the evidence of old antibiotics:** There are significant differences in knowledge gaps for most of the old antibiotics. The optimal dosing recommendations of recently revived older antibiotics is unknown. Firstly, this can be easily underscored by the observation that the dosing regimens of the older antibiotics covers the large spectrum of doses and dose frequencies. Secondly the clinical indications

listed in product information are usually extended beyond the appropriate usage of recognised drug. Such kind of unsuitable indications results in inadequate treatment options as well as in appropriate doses for the patient care (Asante et al., 2017). At present time the needs for the regulatory approval of the antibiotics becoming more stringent and the methods that are required for the updated product information or defining the drug characteristics are either insufficient or in non existence (Zayyad et al., 2017). Therefore the optimal usage and how older antibiotics perform their function is not consistently translated into the official guidelines of product characteristics summary of an older drug. Additionally there is no incentivization for the companies to make continuous development of an antimicrobial drug once it is approved, even if there is critical need beyond the commercial interest.

V. OPTIMIZING THE USAGE OF REVIVED ANTIBIOTICS

Due to increasing evidence of antibiotic resistance and few treatment options for combating infections caused by drug resistant bacteria, application of older drugs that exhibit activity against MDR becomes much more fascinating. Some of the older antibiotics that are currently used include fosfomycin, mecillinam, temocilline, nitrofurontoin and colistin for MDR gram negative bacteria but these antibiotics lack regulatory approval according to current standards. Some of the recently used older antibiotics that in combating MDR pathogens are listed in table:1.

Due to increasing use of old antibiotics several publicly funded initiatives have been started that generates essential information regarding to them, maximise their potential and ensure that we do not lose these important drugs quickly to resistance. Recently in ESCMID conference discussion have been made on the current issues for creating a structured process in potential use of older drugs. Some of them are listed here:

1. **Minimizing evolution of resistance:** Number of factors determine the risk of resistance development to an antibiotic, instead the individual drug exposure at the site of infection. The detailed knowledge or understanding of the risk associated with old antibiotics might support their improved usage and also which antibiotic to invest in.   In a study of Anderson (2015) who suggested different methods for the prediction of emergence of antibiotic resistance like metagenomic analyses complex modelling, PK/PD studies and fitness assessments to predict resistance emergence. The emerging threat of antibiotic resistance can be minimized by the concerted efforts of all the members of a society for making continued efficiency of antimicrobial drugs. The problem can be reduced by by following up antimicrobial stewardship programs (ASPs), diagnostic testings, clinical response, antimicrobial susceptibility testing (AST) as well as development new with novel mode of action antibiotics

2. **Generating high quality clinical data:** At the time when antibiotics were going to be firstly approved there was lack of guidance on the minimal evidence-base that is needed for the safety and efficacy of dug before it entered in clinical settings. At that time there was no effective recommendations on the reporting and designing of randomized control trials (RCTs). However at present time, these kind of revived drugs are now considered for indications instead for which purpose they were originally developed and utilized.

Like the case of trimethoprim-sulfamethoxazole is recommended for the treatment of MRSA and fosfomycin for combating severe infections associated with MDR gram negative bacteria (Pontkis et al., 2014; Paul et al., 2015). Hence, evidences for the clinical safety and efficacy are required to be generated for the indications for which the old antibiotics in current time intended. In RCTs ,there must examination of combinational regimens including older antibiotics (Yahav et al., 2012). Pharma companies of generic antibiotics are not taking incentives to generate such evidence, so public funding is equally needed. Laterre and Francois (2015) represented a brief overview on advantages and limitations of industry sponsored and academic randomized control trials ansd strongly point out that collaboration between them can make improvement in both types of research.

3. **International availability of drugs:** In a survey of antibiotic availability only few of the revived antibiotics are licensed in all countries. Like in Europe, overall two third of 33 antibiotics examined were found in fewer than half of the countries. This was especially associated with revived antibacterial drugs (Pulcini et al., 2012). It is totally based on the public's interest to encourage the production, regulatory approval and distribution of high quality revived drugs to make sure uniform global availably of drug.

4. **Generating universal drug susceptibly data:** In monitoring resistance trends peoples generally rely on regional or hospital- specific information. Selective testing of drug resistant organisms in specific settings or individual hospitals generates susceptibly data that is biased towards resistance. The reports of increasing resistance rates of colistin among the members of carbapenemase producing Enterobacteriaceae exemplified the need for the incorporating the older antibiotics into the panels of antibiotic resistance surveillance system (Capone et al., 2013).

5. **Updating drug information:** Sometimes in number of cases it happens that the drugs that are approved decades ago, their information that resembles from the original data become simply wrong or insufficient. This is particularly the case of dosing recommendations and PK data. Like the drugs that are approved through national regulatory agencies have some differences regarding in product information as well as dosing recommendations (Theuretzbacher et al., 2014). In a current scenario, there is almost none of the regulatory pathways have been established that generate structured process for the drug re assessment and new updates of the product regarding older antibiotics (Theuretzbacher et al., 2015). Accurate and updated product information is the prerequisite need for incorporating the advance knowledge in guidelines and treatment options.

VI. CONCLUSION AND FUTURE PERSPECTIVE

There is an urgent need for the redevelopment of the older drugs specially the revived ones by means of structures process and collaborative work that looks like the development of new antimicrobial drug (Falagas et al., 2008). Both clinicians and academia are performing their work in an uncoordinated manner filling some knowledge gaps as well as there is no incentives provided to pharma companies or the industries to invest in redevelopment process of older antibiotics. In particular strategies are urgently needed that enhance the structured

and coordinated redevelopment process associated with exposure-outcome relationships, appropriate dosing regimens and re-evaluation. In light of dryness of pipeline of the newer antibacterial drugs and high cost associated with their development, it is often important to prevent the decisions of new product development or the reintroduction of revived antibiotics should be based on experimental data with regard to predicting the risk associated from resistance emergence (Cheng et al., 2016). If we don't do this, we erroneously discard the older antibiotics with promising activity by means of assuming that high in vitro mutations towards resistance leads to fast resistance development, but contrary to it, we might also make much more expenditure in new drug development we mistakenly generate slow mutation rates that results in slow resistance development. Therefore, without a systemic methodology to redevelop the old antibiotics and rigorously testing them in health care settings with the patients, we take further risk of increasing multidrug resistance. In a current situation, the challenge is to search much needed resources like funds and regulatory agencies, time and people to fast track the optimization of these potentially active life saving drugs and making them available to patients in critical medical care. In structured redevelopment process of antibiotic there is immediate need of public funds, international coordination, multidisciplinary communication and methods that provide recruitment of severely ill patients infected by drug resistant bacteria.

Table 1: Some of the Revived Old Antibiotics against Multidrug Resistant Bacteria

Old Antibiotic	Year of first Publication	Recently Active Against	References
Chloramphenicol	1947	*Chlamydia pecorum*	Black et al., 2015
Colistin	1947	*P. aeruginosa* associated with cystic fibrosis NDM-1-producing *K. pneumoniae* Gram negative bacteria (*P. aeruginosa*, *E. coli* and *K. pneumoniae)*	Pompilio et al., 2015 Lagerbäck et al., 2016 Dosler et al., 2016
Fosfomycin	1969	Infections caused by gram-negative and gram-positive bacteria ESβL producing *E. coli* related urinary tract infections	Falagas et al., 2008; Keating et al., 2013 Zykov et al., 2016
Mecillinam	1975	ESβL producing *E. coli* and *K. pneumoniae* related urinary tract infections	Titelman et al., 2012; Zykov et al., 2016
Minocycline	1966	Carbapenem-resistant *A. baumannii* *A. baumannii* *S. aureus* Carbapenemase (KPC)-producing *Enterobacteriaceae* isolates	Pei et al., 2012; Castanheira et al., 2014 Guerra et al., 2017 Chen et al., 2017; Wentao et al., 2018
Nitrofurantoin	1954	Multidrug-resistant urinary *E. coli* ESβL producing *E. coli* related urinary tract infections	Sanchez et al., 2014; Tasbakan et al., 2012; Zykov et al., 2016
Temocillin	1988	Urinary tract infections ESβL	Livermore and

		producing *E. coli* related urinary tract infections	Tulkens, 2008 Zykov et al., 2016
Trimethoprim-sulfamethoxazole	1967	Carbapenem-resistant *A. baumannii* Carbapenem-Resistant *Klebsiella pneumoniae*	Nepka et al., 2016 Su et al., 2018

Table 2: Problematic Group of MDR Bacteria Which Requires Revival of Old Antibiotics (Baucher et al., 2009; Van Duin and Paterson, 2016)

Problematic MDR group	Types of Colonization	Current susceptibility towards antibiotics	References
Methicilline Resistant *Staphylococcus aureus* (MRSA)	Skin infection, blood stream infection, osteomylitis, Endocarditis	Ceftobiprol, Ceftaroline, ME1036, tigecycline	Khan et al., 2018, Isnard et al., 2018, FDA, 2008
Vancomycin resistant Enterococci (VRE)	Blood stream infectiom (BSI), urinary tract infection (UTI), heart valves	Linezolid, daptomycine, tigecycline	Cannon et al., 2006, Erlandson et al., 2008, Frakking et al., 2018
ESßL producing *E.coli* and *Klebsiella species*	Community acquired urinary tract infections, BSI	Doripenem, Pivmecillinam,	Dewaele et al., 2018, Woerther et al., 2018, Dewar et al., 2013
MDR *Acinetobacter baumanii*	BSI and burn infections, native or prosthetic valve endocarditis, ocular infections, dominating respiratory infections, sepsis	Tigecycline, daptomycin+Vancomycin	Schafer et al., 2007, Claeys et al., 2014, Irvem, 2018
MDR *Pseudomonas aeruginosa*	Biofilm associated infections,GI tract, upper respiratory tract,Cystic fibrosis	Imipenem, Amikacin, Ceftazidime-avibactam, Combination therapy (Imipenem/doripenem+Colistin)	Carmeli et al., 2016, Tangden, 2014
Carbapenemase producing Enterobacteriaceae	Both health care and community settings, blood stream infection, wound infection, pneumonia and	polymixinB+doripenem +rifampicin, ceftazidime-avibactam, Meropenem and vaborbactam, Imipenem and relebactam(currently in phase 3 trial)	Urban et al., 2010, Zavascki et al., 2013, Paul et al., 2014, Nelson et al., 2015, Jorgensen et al., 2018

	UTI		

REFERENCES

[1]   Ahmad I, Aqil F, editors. New strategies combating bacterial infection. John Wiley & Sons; 2008.

[2]   Ambrose PG, Bhavnani SM, Rubino CM, Louie A, Gumbo T, Forrest A, Drusano GL. Pharmacokinetics-pharmacodynamics of antimicrobial therapy: it's not just for mice anymore. Clinical Infectious Diseases. 2007, 44(1):79-86.

[3]   Andersson DI. Improving predictions of the risk of resistance development against new and old antibiotics. Clinical Microbiology and Infection. 2015, 21(10):894-8.

[4]   Asante KP, Boamah EA, Abdulai MA, Buabeng KO, Mahama E, Dzabeng F, Gavor E, Annan EA, Owusu-Agyei S, Gyansa-Lutterodt M. Knowledge of antibiotic resistance and antibiotic prescription practices among prescribers in the Brong Ahafo Region of Ghana; a cross-sectional study. BMC health services research. 2017 Dec;17(1):422.

[5]   Benattar YD, Omar M, Zusman O, Yahav D, Zak-Doron Y, Altunin S, Elbaz M, Daitch V, Granot M, Leibovici L, Paul M. The effectiveness and safety of high-dose colistin: prospective cohort study. Clinical Infectious Diseases. 2016, :ciw684.

[6]   Black LA, Higgins DP, Govendir M. In vitro activity of chloramphenicol, florfenicol and enrofloxacin against Chlamydia pecorum isolated from koalas (Phascolarctoscinereus). Australian veterinary journal. 2015, 93(11):420-3.

[7]   Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, Scheld M, Spellberg B, Bartlett J. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clinical infectious diseases. 2009, 48(1):1-2.

[8]   Cannon JP, Pachucki CT, Aneziokoro CO, Lentino JR. The effectiveness and safety of oral linezolid as primary or secondary treatment of bloodstream infections: a retrospective observational analysis. Infectious Diseases in Clinical Practice. 2006, 14(4):221-6.

[9]   Carmeli Y, Armstrong J, Laud PJ, Newell P, Stone G, Wardman A, Gasink LB. Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and Pseudomonas aeruginosa complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study. The Lancet Infectious Diseases. 2016, 16(6):661-73.

[10] Castanheira M, Mendes RE, Jones RN. Update on Acinetobacter species: mechanisms of antimicrobial resistance and contemporary in vitro activity of minocycline and other treatment options. Clinical Infectious Diseases. 2014, 59(suppl_6):S367-73.

[11] Chen A, Smith KP, Whitfield BA, Zucchi PC, Lasco TM, Bias TE, Kirby JE, Hirsch EB. Activity of minocycline against Klebsiella pneumoniae carbapenemase (KPC)-producing Enterobacteriaceae clinical isolates, with comparison to doxycycline and tigecycline. Diagnostic microbiology and infectious disease. 2017, 88(4):365-7.

[12] Cheng G, Dai M, Ahmed S, Hao H, Wang X, Yuan Z. Antimicrobial drugs in fighting against antimicrobial resistance. Frontiers in microbiology. 2016 Apr 8;7:470.

[13] Claeys KC, Fiorvento AD, Rybak MJ. A review of novel combinations of colistin and lipopeptide or glycopeptide antibiotics for the treatment of multidrug-resistant Acinetobacter baumannii. Infectious diseases and therapy. 2014, 3(2):69-81.

[14] De Waele JJ, Akova M, Antonelli M, Canton R, Carlet J, De Backer D, Dimopoulos G, Garnacho-Montero J, Kesecioglu J, Lipman J, Mer M. Antimicrobial resistance and antibiotic stewardship programs in the ICU: insistence and persistence in the fight against resistance. A position statement from ESICM/ESCMID/WAAAR round table on multi-drug resistance. Intensive care medicine. 2018, 44(2):189-96.

[15] Dewar S, Reed LC, Koerner RJ. Emerging clinical role of pivmecillinam in the treatment of urinary tract infection in the context of multidrug-resistant bacteria. Journal of Antimicrobial Chemotherapy. 2013, 69(2):303-8.

[16] Dong Y, Zhao X, Domagala J, Drlica K. Effect of fluoroquinolone concentration on selection of resistant mutants of Mycobacterium bovis BCG andStaphylococcus aureus. Antimicrobial agents and chemotherapy. 1999, 43(7):1756-8.

[17] Dosler S, Karaaslan E, AlevGerceker A. Antibacterial and anti-biofilm activities of melittin and colistin, alone and in combination with antibiotics against Gram-negative bacteria. Journal of Chemotherapy. 2016, 28(2):95-103.

[18] Drlica K. The mutant selection window and antimicrobial resistance. Journal of Antimicrobial Chemotherapy. 2003, 52(1):11-7.

[19] Erlandson KM, Sun J, Iwen PC, Rupp ME. Impact of the more-potent antibiotics quinupristin-dalfopristin and linezolid on outcome measure of patients with vancomycin-resistant Enterococcus bacteremia. Clinical infectious diseases. 2008, 46(1):30-6.

[20] Falagas ME, Giannopoulou KP, Kokolakis GN, Rafailidis PI. Fosfomycin: use beyond urinary tract and gastrointestinal infections. Clinical infectious diseases. 2008, 46(7):1069-77.

[21] Falagas ME, Grammatikos AP, Michalopoulos A. Potential of old-generation antibiotics to address current need for new antibiotics. Expert review of anti-infective therapy. 2008 Oct 1;6(5):593-600.

[22] FDA issues approvable letter for ceftobiprole, a new anti-MRSA broad-spectrum antibiotic. 18 March 2008 eds , 2009 Basel, Switzerland Basilea Pharmaceutica

[23] Frakking FN, Bril WS, Sinnige JC, van't Klooster JE, de Jong BA, van Hannen EJ, Tersmette M. Recommendations for the successful control of a large outbreak of vancomycin-resistant Enterococcus faecium in a non-endemic hospital setting. Journal of Hospital Infection. 2018.

[24] Giacobbe DR, Del Bono V, Trecarichi EM, De Rosa FG, Giannella M, Bassetti M, Bartoloni A, Losito AR, Corcione S, Bartoletti M, Mantengoli E. Risk factors for bloodstream infections due to colistin-resistant KPC-producing Klebsiella pneumoniae: results from a multicenter case–control–control study. Clinical Microbiology and Infection. 2015, 21(12):1106-e1.

[25] Grégoire N, Mimoz O, Mégarbane B, Comets E, Chatelier D, Lasocki S, Gauzit R, Balayn D, Gobin P, Marchand S, Couet W. New colistin population pharmacokinetic data in critically ill patients suggesting an alternative loading dose rational. Antimicrobial agents and chemotherapy. 2014, AAC-03508.

[26] Guerra AD, Rose WE, Hematti P, Kao WJ. Minocycline modulates NFκB phosphorylation and enhances antimicrobial activity against Staphylococcus aureus in mesenchymal stromal/stem cells. Stem cell research & therapy. 2017, 8(1):171.

[27] Hughes D, Karlén A. Discovery and preclinical development of new antibiotics. Upsala journal of medical sciences. 2014 May 1;119(2):162-9.

[28] Humeniuk C, Arlet G, Gautier V, Grimont P, Labia R, Philippon A. β-Lactamases of Kluyvera ascorbata, probable progenitors of some plasmid-encoded CTX-M types. Antimicrobial agents and chemotherapy. 2002, 46(9):3045-9.

[29] Irvem A. Colistin-daptomycin, colistin-linezolid, colistin-vancomycin combination effects on colistin in multi-resistant acinetobacter baumannii strains. MSD.2018, 5(2):124-9

[30] Isnard C, Dhalluin A, Malandain D, Bruey Q, Auzou M, Michon J, Giard JC, Guérin F, Cattoir V. In vitro activity of novel anti-MRSA comparator agents against staphylococci involved in prosthetic joint infections. Journal of global antimicrobial resistance. 2018 Feb.

[31] Jorgensen SC, Rybak MJ. Meropenem and Vaborbactam: Stepping up the Battle against Carbapenem- resistant Enterobacteriaceae. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2018, (4):444-61.

[32] Keating GM. Fosfomycintrometamol: a review of its use as a single-dose oral treatment for patients with acute lower urinary tract infections and pregnant women with asymptomatic bacteriuria. Drugs. 2013, 73(17):1951-66.

[33] Khan A, Wilson B, Gould IM. Current and future treatment options for community-associated MRSA infection. Expert opinion on pharmacotherapy. 2018, 19(5):457-70.

[34] Kotwani A, Wattal C, Joshi PC, Holloway K. Irrational use of antibiotics and role of the pharmacist: an insight from a qualitative study in New Delhi, India. Journal of clinical pharmacy and therapeutics. 2012, 37(3):308-12.

[35] Lagerbäck P, Khine WW, Giske CG, Tängdén T. Evaluation of antibacterial activities of colistin, rifampicin and meropenem combinations against NDM-1-producing Klebsiella pneumoniae in 24 h in vitro time–kill experiments. Journal of Antimicrobial Chemotherapy. 2016, 71(8):2321-5.

[36] Laterre PF, François B. Strengths and limitations of industry vs. academic randomized controlled trials. Clinical Microbiology and Infection. 2015, 21(10):906-9.

[37] Leski TA, Bangura U, Jimmy DH, Ansumana R, Lizewski SE, Stenger DA, Taitt CR, Vora GJ. Multidrug-resistant tet (X)-containing hospital isolates in Sierra Leone. International journal of antimicrobial agents. 2013, 42(1):83-6.

[38] Ling LL, Schneider T, Peoples AJ, Spoering AL, Engels I, Conlon BP, Mueller A, Schäberle TF, Hughes DE, Epstein S, Jones M. A new antibiotic kills pathogens without detectable resistance. Nature. 2015, 517(7535):455.

[39] Livermore DM, Tulkens PM. Temocillin revived. Journal of Antimicrobial Chemotherapy. 2008, 63(2):243-5.

[40] Martin A, Fahrbach K, Zhao Q, Lodise T. Association Between Carbapenem Resistance and Mortality Among Adult, Hospitalized Patients With Serious Infections Due to Enterobacteriaceae: Results of a Systematic Literature Review and Meta-analysis. InOpen forum infectious diseases 2018, (Vol. 5, No. 7, p. ofy150). US: Oxford University Press.

[41] Mehta HH, Prater AG, Shamoo Y. Using experimental evolution to identify druggable targets that could inhibit the evolution of antimicrobial resistance. The Journal of antibiotics. 2018, 71(2):279.

[42] Mouton JW. Setting clinical MIC breakpoints from a PK/PD point of view: it is the dose that matters. InFundamentals of Antimicrobial Pharmacokinetics and Pharmacodynamics 2014, 45-61. Springer, New York, NY.

[43] Muller AE, Theuretzbacher U, Mouton JW. Use of old antibiotics now and in the future from a pharmacokinetic/pharmacodynamic perspective. Clinical Microbiology and Infection. 2015, 21(10):881-5.

[44] Murni IK, Duke T, Kinney S, Daley AJ, Soenarto Y. Reducing hospital-acquired infections and improving the rational use of antibiotics in a developing country: an effectiveness study. Archives of disease in childhood. 2014, archdischild-2014.

[45] Nation RL, Li J, Cars O, Couet W, Dudley MN, Kaye KS, Mouton JW, Paterson DL, Tam VH, Theuretzbacher U, Tsuji BT. Framework for optimisation of the clinical use of colistin and polymyxin B: the Prato polymyxin consensus. The Lancet infectious diseases. 2015, 15(2):225-34.

[46] Nelson BC, Eiras DP, Gomez-Simmonds A, Loo AS, Satlin MJ, Jenkins SG, Whittier S, Calfee DP, Furuya EY, Kubin CJ. Clinical outcomes associated with polymyxin B dose in patients with bloodstream infections due to carbapenem-resistant Gram-negative rods. Antimicrobial agents and chemotherapy. 2015, AAC-00844.

[47] Nepka M, Perivolioti E, Kraniotaki E, Politi L, Tsakris A, Pournaras S. In vitro bactericidal activity of trimethoprim-sulfamethoxazole alone and in combination with colistin, against

carbapenem-resistant Acinetobacterbaumannii clinical isolates. Antimicrobial agents and chemotherapy. 2016, AAC-01082.

[48] Paul M, Bishara J, Yahav D, Goldberg E, Neuberger A, Ghanem-Zoubi N, Dickstein Y, Nseir W, Dan M, Leibovici L. Trimethoprim-sulfamethoxazole versus vancomycin for severe infections caused by meticillin resistant Staphylococcus aureus: randomised controlled trial. bmj. 2015, 350:h2219.

[49] Paul M, Carmeli Y, Durante-Mangoni E, Mouton JW, Tacconelli E, Theuretzbacher U, Mussini C, Leibovici L. Combination therapy for carbapenem-resistant Gram-negative bacteria. Journal of Antimicrobial Chemotherapy. 2014, 69(9):2305-9.

[50] Pei G, Mao Y, Sun Y. In vitro activity of minocycline alone and in combination with cefoperazone-sulbactam against carbapenem-resistant Acinetobacter baumannii.Microbial Drug Resistance. 2012, 18(6):574-7.

[51] Perry JA, Westman EL, Wright GD. The antibiotic resistome: what's new?. Current opinion in microbiology. 2014, 21:45-50.

[52] Plachouras, D., Karvanen, M., Friberg, L.E., Papadomichelakis, E., Antoniadou, A., Tsangaris, I., Karaiskos, I., Poulakou, G., Kontopidou, F., Armaganidis, A. and Cars, O., 2009. Population pharmacokinetic analysis of colistin methanesulfonate and colistin after intravenous administration in critically ill patients with infections caused by gram-negative bacteria. Antimicrobial agents and chemotherapy, 53(8), pp.3430-3436.

[53] Podolsky SH. Antibiotics and the social history of the controlled clinical trial, 1950–1970. Journal of the history of medicine and allied sciences. 2010, 65(3):327-67.

[54] Poirel L, Rodriguez-Martinez JM, Mammeri H, Liard A, Nordmann P. Origin of plasmid-mediated quinolone resistance determinant QnrA. Antimicrobial agents and chemotherapy. 2005, 49(8):3523-5.

[55] Pompilio A, Crocetta V, Pomponio S, Fiscarelli E, Di Bonaventura G. In vitro activity of colistin against biofilm by Pseudomonas aeruginosa is significantly improved under "cystic fibrosis–like" physicochemical conditions. Diagnostic microbiology and infectious disease. 2015, 82(4):318-25.

[56] Pontikis K, Karaiskos I, Bastani S, Dimopoulos G, Kalogirou M, Katsiari M, Oikonomou A, Poulakou G, Roilides E, Giamarellou H. Outcomes of critically ill intensive care unit patients treated with fosfomycin for infections due to pandrug-resistant and extensively drug-resistant carbapenemase-producing Gram-negative bacteria. International journal of antimicrobial agents. 2014, 43(1):52-9.

[57] Pulcini C, Bush K, Craig WA, Frimodt-Møller N, Grayson ML, Mouton JW, Turnidge J, Harbarth S, Gyssens IC, ESCMID Study Group for Antibiotic Policies. Forgotten antibiotics: an inventory in Europe, the United States, Canada, and Australia. Clinical Infectious Diseases. 2012, 54(2):268-74.

[58] Sanchez GV, Baird AM, Karlowsky JA, Master RN, Bordon JM. Nitrofurantoin retains antimicrobial activity against multidrug-resistant urinary Escherichia coli from US outpatients. Journal of Antimicrobial Chemotherapy. 2014, 69(12):3259-62.

[59] Schafer JJ, Goff DA, Stevenson KB, Mangino JE. Early experience with tigecycline for ventilator- associated pneumonia and bacteremia caused by multidrug- resistant Acinetobacter baumannii. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2007, (7):980-7.

[60] Sommer MO, Munck C, Toft-Kehler RV, Andersson DI. Prediction of antibiotic resistance: time for a new preclinical paradigm?. Nature Reviews Microbiology. 2017 Nov;15(11):689.

[61] Su J, Li D, Guo Q, Guo Y, Zheng Y, Xu X. In Vitro Bactericidal Activity of Trimethoprim–Sulfamethoxazole/Colistin Combination Against Carbapenem-Resistant Klebsiella pneumoniae Clinical Isolates. Microbial Drug Resistance.2018 Aug 15.

[62] Tasbakan MI, Pullukcu H, Sipahi OR, Yamazhan T, Ulusoy S. Nitrofurantoin in the treatment of extended-spectrum β-lactamase-producing Escherichia coli-related lower urinary tract infection. International journal of antimicrobial agents. 2012, 40(6):554-6.

[63] Theuretzbacher U, Paul M. Revival of old antibiotics: structuring the re-development process to optimize usage. Clinical Microbiology and Infection. 2015, 21(10):878-80.

[64] Theuretzbacher U. Product information for parenteral colistin varies substantially across Europe. Journal of Antimicrobial Chemotherapy. 2014, 69(7):1987-92.

[65] Titelman E, Iversen A, Kalin M, Giske CG. Efficacy of Pivmecillinam for Treatment of Lower Urinary Tract Infection Caused by Extended-Spectrum β-Lactamase–Producing Escherichia coli and Klebsiella pneumoniae.Microbial Drug Resistance. 2012, 18(2):189-92.

[66] Urban C, Mariano N, Rahal JJ. In vitro double and triple bactericidal activities of doripenem, polymyxin B, and rifampin against multidrug-resistant Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae, and Escherichia coli. Antimicrobial agents and chemotherapy. 2010, 54(6):2732-4.

[67] van Duin D, Paterson DL. Multidrug-resistant bacteria in the community: trends and lessons learned. Infectious Disease Clinics. 2016, 30(2):377-90.

[68] Wentao N, Guobao L, Jin Z, Junchang C, Rui W, Zhancheng G, Youning L. In vitro activity of minocycline combined with aminoglycosides against Klebsiella pneumoniae carbapenemase-producing K. pneumoniae. The Journal of antibiotics. 2018, 7:1.

[69] Woerther PL, Lepeule R, Burdet C, Decousser JW, Ruppé É, Barbier F. Carbapenems and alternative beta-lactams for the treatment of infections due to ESBL-producing Enterobacteriaceae: what impact on intestinal colonization resistance?. International Journal of Antimicrobial Agents. 2018 Aug 31.

[70] Yahav D, Farbman L, Leibovici L, Paul M. Colistin: new lessons on an old antibiotic. Clinical microbiology and infection. 2012, 18(1):18-29.

[71] Zavascki AP, Bulitta JB, Landersdorfer CB. Combination therapy for carbapenem-resistant Gram-negative bacteria. Expert review of anti-infective therapy. 2013, 11(12):1333-53.

[72] Zayyad H, Eliakim-Raz N, Leibovici L, Paul M. Revival of old antibiotics: needs, the state of evidence and expectations. International journal of antimicrobial agents. 2017, 49(5):536-41.

[73] Zorzet A. Overcoming scientific and structural bottlenecks in antibacterial discovery and development. Upsala journal of medical sciences. 2014, 119(2):170-5.

[74] Zykov IN, Sundsfjord A, Småbrekke L, Samuelsen Ø. The antimicrobial activity of mecillinam, nitrofurantoin, temocillin and fosfomycin and comparative analysis of resistance patterns in a nationwide collection of ESBL-producing Escherichia coli in Norway 2010–2011. Infectious Diseases. 2016, 48(2):99-107.