Journal of Research in Medical and Dental Science
2022, Volume 10, Issue 11, Page No: 123-129

Available Online at: www.jrmds.in
eISSN No. 2347-2367: pISSN No. 2347-2545

Challenges and Future Perspectives of Gram Negative Multidrug Resistant Bacilli Causing Skin Infections

Muhammad Musthafa Poyil*

Department of Microbiology, Vivekanandha College of Arts and Sciences for Women, Namakkal, Tamil Nadu, India

ABSTRACT

Skin infections are considered as a group of various conditions that affecting the skin layers and soft tissues resulting superficial uncomplicated to complicated systemic infections which are caused by both gram positive as well as gram negative organisms. Mostly, the complicated skin infections were caused by gram negative bacilli such as Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae and Acinetobacter baumannii gained much attention owing to its multidrug resistance to existing antibiotics which further complicated the skin infection by prolonged hospitalization, cost for health care and mortality. In this review, we mainly focused the risk factor which predominantly complicates the skin infection, current treatment challenges as well as future direction for skin infection treatment and management.

Key words: Multidrug resistance, Skin infection, Gram negative bacilli

HOW TO CITE THIS ARTICLE: Muhammad Musthafa Poyil, Challenges and Future Perspectives of Gram Negative Multidrug Resistant Bacilli Causing Skin Infections, J Res Med Dent Sci, 2022, 10 (11): 123-129.

Corresponding author: Muhammad Musthafa Poyil

e-mail✉**:** pmusthu@gmail.com

Received: 31-Oct-2022, Manuscript No. JRMDS-22-78682;

Editor assigned: 01-Nov-2022, PreQC No. JRMDS-22-78682(PQ);

Reviewed: 15-Nov-2022, QC No. JRMDS-22-78682(Q);

Revised: 19-Nov-2022, Manuscript No. JRMDS-22-78682(R);

Published: 25-Nov-2022

INTRODUCTION

Skin infections are manifested by microbial invasion into the different skin layers as well as underlying soft tissues resulting mild to severe life-threatening infections [1]. The infections are commonly encountered in both ambulatory and hospital settings [2-4]. The severity and its complexity are extensive which is ensuing in bacteraemia, hospitalization, surgery and in some times death [2]. This skin infection includes an extensive clinical range of frequent infectious diseases that are repeatedly required a treatment as well as admission for patients [5]. This infection has a diverse appearance and microbial involvement in the various regions of the skin such as epidermis, dermis etc., Skin infections are very severe in complicated cases which involving deeper tissues which including cellulitis, infection in the wound tissues [6]. Previously, *Staphylococcus aureus* and β- haemolytic Streptococci have been reported as main reason behind the skin infections [7] which accounted for 6.8 to 17.39 % and 3.3 to 8.1% cases respectively [8] but in recent times, gram negative pathogens and mixed pathogens which includes both gram positive as well as gram negative bacteria's, have become a significant cause for acute skin infections [9,10] which leads to health care associated problematical skin infection like diabetic foot infections [11]. The earlier study reported that gram negative bacteria have become an emerging pathogen, including *E. coli* and *K. pneumoniae* related for 28 and 17 % respectively, which affecting the mortality rate of skin infection [8].

The prevalence and the dissemination of skin infections are increased due to antibiotic resistance, particularly, occurrence of multidrug resistant as well as the appearance of the carbapenem resistant Enterobacteriaceae was causing a serious obstacle to the treatment of skin infections which is caused by gram negative pathogens [12]. Many factors were considered while classifying the skin infections such as the infection occurrence place, Rate of infection, causative agent, depth of infection and severity [13,14]. The food and drug administration has announced the new classification category named acute bacterial skin and skin structure infections in 2013, which were defined as wound infection, cellulitis, abscess, skin redness and oedema. This classification was developed for the regulation of the drug of choice for the treatment of skin infections. Most importantly, the complicated skin infection has different microbial community along with gram negative pathogens particularly, the patient who have diabetes, neutropenia patient and malignant patient [15]. However, in this review mainly focused on the multiple antibiotic resistant gram-negative pathogens which cause skin infection and their treatment challenges (Figure 1).

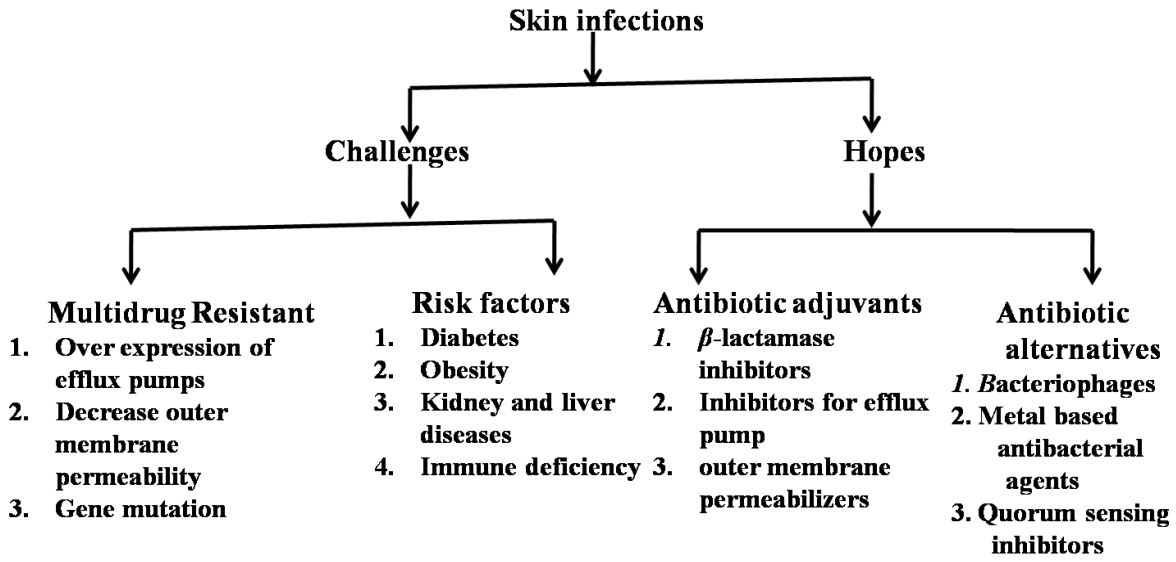

Figure 1: Summary of challenges and hopes for gram negative bacilli causing skin infection.

Microbiology of skin infection

The skin is most important organ which visibly spread out the whole human body as well as it has several layers (epidermis, dermis, subcutaneous and cutaneous) to protect the body from the external sources like microbes and other elements and it provided numerous prospects for infections. Though, the skin and soft tissue infection (SST) has occurred owing to microbial invasion into different skin layers that determines the severity. The largest organ in the body harbour millions of microbes including bacteria, fungi and virus which have played a major role in evading pathogen, immune response and to breakdown the natural products [16]. The skin is niche for many beneficial microorganisms like our gut has which are acting as barrier to prevent the entry of invasive pathogens. In certain conditions when the barrier is breakdown or stability between the commensal and the pathogen gets disturbed, the result will be the complicated and uncomplicated skin diseases. The entry of microbes into the skin and soft tissue through interruption of skin structures are the basis for skin infection but many other risk factors are increasing the susceptibility of the skin infection [17]. In general, skin infections are monomicrobial or polymicrobial in nature. P. aeruginosa, *Klebsiella spp, E. coli, Enterococcus spp, A. baumannii*, Citrobacter are the mainly isolated gram-negative bacilli in patient hospitalized with skin infections [7]. Therefore, the treatment for skin infection caused by polymicrobial or mixed microbes required a multidrug effect that will be effective against all the microbes [18,19]. Apart from gram positive microbe, P. aeruginosa played a major role in skin infection among other gram-negative bacilli [20].

Clinical characteristic features of skin infection

The bacteria can enter the skin through many ways such as bite wounds, existing skin wounds, scratches, and burns wounds to rupture the skin barrier cause skin. The bacteria can develop skin infection after entering the skin by means of adhering to host cell, spreading to tissues and toxin elaboration [21]. Virulence factors possessed by the organism played a major role in the skin infection development. Skin infections produced a wide variety of clinical symptoms like oedema, pain, erythema, warmth, necrosis and ischemia [22].

Treatment options for skin infections

Clinical examination is the primary diagnostic method for skin infection. Identification of skin infection provided the information about the causative agent as well as the choice for antibiotic therapy which helps to start the prognosis of the skin infection. Initially, the skin infection treatment relies on prescription of various β-lactam antibiotics, aminoglycosides, polymyxins, tigecycline, Carbapenems, Fosfomycin, imipenem, ceftazidime, meropenem, Ceftolozane and cephalosporins. Unfortunately, the organisms were developed resistance to any of these antibiotics which makes antibiotic resistant organism leading treatment failure. The skin infections caused by gram negative bacilli (*P. aeruginosa, Klebsiella sp., E. coli* and *A. baumannii*) are the most challenging concern for physicians due to antibiotic resistant.

Current challenges for skin infection

Multi drug resistance

Though the skin infections are able to treat by empirical antimicrobial therapy, every physician faced a most important challenge while treating skin infection caused by gram negative pathogens. The increases of drug resistant organism resulting treatment failure due to the multidrug resistance strains to existing antibiotics have complicated the skin infections. The gram-negative bacilli were developed antibiotic resistance through the antibiotic inactivating enzymatic and non-enzymatic pathways expression resulting increase in the intrinsic resistance by chromosomal gene mutation (target modification) or through the mobile genetic elements which carries the resistant genes like plasmid

encoding beta lactamases transfer, enzyme modification in aminoglycosides plasmid borne quinolone resistant gene. Report says 25% of K. Pneumonia, 20-40 % of P. aeruginosa and 40-70% of *A. baumannii* showed resistance to carbapenem [23].

P. aeruginosa is the one of the most important pathogens causing skin infection which acquired antibiotic resistance via many mechanisms like innate resistance by efflux pumps over expression, outer membrane permeability decreases and also gaining the resistance genes, mutation in genes which code for porin channel and alteration in important proteins are makes the P. aeruginosa treatment difficult. The β- lactam antibiotics (penicillin and carbapenem) as well as third and fourth generation of cephalosporin such as cefepime and ceftazidime were the most important β- lactams which inhibit the cell wall synthesis used for the treatment of P. aeruginosa causing skin infection. The development of resistant to these antibiotics was mediated by the enzyme β- lactamases via cleavage of β- lactam ring which makes antibiotic ineffective. It is also gained resistance to aminoglycosides through the transferable aminoglycoside modifying enzymes which inactivate the antibiotic by the attachment of phosphate to antibiotics resulting decrease in binding affinity to target organism [24].

A. baumannii is the most important organism in multidrug resistance to skin infection. It showed a variety of resistant mechanism such as β- lactams inactivation by β- lactamases, hydrolysis of ESBL makes carbapenem resistance, over expression of multidrug efflux pumps makes resistance in *A. baumannii* to tigecycline as well as resistance to aminoglycosides by transferees, target site alteration, decrease in membrane permeability [25]. *K. pneumonia* and *E. coli* showed resistance to carbapenems.

Risk factors for skin infection

Skin infections are most common in all the competent populations but it was frequently identified in certain populations those who are increased risk for associated co morbidities (Figure 2). The previous report says that, the highest rate of skin infection was observed in children were aged above five years and adults were aged below sixty five when compared to other age groups [7]. The other reports says various co morbid situations like critical illness, obesity, diabetes, kidney disease, vascular insufficiency, liver, immune deficiency as well as immune compromise has affected not only the skin infections development but their outcomes as well [26]. Some co morbid condition like obesity was reported as risk factor for infection in surgical site but also for recurrent infection owing to multidrug resistance resulting treatment failure in patients were admitted in hospitals for prolong period with abscess or cellulitis [20]. Many studies have reported that diabetic condition is the most important risk factor for skin infection among the other co morbid conditions [27].

Diabetes

Skin infections like abscesses, cellulitis was more frequent in diabetic patient when compared to non-diabetic patient. Besides that, it has nearly fourfold risk of complicated skin infection compared to non-diabetic patients [28]. A study reported the patient with diabetes who has admitted in intensive care unit has a risk for skin infections as well as the diabetic patient who undergo for bypass surgery those are more prevalent for surgical site infection [29]. The diabetic patient those who are hospitalized with other risk conditions like surgical site infection, major abscesses and necrotizing fasciitis resulting an increasing and worrying gram

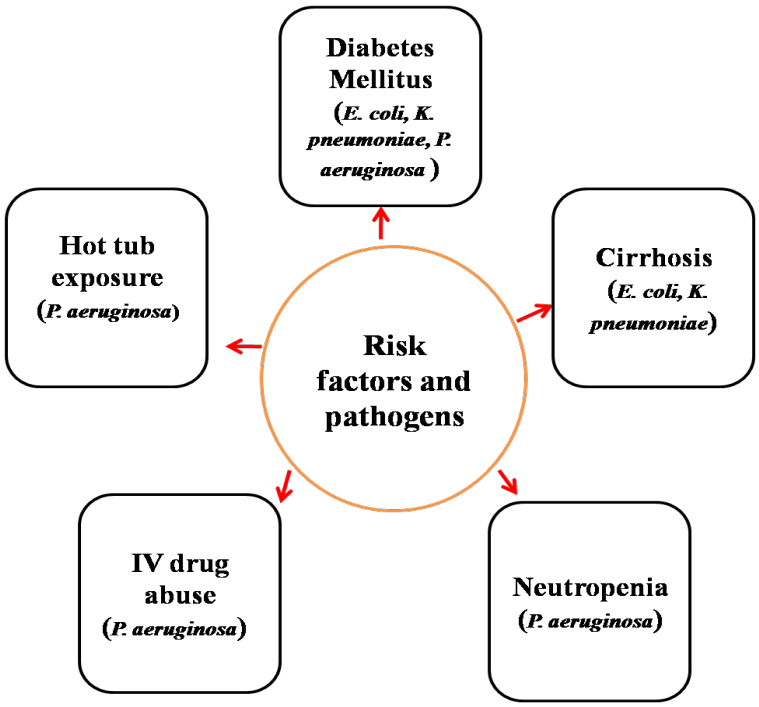

Figure 2: Various risk factors and their causative agents.

negative bacilli detection. Unfortunately, a recent study reported that, the majority of diabetic patients those who had blood stream infections through skin infection but no history of foot infection, among this, one third of the infections were caused by gram negative bacilli particularly, *P. aeruginosa*, *K. pneumoniae* and *E. coli* [30]. Most importantly, gram negative bacilli causing skin infection is the main factor which individually connected with mortality [30]. The prevalence and multidrug resistance among the organism in the hospital settings signifies an important threat to public health along with increasing morbidity and mortality rate mainly in patients with a greater number of co-morbidities [31-33]. Consequently, the patient with no history diabetes but had foot infection was detected with carbapenem-resistance organism including *A. baumannii*, Citrobacter [34].

Diagnosis and management

The rapid diagnostic techniques have been developed for enhancement of the better outcome for the skin infected patients those are affected with other critical conditions, incomplete data and strategies. However, a greater number of studies is immediately required for the establishment of the actual function of the different new diagnostic technologies for the skin infection [35]. Even this highly developed diagnostic is available, the treatment for skin infections were highly challenging because elevated rate of culture negative skin infection in patients with higher menace for infection caused by both gram negative and mixed organisms. Therefore, this is the time for a swift, from intravenous to oral antibiotic therapy but the duration of the treatment was unknown. These swift from IV to oral antibiotic is possible, when the clinical advancement is evident. Along with, an intensive course therapy played a role for some skin infected population but there is a lack for clinical evidence on this particular thing.

Future directions for skin infection

Antibiotic resistance is an emerging and huge concern which causes more than seven hundred thousand deaths annually. Therefore, the development of novel or newer drug is required urgently. Here, we discussed about the novel treatment option for gram negative bacilli which causing skin infection that was emerged from research.

Antibiotic adjuvants

Antibiotic adjuvants are compound which has no antibiotic activity but when it is administered along with the antibiotics and forms the complex. This complex enhances the drug activity or blocks the resistance of the organism to that drug. So, the adjuvants are called as antibiotic resistance breakers [36]. Still, three types of antibiotic adjuvants such as β-lactamase inhibitors, inhibitors for efflux pump system and outer membrane permeabilizers were developed to assist the bacteria to overcome the drug resistant. β-lactamase inhibitors are most widely used antibiotic adjuvant which is used for β-lactam antibiotic against *A. baumannii, P. aeruginosa* and *K. pneumonia* to overcome drug resistance. Clavulanic acid, Sulbactam, tazobactam, Avibactam, Zidebactam, LN-1-255 which is penicillanic acid sulfone substituted 6-alkylidene and diaz bicyclooctane are the potent β-lactamase inhibitors used in clinical practice against multidrug resistant *P. aeruginosa* and *A. baumannii* [37-39]. The other antibiotic adjuvant is vaborbactam a boric acid agent act as serine protease inhibitors against *E. coli* [40] (Figure 3).

Alternative to antibiotics

The abrupt increases of resistance prompted to find an

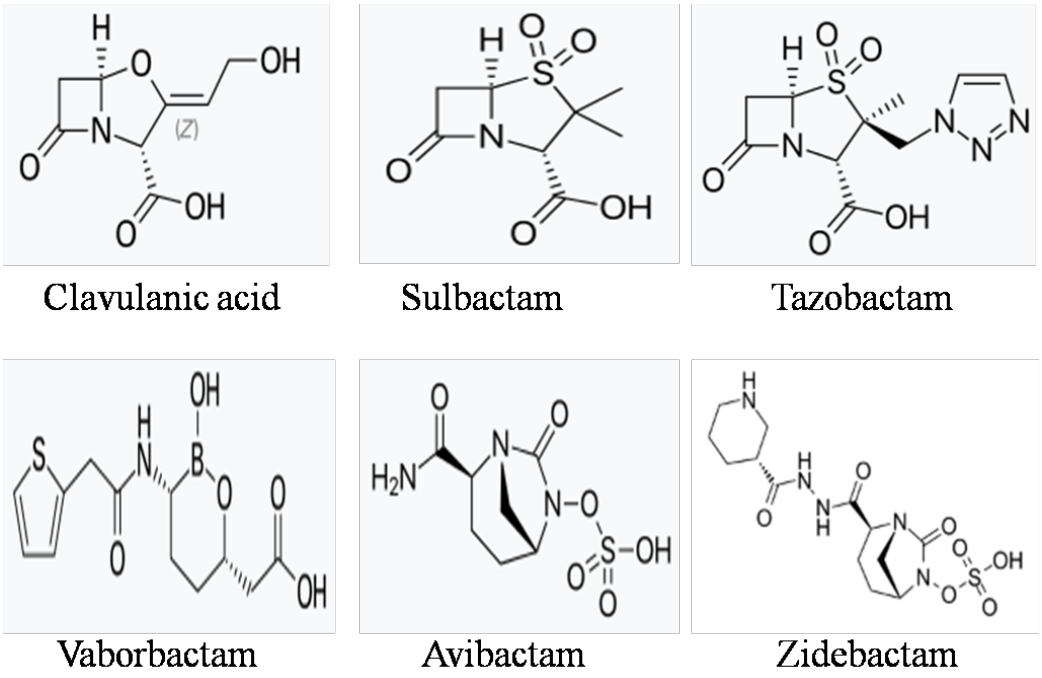

Figure 3: Structures of some important antibiotic adjuvants.

alternative way to fight against multidrug resistance microbes. In this way, bacteriophage and its products played a same role as antibiotics does. The first clinical trial Biophage-PA was attempted against P. aeruginosa in 2017 [41,42]. Another compound called dichloro carbazol propane and peptic benzimidazole were showed a broad-spectrum antibacterial activity against P. aeruginosa and *E. coli* [43,44]. In addition, quorum sensing inhibitors like auto inducer 2 and some metal based antibacterial agents such as gold, silver, ruthenium, gallium, bismuth and copper were used against multidrug resistant *E. coli, P. aeruginosa, A. baumannii* and *K. pnemoniae* [45-49].

Combinational therapy

Though, many antibiotics are available to treat skin infections, newer antibiotic will be discovered or is being developed for the treatment of skin infections owing to its high prevalence of multiple resistant strains. Still, the newer antibiotics has some advantage like expensive as well as least accessible but it may lack the evidence on clinical data for top to bottom comparison among the discovered antibiotics. Consequently, inadequate data for their usage in patient who has high risk factor such as diabetes etc., To achieve the cost effective and synergistic efficacy for treatment for skin infection the rising information is needed on their combination with existing antibiotics.

CONCLUSION

Gram negative multidrug resistant organisms such as *P. aeruginosa, K. pneumonia, E. coli* and *A. baumannii* causing skin infection in patients with risk factors were more challenging to treat. These organisms were getting resistant to antibiotics by over expression of efflux pump, target site alteration, decrease permeability and gene mutation. This resistant property prompted the researcher to find the alternate way like bacteriophage; some metal based antibacterial agents to treat skin infection efficiently. The current data revealed that most of the alternative agents were under trial as well as most of the novel compounds are being developed. It is giving the hope that the compounds under clinical trials will be considered for the treatment skin infection caused by gram negative multidrug resistant organisms.

ACKNOWLEDGEMENT

The authors are grateful to the Deanship of Scientific Research, Prince Sattam bin Abdulaziz University, Al-Kharj, Saudi Arabia, for its support and encouragement in conducting the research and publishing this report.

CONFLICTS OF INTEREST

Authors declare no conflict of interest.

REFERENCES

1. Esposito S, Noviello S, Leone S. Epidemiology and microbiology of skin and soft tissue infections. Curr Opin Infect Dis 2016; 29:109–115.
2. Miller LG, Eisenberg DF, Liu H, et al. Incidence of skin and soft tissue infections in ambulatory and inpatient settings, 2005–2010. BMC Infect Dis 2015; 15:362–69.
3. Edelsberg J, Taneja C, Zervos M, et al. Trends in US hospital admissions for skin and soft tissue infections. Emerg Infect Dis 2009; 15:1516–1518.
4. Hersh AL, Chambers HF, Maselli JH, et al. National trends in ambulatory visits and antibiotic prescribing for skin and soft-tissue infections. Arch Intern Med 2008; 168:1585–1591.
5. Rajan S. Skin and soft-tissue infections: Classifying and treating a spectrum. Cleve Clin J Med 2012; 79:57–66.
6. Merlino JI, Malangoni MA. Complicated skin and soft-tissue infections: Diagnostic approach and empiric treatment options. Cleve Clin J Med 2007; 74:21–28.
7. Ray GT, Suaya JA, Baxter R. Incidence, microbiology, and patient characteristics of skin and soft-tissue infections in a U.S. population: A retrospective population-based study. BMC Infect Dis 2013; 13:252.
8. Ioannou P, Tsagkaraki E, Athanasaki A, et al. Gram-negative bacteria as emerging pathogens affecting mortality in skin and soft tissue infections. Hippokratia 2018; 22:23–28.
9. Lipsky BA, Napolitano LM, Moran GJ, et al. Inappropriate initial antibiotic treatment for complicated skin and soft tissue infections in hospitalized patients: Incidence and associated factors. Diagn Microbiol Infect Dis 2014; 79:273–279.
10. McGinnis E, Cammarata S, Barnes S, et al. Characteristics of patients hospitalized for acute bacterial skin and skin structure infections from 2009–2013. In: ID Week; New Orleans, LA, 2016.
11. Zilberberg MD, Shorr AF, Micek ST, et al. Epidemiology and outcomes of hospitalizations with complicated skin and skin-structure infections: implications of healthcare-associated infection risk factors. Infect Control Hosp Epidemiol 2009; 30:1203–1210.
12. Neuner EA, Yeh JY, Hall GS. Treatment and outcomes in carbapenem-resistant *Klebsiella pneumoniae* blood-stream infections. Diagn Microbiol Infect Dis 2011; 69:357–362.
13. Mohanty S, Kapil A, Dhawan B, et al. Bacteriological and antimicrobial susceptibility profile of soft tissue infections from Northern India. Indian J Med Sci 2004; 58:10–15.
14. Moet GJ, Jones RN, Biedenbach DJ, et al. Contemporary causes of skin and soft tissue infections in North America, Latin America, and Europe: Report from the SENTRY antimicrobial surveillance program (1998-2004). Diagn Microbiol Infect Dis 2007; 57:7–13.
15. Jenkins TC, Knepper BC, Jason Moore S, et al. Comparison of the microbiology and an¬tibiotic treatment among diabetic and nondiabetic patients hospitalized for cellulitis or cutaneous abscess. J Hosp Med 2014; 9:788-794.
16. Grice EA. The intersection of microbiome and host at the skin interface: genomic- and metagenomic-based

insights. Genome Res 2015; 25:1514–1520.

17. Esposito S, Bassetti M, Bonnet E, et al. Hot topics in the diagnosis and management of skin and soft-tissue infections. Int J Antimicrob Agents 2016; 48:19–26.
18. Lipsky BA, Tabak YP, Johannes RS, et al. Skin and soft tissue infections in hospitalised patients with diabetes: culture isolates and risk factors associated with mortality, length of stay and cost. Diabetologia 2010; 53:914–923.
19. Dryden MS. Complicated skin and soft tissue infection. J Antimicrob Chemother 2010; 65:35–44.
20. Villegas MV, Lolans K, Correa A, et al. First identification of Pseudomonas aeruginosa isolates producing a KPC-type carbapenem-hydrolyzing beta-lactamase. Antimicrob Agents Chemother 2007; 51:1553–1555.
21. McAdam AJ, Sharpe AH. Infectious diseases–bacterial infections. In: Kumar V, Abbas AK, Fausto N, eds. Robbins & Cotran Pathologic Basis of Disease. Philadelphia: Elsevier Inc 2005; 371-96.
22. Kumar V, Abbas AK, Fausto N. Acute and chronic inflammation. In: Robbins and Cotran Pathologic Basis of Disease. Philadelphia: Elesvier Inc, 2005; 47-86.
23. Ruppé E, Woerther PL, Barbier F. Mechanisms of antimicrobial resistance in Gram-negative bacilli. Ann Intensiv Care 2015; 5:61.
24. Pachori P, Gothalwal R, Gandhi P. Emergence of antibiotic resistance Pseudomonas aeruginosa in intensive care unit; A critical review. Genes Dis 2019; 6:109-119.
25. Lee CR, Lee JH, Park M, et al. Biology of *Acinetobacter baumannii*: Pathogenesis, antibiotic resistance mechanisms, and prospective treatment options. Front Cell Infect Microbiol 2017; 7:55.
26. Bassetti M, Vena A, Croxatto A, et al. How to manage Pseudomonas aeruginosa infections. Drugs in Context 2018; 7:212527.
27. Muller LM, Gorter KJ, Hak E, et al. Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. Clin Infect Dis 2005; 41:281-288.
28. Suaya JA, Eisenberg DF, Fang C, et al. Skin and soft tissue infections and associated complications among commercially insured patients aged 0–64 years with and without diabetes in the U.S. PLoS ONE 2013; 8:e60057.
29. Martin ET, Kaye KS, Knott C, et al. Diabetes and risk of surgical site infection: A systematic review and meta-analysis. Infect Control Hosp Epidemiol 2016; 37:88-99.
30. Benavent E, Murillo O, Grau I, et al. The impact of gram-negative bacilli in bacteremic skin and soft tissue infections among patients with diabetes. Diabetes Care 2019; 42:e110-e112.
31. Falcone M, Bassetti M, Tiseo G, et al. Time to appropriate antibiotic therapy is a predictor of outcome in patients with bloodstream infection caused by KPC-producing *Klebsiella pneumoniae*. Crit Care 2020; 24:29.
32. Falcone M, Tiseo G, Antonelli A, et al. Clinical features and outcomes of bloodstream infections caused by New Delhi Metallo-β-lactamase-producing Enterobacterales during a regional outbreak. Open Forum Infect Dis 2020; 7:ofaa011.
33. Falcone M, Daikos GL, Tiseo G, et al. Efficacy of ceftazidime-avibactam plus aztreonam in patients with bloodstream infections caused by MBL-producing Enterobacterales. Clin Infect Dis 2020; 586.
34. Karmaker M, Sanyal SK, Sultana M, et al. Association of bacteria in diabetic and non-diabetic foot infection-An investigation in patients from Bangladesh. J Infect Public Health 2016; 9:267-277.
35. Esposito S, De Simone G, Pan A, et al. Epidemiology and microbiology of skin and soft tissue infections: Preliminary results of a national registry. J Chemother 2019; 31:9-14.
36. Gill EE, Franco OL, Hancock REW. Antibiotic adjuvants: Diverse strategies for controlling drug-resistant pathogens. Chem Boil Drug Des 2014; 85:56–78.
37. Gonzalez-Bello C. Antibiotic adjuvants–A strategy to unlock bacterial resistance to antibiotics. Bioorganic Med Chem Lett 2017; 27:4221–4228.
38. Vallejo JA, Guitián MM, Vázquez-Ucha JC, et al. LN-1-255, a penicillanic acid sulfone able to inhibit the class D carbapenemase OXA-48. J Antimicrob Chemother 2016; 71;2171–2180.
39. Mangoni AA, Guillou C, Vanden Eynde JJ, et al. Breakthroughs in medicinal chemistry: New targets and mechanisms, new drugs new hopes (-) 4. Molecules 2018; 2:130.
40. Hecker SJ, Reddy KR, Totrov M, et al. Discovery of a cyclic boronic acid-lactamase inhibitor (RPX7009) with utility *vs.* class a serine carbapenemases. J Med Chem 2015; 58:3682–3692.
41. Jault P, Leclerc T, Jennes S, et al. Efficacy and tolerability of a cocktail of bacteriophages to treat burn wounds infected by Pseudomonas aeruginosa (PhagoBurn): A randomised, controlled, double-blind phase 1/2 trial. Lancet Infect Dis 2019; 19:35–45.
42. Calero-Caceres W, Ye M, Balcázar JL. Bacteriophages as environmental reservoirs of antibiotic resistance. Trends Microbiol 2019; 27:570–577.
43. Bird M, Silvestri AP, Dawson PE. Expedient on-resin synthesis of peptidic benzimidazoles. Bioorganic Med Chem Lett 2018; 28:2679–2681.
44. Bugday N, Kucukbay FZ, Apohan E, et al. Synthesis and evaluation of novel benzimidazole conjugates incorporating amino acids and dipeptide moieties. Lett Org Chem 2017; 14:198–206.
45. Stotani S, Gatta V, Medda F, et al. A versatile strategy for the synthesis of 4,5-Dihydroxy-2,3-Pentanedione (DPD) and related compounds as potential modulators of bacterial quorum sensing. Molecules 2018; 23:2545.
46. Stotani S, Gatta V, Medarametla P, et al. DPD-Inspired discovery of novel LsrK Kinase inhibitors: An opportunity to fight antimicrobial resistance. J Med Chem 2019; 62:2720–2737.

47. Frei A. Metal complexes, an untapped source of antibiotic potential? Antibiotics 2020; 9:90.

48. Kareem A. Combination effect of edible mushroom–Sliver nanoparticles and antibioticsagainst selected multidrug biofilm pathogens. Int J Res Pharm Sci 2018; 9.

49. Werrett MV, Herdman ME, Brammananth R, et al. Bismuth phosphinates in Bi-nanocellulose composites and their e_cacy towards multi-drug resistant bacteria. Chem A Eur J 2018; 24:12938–12949.