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A SYSTEMATIC STUDY OF B -LACTAM ANTIBIOTIC

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ABSTRACT

Beta-lactam antibiotics were the first and most common therapy in the treatment of bacterial infections. Multiple resistance emerged and became a major public health problem. To overcome this problem there are several techniques. The main objective of this research is to systematically review and evaluate of b-lactam antibiotic. In this paper, will try to answer the question: what are the techniques and modification that use to enhance drug activity and prevent bacterial resistance. Will start by explaining the meaning of β-lactam antibiotic, then followed by reviewing a type of technique found to decrease bacterial resistance, in the literature review part. It is not in detail, but covers some about b-lactam antibiotic and techniques that overcome the problem of bacterial resistance. Finally, a discussion and the result will be presented to answer the asked question and the conclusion summarizes the reasons why antibiotic resistance is very critical.

Keywords:

β-lactam antibiotic.

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INTRODUCTION

Types of antibiotics and its mechanism: Antibodies are divided into three groups according to their mechanism of action on the bacteria as shown in Fig (1) there are three attack sites for antibiotic: a) Biosynthesis of protein, b) Cell wall synthesis and c) DNA replication (1).

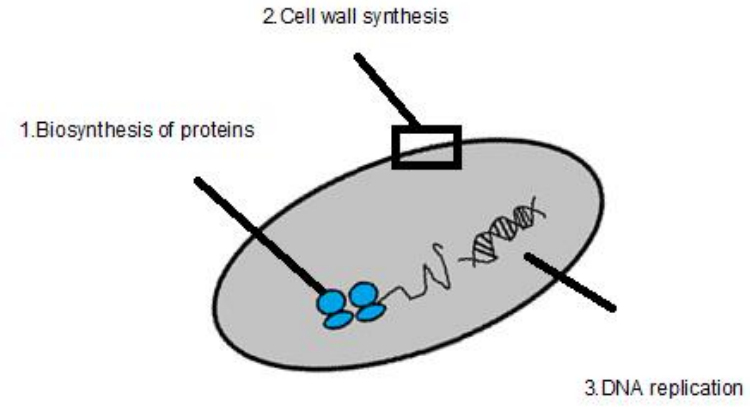


Figure (1):show the mechanism of action of antibiotic class.

β-lactam antibiotic and the bacterial resistance: β-lactam antibiotic means all antibiotic that contains β-lactam in its structure, mechanism of action of these antibiotics by inhibiting cell wall synthesis of the bacterial organism. By permanently bind between the bacterial cell wall and a b-lactam ring of antibiotic, These types of antibiotics the most widely used for all groups of antibiotics (2-6). This group includes penicillin, penicillin combination (penicillin with inhibitors) and cephalosporin and its generation. The bacteria quickly develop resistance to Antibiotics As soon as they are released and started to use. In fact, rapid clinical resistance usually occurs in months to several years after the release of the antibiotic (7). The resistance against this group emerges when continuously used. Bacterial enzymes called β-lactamase that inhibit the therapeutic effect of the β-lactam antibiotic. β-lactamase attacks the lactam loop and prevent the therapeutic action of an antibiotic, the increase of this clinical problem led to discovering β-lactamase inhibitor that used to restore antibiotic action (8-9).

II. Research Question: The aim of this research paper is to get the answer to this question: **Q1** what are the techniques and modification that use to enhance drug activity and prevent bacterial resistance?

III. Research methodology: My research methodology by following a systematic mapping of the published article and researches related to my topic. And to discover the technique use to prevent bacterial resistance. I reviewed the set of paper in the literature part and analyze it. All the paper that I reviewed was published from 2010 to 2019, and collected from the Science Direct library. My research methodology steps are summarized in table 1,2 and 3. After the exclusion criteria 37 papers remain, when just focus on techniques used to prevent the resistance become 10 papers.

Search strategy	
Academic database searched:	Science direct.
Other data sources:	Google scholar.
Target item:	Journal papers & conferences.
Search applied to:	Title, abstract, and key word.
Language:	Papers written in English.
Publication years:	2010-2019

Table1: search strategy

Major term	Alternative term
B-lactam antibiotic.	----

Table2: search string.

Inclusion & exclusion criteria	
Inclusion criteria:	Publication date : 2010-2019 Journal paper& conferences related with research term. Publication title: advanced drug delivery review.
exclusion criteria:	Papers don't focus on b-lactam antibiotic and techniques used to overcome the problem of bacterial resistance.

Table3: selection strategy.

IV. The techniques that are used to enhance drug activity and overcome the problem of bacterial resistance are:

1. Drug combination:β-lactamase inhibitor:

Majority study in bacterial resistance at today is on the b-lactamase field in gram positive and gram negative bacteria (10). B-lactamase inhibitors, non therapeutic agent, but when combined with antibiotic, act to restore the activity of antibiotic by preventing bacterial resistance (11). Up to now, just three b-lactamase (b-lactam class) discovered (Tazobactam, Clavulanic acid, and Sulbactam). Also, a new inhibitor that discovered lately (Avibactam) as a b-lactamase inhibitor (non-b-lactam class) (12). For now only four β-lactamase inhibitors approved by FDA, and more than fifty β-lactam Class antibiotics approved, this is encouraging the discovery of other b-lactamase inhibitors (13,14).

2. Antimicrobial delivery system:

2.1. Antimicrobial polymers: In contrast to conventional antibiotics, antimicrobial polymers were designed to treat surface-related bacteria (15,16,17). Active polymers significantly reduced the burden on systemic antibiotics and also contributed to prolonging the life of traditional antibiotics and inhibiting the development of resistant microbes. In the past, amino acids were the preferred fraction To develop antibiotic polymers, research has recently expanded to include polymers with chemical modifications, polymers with organic or inorganic compounds against bacteria (18,19,20). The combination of an antibiotic with polymers leads to the stability of antibiotics and reduce their toxicity and increase the half-life of the antibody and its effectiveness.

A type of polymer delivery:

2.1.1 Polymers with chemical anti-bacterial modifications: Polymers were modified from 1965 to provide antibacterial and bacterial resistance (21). These modifications are divided into three sections: 1) Very small particles connected to the polymer backbone (22.23). 2) A peptide with antibiotic activity related to biological inactive polymers (24.25). 3) Antimicrobial polymers with biologically inactive polymers (26.27).

2.1.2. Polymers that contain antimicrobial organic compounds: This is the most widely used methods for the manufacture of antimicrobial polymers. However, this method is complex and may enhance bacterial resistance unintentionally. (28)(29.30).

2.1.3. Polymers that contain inorganic compounds antimicrobial: Inorganic compounds such as minerals and mineral oxides. Silver is one of the oldest anti-bacterial polymers in its various forms (ions, salts, Nanoparticles.....), There are many studies related to these polymers (31). There are also other successful strategies such as zinc oxide (32), gold and titanium oxide (33). All these techniques Used in the nano-barticles form (34).

2.1.4. Intrinsic antimicrobial activity polymer: Some of the polymers have antibacterial properties in their composition, often chemical or other structural elements. The most commonly studied types are polymers with a natural -peptides (e.g. Oligo-n-substitutes glycines,(35) and halogen polymers (Containing fluorine or chlorine), polyphenyl ethynylenes (36), polymeric N-halamines (37), and organometallic polymers, and the group may also contain cationic polymers (eg, quarternary pyridinium -salts, quaternary ammonium salts, biguanide, and phosphonium salts) (38,39), or cationic conjugates (e.g. polyoxazolines , polysiloxanes, polyelectrolytes, polyionenes,…etc).

2.2. Nanoparticle /liposome delivery system:

2.2.1 Nanoparticle: Drug delivery system in the nanopartical form it is the approach to improve 1) the therapeutic index, 2) dose administration, 3) bacterial resistance(40), 4) organ targeting to decrease side effects (41,42)**.** Metal nanoparticles like a silver compound used in pharmaceutics and medicine as a carrier of the antibiotic agent(43,44) this is in past .put recently the researchers try to mixed the gold nanoparticles with different species of antibiotic for example :(ciprofloxacillin, and another fluoroquinolone antibiotic)(45), gentamicin (46), vancomycin (47)....etc but the result it is not equal, the researchers found that when decorating the surface of gentamicin with golden nanoparticle enhance the activity against gentamicin resistance (47), but other researchers showed no enhancement in gentamicin resistance (46). This variation may be because of some affect efficacy parameter: for example 1) the characterization of antibiotic. 2) nanoparticle size, 3) experimental condition. Relatively, there are a few drugs in nanoparticle form (48), this is maybe because of complexation of nanoparticle technology(49).

2.2.2. Liposome: The most route of administration of liposome by Intravenous injection the advantage of this technique. 1) Used in biological and hydrophilic compound, 2) antibiotic stability, 3) increase therapeutic index and decrease toxicity.4) targeting of organ (50,51). The advantage of this technique his similarity of membrane structure that leads to easier to fuse in cellular membranes, then delivers a drug directly to inside cytoplasm and prevents bacterial resistance (52). Unfortunately, lipid-based drug delivery has limited efficiency (42), the short half-life of the drug due to the instability of lipid bonds, a fusion of liposomes and aggregation, sensitivity to temperature (49), these reasons can lead to not enough delivery of the drug. The liposome stability can improve by different modification (e.g. Act on a long chain of polymer in hydrophilic part or in charge chain....etc.)**.**

V. Discussion and result:
distribution of papers by years as shown in figure 2

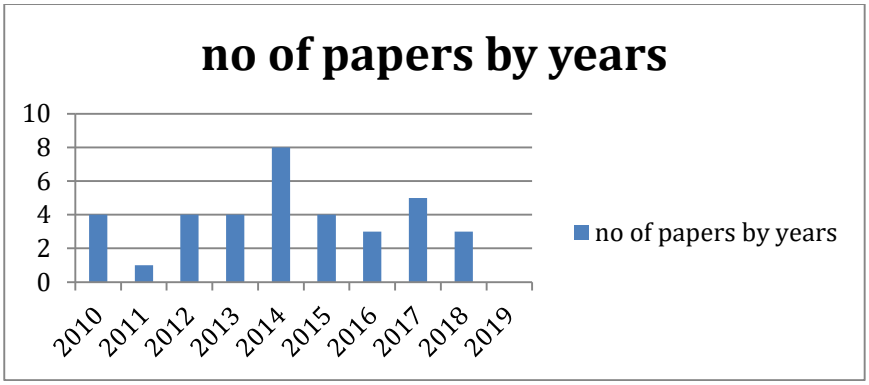


Figure 2: distribution of papers by publication date

Also the type of paper that review show in figure 3

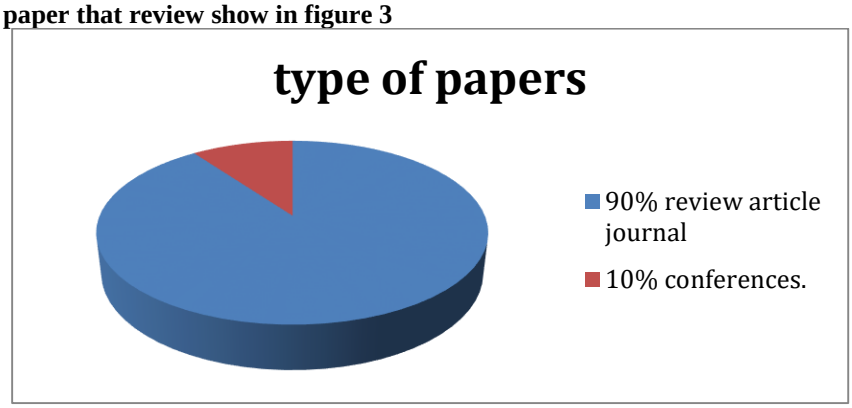


Figure3: distribution of papers by type

Result in techniques thous used to overcome the problem of resistance that collect from reviewing papers {(53), (54), (55), (56), (57), (58), (59), (60).}:

Drug combination: (b-lactamase inhibitor): the Beta-lactamase inhibitors were shown effective as a treatment of bacterial infections in infants, children, and adults. The safety and efficacy of Beta-lactamase inhibitors were evaluated in six prophylaxis studies and 39 therapeutic studies in both pediatric patients and adult.36 shown in both excellent safety and efficacy, with little adverse reported around 10% of patients in most studies. Type of side effect different according to the administration route of the combination drug. Gastrointestinal disturbances and diarrhea are the side-effects that most frequently reported with the orally taken antibiotic, this is due to the antibiotic effect on the normal bacteria in intestinal flora. In the studies show, side effect rarely leads to incomplete treatment and always the problem resolve during therapy or after the end of therapy. It is interesting to note that in the reviewed paper reported a reduction in diarrhea side effect in patients taken the antibiotic in the parenteral route.in Journal of International Medical Research 2002 (45) show the clinical and biological response of infection treated with drug combinations. The result indicates on greater effective of drug combination against bacterial resistance (60).

Clinical and bacteriological response in various infections treated by b-lactamase inhibitor combination as mentioned in the papers reviewed (60).

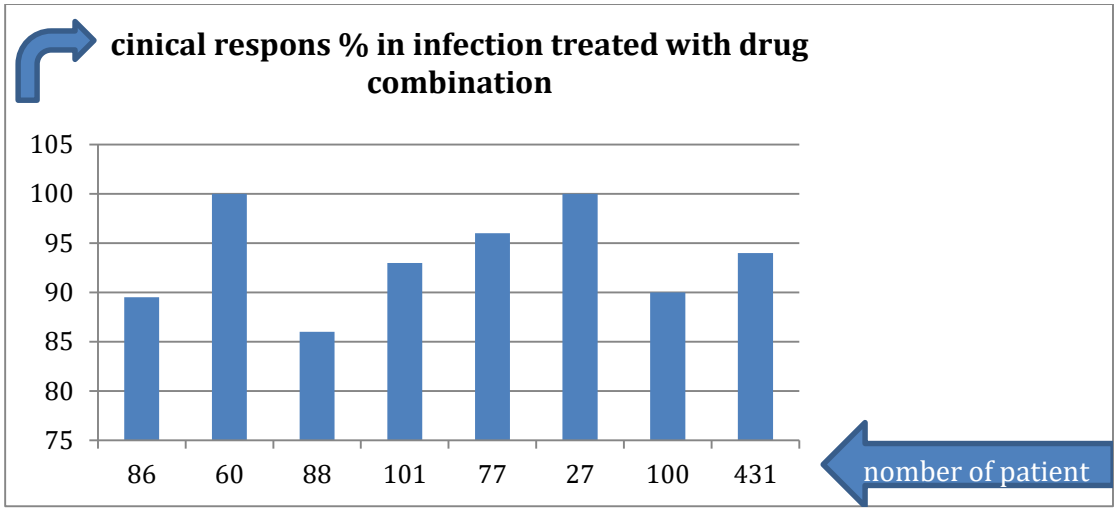


Figure 4: clinical response in infection treated by drug combination technique

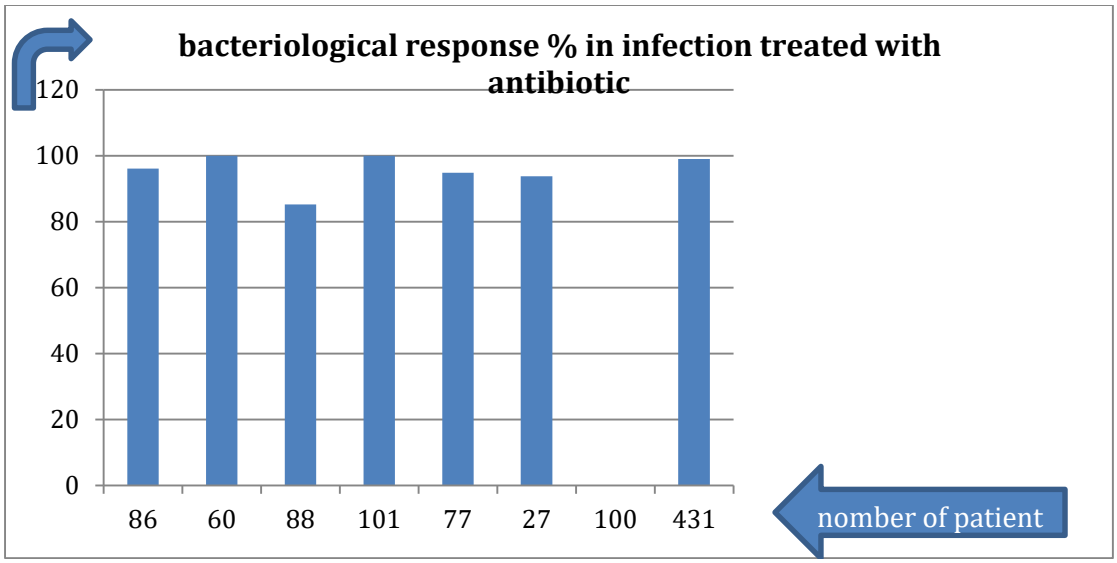


Figure 5: bacteriological response in infection treated with drug combination techniques

Drug delivery system:

Polymer: Advantages and disadvantages of polymer as mentioned in the papers reviewed (57,58) summarized in table 4**:**

Advantages	Disadvantages
Local delivery of drug. Increase sustained drug. Stability. Decrease frequents taken drugs. Decrease side effect. Patient compliance improved.	Some substance may cause the issue to body after degradation (toxic) High drug release after administration of drug.

Table 4: advantage and disadvantage of polymer

Nano-particle and liposome:

Nano-particle: Advantages and disadvantages of different type of nano-particles as mentioned in the papers reviewed (53,54,55,56) summarized in table 5:

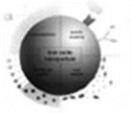
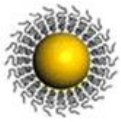
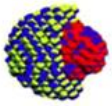
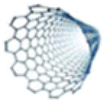
Type of nano-particle	Advantage	Disadvantage
Metal oxide 	_Aproved by FDA for clinical use. _intrinsic magnetic properties. _flexible surface modification with different coating.	_toxicity and bio-compatibility concerns. _inflammation to respiratory system.
Gold nano-particle 	_able to absorb light. _flexible surface modification.	_toxicity. _expensive.
Quantum dots 	_narrow wavelength emission. _high fluorescence efficiency and Photostability.	_Toxicity and bio-compatibility , especially the heavy metals.
Carbon nanotube 	_Intrinsic properties, enabling imaging modalities. _ultra high surface area with inside hollow space for drug efficient and bio-conjugation.	_ Toxicity and bio-compatibility
Radio and fluorescent molecule 	_the highest flexible. _Ability to perform as non invasive real time treatment monitoring.	_short half life. _ Toxicity and bio-compatibility

Table5: advantages & disadvantages of nano-particle type

Distribution of nanoparticle type used in drug delivery system show in figure 6:

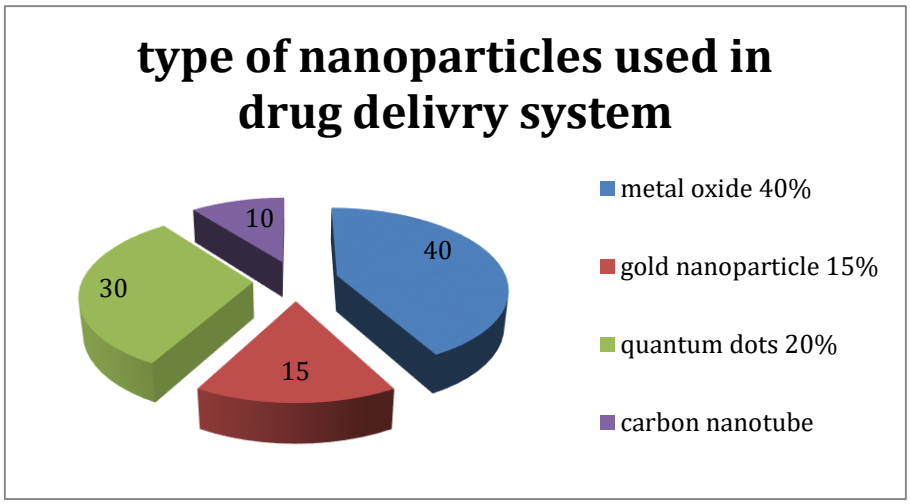


Figure 6: distribution of nano-particle type used as an antibiotic drug form.

Liposome: Advantages of Use Liposomes form was mention in papers reviewed(53,54) can be summarized as: reduced toxicity, increase the time of drug retention, enhance the efficacy of the drug, targeted of specific site delivery (only the infected cells affected by the drug), reduce adverse side effects, and finally, Liposomes have shown to significantly reduce the toxicity of the drug in the free form. The advantages and disadvantages of liposome should be balanced to achieve the desirable results.

In the diagram (figure 7) show the distribution of drug delivery system that used in antibiotic to prevent bacterial resistance, this according to papers reviewed (59).

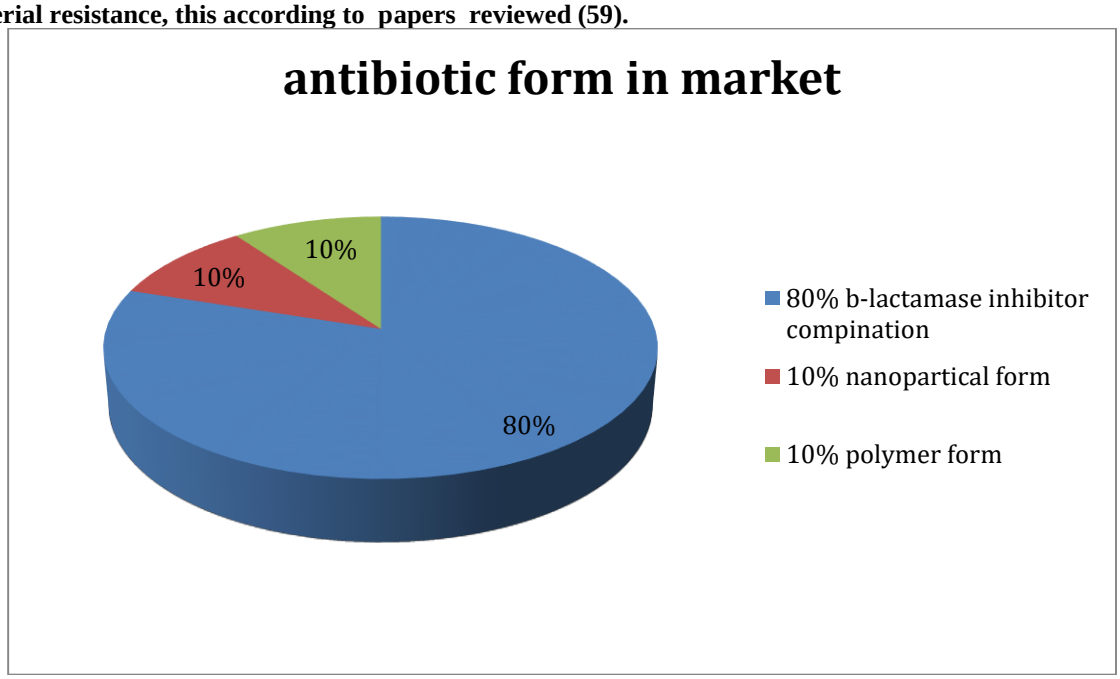


Figure 7: distribution of antibiotic form found in the market.

VI.CONCLUSION

Beta-lactam antibiotics the first and most common therapy in the treatment of bacterial infections. Multiple resistance with b-lactamas emerged and became a major public health problem. To overcome this problem, Antibiotics are given with a combination with a β-lactamase inhibitor. The b-lactam antibiotic combination is an ideal therapy for infections, in adult and pediatric patients, it is safe and has a broad spectrum of activity, and it is available in a variety of formulations that are suitable for sequential therapy, thus ensuring a smooth transition into community management of the hospital. Moreover, a short course of therapy and, simple treatment regimens, that lead to patient compliance with this combination. The b-lactam combination becomes increasingly important for the pediatric and adult infections, especially if there is no bacterial resistance.

Nano-particles drug is designed to improve the therapeutic and pharmacological properties of drugs, by protecting a drug from degradation and enhance the targeting and controlled release. Due to the small diameters, nano-particles are able to cross the blood-brain barrier and act on a cellular level. In comparison with the classical form of drugs, nano-particles drugs are more effective and selective. They can reduce the toxicity and side effects in normal tissues.

In the development of drug delivery technology Polymer play a vital role by offering a release of both type of drugs (hydrophobic & hydrophilic), repeated dosage, and constant release of the drug over extended periods**.**

REFERENCES

(1) Mira, P. M. (2018). Understanding the impacts of sub-inhibitory concentrations and clinical use of beta-lactam antibiotics on the evolution of beta-lactamase resistance genes (Order No. 10816144). Available from ProQuest Dissertations & Theses Global. (2068051065). Retrieved from https://search.proquest.com/docview/2068051065?accountid=25087.

(2) Kong, K.F., L. Schneper, and K. Mathee, Beta-lactam antibiotics: from antibiosisto resistance and bacteriology. Apmis, 2010. 118 (1): p. 1-36.

(3) Pimenta, A.C., R. Fernandes, and I.S. Moreira, Evolution of Drug Resistance: Insight on TEM beta-Lactamases Structure and Activity and beta-Lactam Antibiotics. Mini-Reviews in Medicinal Chemistry, 2014. 14 (2): p. 111-122.

(4) Shahada, F., et al., Genetic analysis of multi-drug resistance and the clonal dissemination of beta-lactam resistance in Salmonella Infantis isolated from broilers. Veterinary Microbiology, 2010. 140 (1-2): p. 136-141.

(5) Abeylath, S.C. and E. Turos, Drug delivery approaches to overcome bacterial resistance to beta-lactam antibiotics. Expert Opinion on Drug Delivery, 2008. 5 (9): p. 931-949.

(6) Tomasz, A., "Intelligence coup" for drug designers: crystal structure of Staphylococcus aureus beta-lactam resistance protein PBP2A. Lancet, 2003. 361 (9360): p. 795-796. Ventola cl. The antibiotic resistance crisis: part 1: causes and threats PT 2015;40 (4): 277-83.

(7) Ndugulile, F., et al., Extended Spectrum beta-Lactamases among Gram-negative bacteria of nosocomial origin from an Intensive Care Unit of a tertiary health facility in Tanzania. Bmc Infectious Diseases, 2005. 5.

(8) Giamarellou, H., Multidrug resistance in gram-negative bacteria that produce extended-spectrum beta-lactamases (ESBLs). Clinical Microbiology and Infection, 2005. 11: p. 1-16.

(9) goularCP, mahmudi M, crona KA, jacobs SD,Kallmann M, Hall BG, et al. designing antibiotic cycling strategies by detrmining and understanding local adeptive landscapes. PLos one. 2013 ;8 (2):e56040.

(10) Shin, W. S. (2016). Combination antibacterial therapy against β-lactam drug resistance (Order No. 10155499). Available from ProQuest Dissertations & Theses Global. (1817632347). Retrieved from https://search.proquest.com/docview/1817632347?accountid=25087.

(11) Drawz, S.M. And R.A. Bonomo, Three Decades of beta-Lactamase Inhibitors Clinical Microbiology Reviews, 2010. 23 (1): p. 160-+.

(12) Aronson, J.K., Penicillins, cephalosporins, other beta-lactam antibiotics, and tetracyclines. Side Effects of Drugs Annual 34: A Worldwide Yearly Survey of New Data in Adverse Drug Reactions and Interactions, 2012. 34: p. 385-397.

(13) Page, M.G.P., Beta-Lactam Antibiotics. Antibiotic Discovery and Development, Vols 1 and 2, 2012: p. 79-117.

(14) A. Cavallaro, S. Taheri, K. VasilevResponsive and "smart" antibacterial surfaces: common approaches and new developments Biointerphases, 9 (2014), p. 029005, 10.1116/1.4866697 Cross RefView Record in ScopusGoogle Scholar.

(15) K. Vasilev, J. Cook, H.J. GriesserAntibacterial surfaces for biomedical devices Expert Rev. Med. Devices, 6 (2009), pp. 553-567 CrossRefView Record in ScopusGoogle Scholar.

(16) K. Vasilev, V. Sah, K. Anselme, C. Ndi, M. Mateescu, B. Dollmann, et al.Tunable antibacterial coatings that support mammalian cell growth Nano Lett., 10 (2010), pp. 202-207, CrossRefView Record in ScopusGoogle Scholar.

(17) F. Siedenbiedel, J.C. TillerAntimicrobial polymers in solution and on surfaces: overview and functional principles Polymers, 4 (2012), pp. 46-71, 10.3390/polym4010046 CrossRefView Record in ScopusGoogle Scholar.

(18) L. Timofeeva, N. KleshchevaAntimicrobial polymers: mechanism of action, factors of activity, and applications Appl. Microbiol. Biotechnol., 89 (2011), pp. 475-492, 10.1007/s00253-010-2920-9 CrossRefView Record in ScopusGoogle Scholar

(19) K. Kuroda, G.A. CaputoAntimicrobial polymers as synthetic mimics of host-defense peptides

(20) Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol., 5 (2013), pp. 49-66, 10.1002/wnan.1199 CrossRefView Record in ScopusGoogle Scholar.

(21) R.J. Cornell, L.G. Donaruma2-Methacryloxytropones. intermediates for the synthesis of biologically active polymers J. Med. Chem., 8 (1965), pp. 388-390 CrossRefView Record in ScopusGoogle Scholar.

(22) B. Dizman, M.O. Elasri, L.J. MathiasSynthesis, characterization, and antibacterial activities of novel methacrylate polymers containing norfloxacin Biomacromolecules, 6 (2005), pp. 514-520, 10.1021/bm049383 CrossRefView Record in ScopusGoogle Scholar.

(23) M.C. Lawson, R. Shoemaker, K.B. Hoth, C.N. Bowman, K.S. AnsethPolymerizable vancomycin derivatives for bactericidal biomaterial surface modification: structure–function evaluation Biomacromolecules, 10 (2009), pp. 2221-2234, 10.1021/bm900410a CrossRefView Record in ScopusGoogle Scholar[162].

(24) V.E. Wagner, J.T. Koberstein, J.D. BryersProtein and bacterial fouling characteristics of peptide and antibody decorated surfaces of PEG-poly(acrylic acid) co-polymers Biomaterials, 25 (2004), pp. 2247-2263 ArticleDownload PDFView Record in ScopusGoogle Scholar.

(25) B. Gottenbos, H.C. van der Mei, F. Klatter, P. Nieuwenhuis, H.J.BusscherIn vitro and in vivo antimicrobial activity of covalently coupled quaternary ammonium silane coatings on silicone rubber Biomaterials, 23 (2002), pp. 1417-1423, 10.1016/S0142 9612(01)00263-0 ArticleDownload PDFView Record in ScopusGoogle Scholar[164].

(26) A.E. Madkour, J.M. Dabkowski, K. Nusslein, G.N. TewFast disinfecting antimicrobial surfaces Langmuir, 25 (2009), pp. 1060-1067, 10.1021/la802953v CrossRefView Record in ScopusGoogle Scholar.

(27) L.G. Harris, S. Tosatti, M. Wieland, M. Textor, R.G. RichardsStaphylococcus aureus adhesion to titanium oxide surfaces coated with non-functionalized and peptide-functionalized poly(L-lysine)-grafted-poly(ethylene glycol) copolymers Biomaterials, 25 (2004), pp. 4135-4148, 10.1016/j.biomaterials.2003.11.033 ArticleDownload PDFView Record in ScopusGoogle Scholar.

(28) H.L. Tan, W.T. Lin, T.T. TangThe use of antimicrobial-impregnated PMMA to manage periprosthetic infections: controversial issues and the latest developments Int. J. Artif. Organs, 35 (2012), pp. 832 839, 10.5301/ijao.5000163 View Record in ScopusGoogle Scholar Google Scholar.

(29) A.E. Brooks, B.D. Brooks, S.N. Davidoff, P.C. Hogrebe, M.A. Fisher, D.W.GraingerPolymer-controlled release of tobramycin from bone graft void filler Drug Deliv. Transl. Res., 3 (2013), pp. 518 530, 10.1007/s13346-013-0155-x CrossRefView Record in ScopusGoogle Scholar.

(30) B.D. Brooks, K.D. Sinclair, S.N. Davidoff, S. Lawson, A.G. Williams, B.Coats, et al.Molded polymer-coated composite bone void filler improves tobramycin controlled release kinetics J. Biomed. Mater. Res. B Appl. Biomater. (2013), 10.1002/jbm.b.33089 Google Scholar.

(31) A.M. Fayaz, K. Balaji, M. Girilal, R. Yadav, P.T. Kalaichelvan, R.VenketesanBiogenic synthesis of silver nanoparticles and their synergistic effect with antibiotics: a study against gram-positive and gram-negative bacteria Nanomedicine, 6 (2010), pp. 103-109, 10.1016/j.nano.2009.04.006 ArticleDownload PDFView Record in ScopusGoogle Scholar

(32) J.T. Seil, T.J. WebsterReduced Staphylococcus aureus proliferation and biofilm formation on zinc oxide nanoparticle PVC composite surfaces Acta Biomater., 7 (2011), pp. 2579-2584, 10.1016/j.actbio.2011.03.018 ArticleDownload PDFView Record in ScopusGoogle Scholar.

(33) A. Azam, A.S. Ahmed, M. Oves, M.S. Khan, S.S. Habib, A. MemicAntimicrobial activity of metal oxide nanoparticles against Gram-positive and Gram-negative bacteria: a comparative study Int. J. Nanomedicine, 7 (2012), pp. 6003-6009, 10.2147/IJN.S35347 CrossRefView Record in ScopusGoogle Scholar.

(34) R.Y. Pelgrift, A.J. FriedmanNanotechnology as a therapeutic tool to combat microbial resistance Adv. Drug Deliv. Rev., 65 (2013), pp. 1803-1815, 10.1016/j.addr.2013.07.011 ArticleDownload PDFView Record in ScopusGoogle Scholar.

(35) G.J. Gabriel, A. Som, A.E. Madkour, T. Eren, G.N. TewInfectious disease: connecting innate immunity to biocidal polymers Mater. Sci. Eng. R. Rep., 57 (2007), pp. 28-64, 10.1016/j.mser.2007.03.002 ArticleDownload PDFView Record in ScopusGoogle Scholar.

(36) G.N. Tew, D. Clements, H. Tang, L. Arnt, R.W. ScottAntimicrobial activity of an abiotic host defense peptide mimic Biochim. Biophys. Acta, 1758 (2006), pp. 1387-1392, 10.1016/j.bbamem.2006.03.001 ArticleDownload PDFView Record in ScopusGoogle Scholar.

(37) X. Ren, C. Zhu, L. Kou, S.D. Worley, H.B. Kocer, R.M. Broughton, et al.Acyclic N-halamine polymeric biocidal films J. Bioact. Compat. Polym., 25 (2010), pp. 392-405, 10.1177/0883911510370387 View Record in ScopusGoogle Scholar.

(38) M. GorbunovaNovel guanidinium and phosphonium polysulfones: synthesis and antimicrobial activity J. Chem. Pharm. Res., 5 (2013), pp. 185-192 View Record in ScopusGoogle Scholar.

(39) A.M. Carmona-Ribeiro, L.D. de Melo CarrascoCationic antimicrobial polymers and their assemblies Int. J. Mol. Sci., 14 (2013), pp. 9906-9946, 10.3390/ijms14059906 CrossRefView Record in ScopusGoogle Scholar.

(40) L. Zhang, D. Pornpattananangkul, C.-M. Hu, C.-M. HuangDevelopment of nanoparticles for antimicrobial drug delivery Curr. Med. Chem., 17 (2010), pp. 585-594, 10.2174/092986710790416290 CrossRefView Record in ScopusGoogle Scholar.

(41) F. Andrade, M. Videira, D. Ferreira, B. SarmentoMicelle-based systems for pulmonary drug delivery and targeting Drug Deliv. Lett., 1 (2011), pp. 171-185, 10.2174/2210304x11101020171 CrossRefView Record in ScopusGoogle Scholar

(42) H. Pinto-Alphandary, A. Andremont, P. CouvreurTargeted delivery of antibiotics using liposomes and nanoparticles: research and applications Int. J. Antimicrob. Agents, 13 (2000), pp. 155-168 ArticleDownload PDFView Record in ScopusGoogle Scholar.

(43) K.I. Wolska, K. Grześ, A. KurekSynergy between novel antimicrobials and conventional antibiotics or bacteriocins Pol. J. Microbiol., 61 (2012), pp. 95-104 View Record in ScopusGoogle Scholar.

(44) E. Taylor, T.J. WebsterReducing infections through nanotechnology and Nanoparticles Int. J. Nanomedicine, 6 (2011), pp. 1463 1473, 10.2147/IJN.S22021 View Record in ScopusGoogle Scholar.

(45) R.T. Tom, V. Suryanarayanan, P.G. Reddy, S. Baskaran, T. PradeepCiprofloxacin-protected gold Nanoparticles Langmuir, 20 (2004), pp. 1909-1914 CrossRefView Record in ScopusGoogle Scholar.

(46) G. Burygin, B. Khlebtsov, A. Shantrokha, L. Dykman, V. Bogatyrev, N.KhlebtsovOn the enhanced antibacterial activity of antibiotics mixed with gold Nanoparticles Nanoscale Res. Lett., 4 (2009), pp. 794-801, 10.1007/s11671-009-9316-8 CrossRefView Record in ScopusGoogle Scholar.

(47) H. Gu, P.L. Ho, E. Tong, L. Wang, B. XuPresenting vancomycin on nanoparticles to enhance antimicrobial activities Nano Lett., 3 (2003), pp. 1261-1263, 10.1021/nl034396z CrossRefView Record in ScopusGoogle Scholar.

(48) R. Duncan, R. GasparNanomedicine(s) under the microscope Mol. Pharm., 8 (2011), pp. 2101-2141, 10.1021/mp200394t CrossRefView Record in ScopusGoogle Scholar

(49) C. Jones, D.W. GraingerIn vitro assessments of nanomaterial toxicity Adv. Drug Deliv. Rev., 61 (2009), pp. 438-456, 10.1016/j.addr.2009.03.005 ArticleDownload PDFView Record in ScopusGoogle Scholar.

(50) M. Alhariri, A. Azghani, A. OmriLiposomal antibiotics for the treatment of infectious diseases Expert Opin. Drug Deliv., 10 (2013), pp. 1515-1532, 10.1517/17425247.2013.822860 CrossRefView Record in ScopusGoogle Scholar.

(51) Z. Drulis-Kawa, A. Dorotkiewicz-JachLiposomes as delivery systems for antibiotics Int. J. Pharm., 387 (2010), pp. 187-198, 10.1016/j.ijpharm.2009.11.033 ArticleDownload PDFView Record in ScopusGoogle Scholar.

(52) F. Andrade, D. Rafael, M. Videira, D. Ferreira, A. Sosnik, B. SarmentoNanotechnology and pulmonary delivery to overcome resistance in infectious diseases Adv. Drug Deliv. Rev., 65 (2013), pp. 1816-1827, 10.1016/j.addr.2013.07.020 ArticleDownload PDFView Record in ScopusGoogle Scholar.

(53) Journal of International Medical Research 2002; 30 (Suppl 1): 10A – 19A. Robert Y. Pelgrift, Adam J. Friedman, Nanotechnology as a therapeutic tool to combat microbial resistance, Advanced Drug Delivery Reviews, Volume 65, Issues 13–14, 2013, Pages 1803-1815, ISSN 0169 409X,https://doi.org/10.1016/j.addr.2013.07.011. (http://www.sciencedirect.com/science/article/pii/0169409X13001658).

(54) Ching-Wen Chen, Chia-Yen Hsu, Syu-Ming Lai, Wei-Jhe Syu, Ting-Yi Wang, Ping-Shan Lai, Metal nanobullets for multidrug resistant bacteria and biofilms, Advanced Drug Delivery Reviews, Volume 78, 2014, Pages 88-104, ISSN 0169409X, https://doi.org/10.1016/j.addr.2014.08.004. (http://www.sciencedirect.com/science/article/pii/S0169409X14001707).

(55) Nanomaterials and molecular transporters to overcome the bacterial envelope barrier: Towards advanced delivery of antibiotics, Advanced Drug Delivery Reviews, Volumes 136–137, 2018, Pages 28-48, ISSN0169-409Xhttps://doi.org/10.1016/j.addr.2017.12.010. (http://www.sciencedirect.com/science/article/pii/S0169409X17303137).

(56) Santos, R. S., Figueiredo, C., Azevedo, N. F., Braeckmans, K., & De Smedt, S. C. (2018,November1). Nanomaterials and molecular transporters to overcome the bacterial envelope barrier: Towards advanced delivery of antibiotics. Advanced Drug Delivery Reviews. Elsevier B.V. https://doi.org/10.1016/j.addr.2017.12.010.

(57) Meng-Hua Xiong, Yan Bao, Xian-Zhu Yang, Yan-Hua Zhu, Jun Wang, Delivery of antibiotics with polymeric particles, Advanced Drug Delivery Reviews, Volume 78, 2014, Pages 63-76, ISSN 0169-409X, https://doi.org/10.1016/j.addr.2014.02.002. (http://www.sciencedirect.com/science/article/pii/S0169409X14000246).

(58) Nicholas D. Stebbins, Michelle A. Ouimet, Kathryn E. Uhrich, Antibiotic-containing polymers for localized, sustained drug delivery, Advanced Drug Delivery Reviews, Volume 78, 2014, Pages 77-87, ISSN 0169-409X, https://doi.org/10.1016/j.addr.2014.04.006. (http://www.sciencedirect.com/science/article/pii/S0169409X14000817).

(59) Benjamin D. Brooks, Amanda E. Brooks, Therapeutic strategies to combat antibiotic resistance, Advanced Drug Delivery Reviews, Volume 78, 2014, Pages 14-27, ISSN 0169-409X, https://doi.org/10.1016/j.addr.2014.10.027. (http://www.sciencedirect.com/science/article/pii/S0169409X1400235X).

(60) Sarah S. Tang, Anucha Apisarnthanarak, Li Yang Hsu,Mechanisms of β-lactam antimicrobial resistance and epidemiology of major community- and healthcare-associated multidrug-resistant bacteria, Advanced Drug Delivery Reviews, Volume 78,2014,Pages 3-13,ISSN 0169-409X, https://doi.org/10.1016/j.addr.2014.08.003. (http://www.sciencedirect.com/science/article/pii/S0169409X14001690).