IOSR Journal Of Pharmacy And Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 15, Issue 5 Ser. III (Sep. –Oct. 2020), PP 52-57
www.Iosrjournals.Org

Aerosolized Polymyxin-E for the Treatment of Multidrug Resistant Respiratory Tract Infections.

Govindaraju Gayathiri [1], Noble Noby[1], T.M Umamageswari[2], Arumugam Vijayakumar*

Clinical Pharmacist – General Medicine Department, Kovai Medical center and Hospital - Coimbatore[1].
Associate Professor of Pharmacology, KMCH Institute of Health Sciences and Research – Coimbatore[2].
Manager Pharmacy Services, Kovai Medical center and Hospital – Coimbatore[*].
Corresponding Author: Mr. Vijayakumar Arumugam
Manager Pharmacy Services Kovai Medical center and Hospital Coimbatore.

Abstract:
Background:
Bacterial Pneumonia caused by multidrug resistant gram negative organisms were successfully treated with nebulized colistimethate sodium. The mainstay of therapy deals with early and vigorous antibiotic treatment to prevent further deterioration. An important consideration is to identify the causative organism and recognize the resistance pattern so as to optimize antimicrobials. Intravenous administration of antibiotics donot provide sufficient concentration of the drug to the lung tissues for underlying infection to be treated. Nebulizing certain antibiotics, accomplishing therapeutic concentration at the lung tissues provide promising effect in eradicating the pathogenic organism.
Materials and methods:
In order to trace the efficacy of nebulization, a retrospective observational study was done with 53 inpatients including three neonates who required colistimethate nebulization. Medical records were accessed using pharmacy databases based on patient who received colistin 1 MIU. We excluded those patients whose dose was adjusted on the basis of renal impairment or administered intrathecally.
Results:
The most common organisms causing pneumonia were Klebsiella pneumoniae 42 (32.5%), Acinetobacter baumannii 35 (27.1%) and Pseudomonas aeruginosa 32 (24.8%). 82.8% Acinetobacter baumannii, 69% Klebsiella pneumoniae, 28.5% Escherichia coli, and 28.1% Pseudomonas aeruginosa were resistant tocarbapenems, requiring Polymyxin therapy. Nebulized colistin was considered as a therapeutic option after failure of available broad spectrum antibiotic or the documentation of Carbapenemase producing multidrug resistant pathogen. About 14/22 (63.6%) of Multi Drug Sensitive (MDS) organism and 26/37 of Extensive Drug Resistant (XDR) organism had cure at day 7 of nebulization with Polymyxin E.
Conclusion:
Most of the XDR organisms like Klebsiella pneumoniae, Pseudomonas aeruginosa and Acinetobacter baumannii required more than 7 days of nebulization or an add-on with another anbtibiotic. We conclude that nebulization with higher dose of Polymyxin E is an effective therapy for multidrug resistant gram negative organisms.

Keywords: *Colistimethate sodium, Polymyxin E, Nebulization.*

Date of Submission: 10-09-2020 Date of Acceptance: 24-09-2020

I. Introduction

Pneumonia – an acute respiratory infection affecting the lungs, caused most frequently by bacteria, viruses and fungi [(1)]. Pneumonia is the leading cause of deaths in the world about 8 million children under the age of 5 were died in 2017[(2)]. As reported by UNICEF 2018, India has a death rate of 1.25 million due to pneumonia[(3)]. Infectious Diseases Society of America (IDSA) defined Community Acquired Pneumonia as acute infection of the pulmonary parenchyma that is accompanied by the presence of an acute infiltrate in chest radiography or ascultatory findings consistent with pneumonia, in a patient not hospitalized or residing in a long term care facility for more than 14 days before onset of symptoms[(4)]. Epidemiologically pneumonia can be classified as Community Acquired Pneumonia (CAP), Hospital Acquired Pneumonia (HAP) and Ventilator Associated Pneumonia (VAP). CAP being the most common type of pneumonia affecting people in-spite VAP has the higher incidence of mortality during hospitalization[(5)]. Pneumonia was considered to be ventilator associated when the onset is 48 hrs after initiation of mechanical ventilation and was judged not to be incubating

before the initiation of mechanical ventilation[6].

Multi drug resistant gram negative bacteria such as *Pseudomonas aeruginosa, Klebsiella pneumonia* and *Acinetobacter baumannii* are the leading cause of nosocomial infections in VAP involving chronic colonization, frequent exacerbation associated with high mortality[7]. The increasing prevalence of pan resistant gram negative organisms showing resistance to almost all frequently used antimicrobials have led to the decline in efficacy of antibiotics[6]. For better clinical outcomes IDSA emphasize prompt initiation of both empirical and definitive therapy[8]. Penicillins, Cephalosporins, Quinolones and Macrolides are used as empirical therapy which were then escalated based on the microbial documentation to Carbapenems, Monobactams or Polymyxins. Nebulized Polymyxin therapy is introduced as a salvage therapy in the management caused by multidrug resistant gram negative pathogens[9]. Carbapenem resistant strains of *Acinetobacter baumannii* and *Klebsiella pneumoniae* exhibits resistance to all antibiotics except Polymyxins. Polymyxins used intravenously (IV) or nebulized form is effective against such organisms, add on IV therapy is decided based on the dissemination. If infection is contained only in the lungs nebulization is preferred[10].

Polymyxins are a group of cationic polypeptide antibiotics having five different components[9]. Polymyxin B and E being in use both exert bactericidal effect on Gram Negative Bacilli (GNB). Polymyxin E or Colistimethate sodium competitively displaces calcium and magnesium cations of lipo-polysaccharides and phospholipids in the bacterial structural components. This change damages the osmotic barrier and lead to leakage of intracellular components[11]. Intravenous colistin doesn't give sufficient concentration of drug to the lung tissue in treating pneumonia. Nebulized colistin came into practice in the early 2000 to treat GNB infection in cystic fibrosis [9].

Polymyxin B - another agent from the group Polymyxin contains D-Phenylalanine in place of D-Leucine therefore causing more broncho spasm makes it unfit for use in inhalational route[12]. Colistin has an extensive coverage against *Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli, Enterobacter spp, Salmonella spp, Shigella* and *Acinetobacter baumannii* but are intrinsically resistant to *Burkholderia cepacia, Serratia marcescens* and *Proteus mirabilis*[13]. Being a concentration dependent antibiotic, it is bacteriostatic at low concentration and bactericidal at higher concentration. It also posses post antibiotic effect making the organism to develop resistance rarely. Although colistin has toxic side effects as nephrotoxicity and neurotoxicity there are some non toxic side effects as pharyngitis, cough and throat irritation. Side effects vary with route of administration[12]. Aerosolized therapy was advantageous in reducing the side effects caused by parenteral administration. As inhaled colistin achieves higher concentration in the lung epithelium, a dose of 30 – 150 mg Colistin Base Activity (CBA) / day in divided doses is useful in patients with pulmonary colonization or infection with susceptible organism[8,14].

II. Methodology

Study design and data collection*:*

Retrospective observational study was conducted in a tertiary care private hospital, Coimbatore. Patients who received nebulized colistin for more than 72 hours for the treatment of MDR gram negative pathogens from March 2018 - March 2019 were located from pharmacy electronic databases and their medical records were reviewed. Demographic, clinical and microbiological data were collected. Patients who received 1 Million International Unit (MIU) of nebulized colistin were included in this study. Patients intended with colistin 1 MIU vials but received intravenous or intrathecal or other routes were excluded from the study.

Administration of inhaled colistin:

Selected patients with positive Endotracheal (ET)/Bronchio Alveolar Lavage (BAL) microbial documentation received Colistimethate Sodium (CMS) as inhalation at a dose of 1 MIU (80 mg CMS) every 8 hours dissolved in 3 ml NS or ½ NS through a vibrating mesh or aerojet nebulizer. Patients requiring mechanical ventilation or Continuous Positive Airway Pressure (CPAP), a T-piece was attached with ET tube and nebulized for 15 - 20 minutes. Patients without respiratory support where nebulization was done with vibrating mesh nebulizer or an aerosol jet nebulizer or with face mask 8 liter / minute oxygen flow.

Clinical and Microbial assessments:

Patients with suspected respiratory tract infections had purulent secretions, elevated leukocyte counts, hyperthermia and documented microbial growth in either BAL or throat swabs. A positive sample was defined as the growth of organism in the suspected sample with $> 10^5$ Colony Forming Units (CFU)/ml. Patients showing symptoms of respiratory tract infections are empirically started on either Penicillins or Cephalosporins post culture specimens and treated for a period of 7 or 14 days. If the symptom persists or patient gets worse clinically, antibiotics were escalated accordingly. Clinical responses were classified at the end of therapy with restricted antibiotics at 7 days by primary physicians as cure, persistent pneumoniae, recurrence or super-infection.

III. Results

Patient characteristics:

During the study period we had 53 patients requiring nebulized colistin in treatment of Multi Drug Resistant (MDR) gram negative organisms. About 62.2% (33 cases) were adults and we had 3 neonates who required nebulized Polymyxin E. 49 (92.4%) of them were male and 32 % of the study population were elderly. In the total study population about 56.6 % (30 cases) required hospitalization of more than a month and this varied based on other underlying conditions.

Microbe and antibiotic:

We encountered 129 episodes of isolating organisms that require nebulized colistin. The most common causative organism was *Klebsiella pneumoniae* 42 (32.5%), *Acinetobacter baumannii* 35 (27.1%) followed by *Pseudomonas aeruginosa* 32 (24.8%). There were one cases each of *Citrobacter koseri*, *Burkholderia cepacia*, *Morganella morganii*, *Stenotrophomonas maltophilia* as some other least common organisms requiring nebulized Polymyxin E. A total of 11 different organisms were isolated as shown in table 1. 29/42 *Klebsiella pneumoniae* were producing carbapenamase and were sensitive only to Polymyxins and Fosfomycin. We also had 9/42 Multidrug Sensitive *Klebsiella pneumoniae*, 3/42 producing Extended Spectrum Beta Lactamases (ESBL) and 1/42 AmPC beta lactamase producer in the *Klebsiella pneumoniae* group. *Acinetobacter baumannii* was the second most predominant organism requiring the need for nebulized Polymyxin E. 29/35 were Extensively Drug Resistant (XDR) which were sensitive only to colistin and 6/35 of them were either multidrug sensitive or showing sensitivity to carbapenems. *Pseudomonas aeruginosa* isolates requiring colistin nebulization were mostly Multi drug sensitive 20/32 or sensitive to aminoglycosides and carbapenem 3/32, extensively drug resistant *Pseudomonas* were only 28.1 % (9/32). We had 3/129 isolates of *Elizabethkingia meningosptica*, all of which are resistant to Polymyxins and isolated as super-infection rather than a primary organism requiring therapy with nebulized or intravenous colistin.

Table:1 Organisms isolated and their resistance patterns

Organisms	Total no of cases	Resistance pattern	No of cases
Klebsiella pneumoniae	42	MDS	9
		ESBL	3
		AmPC	1
		PCP	29
Acinetobacter baumannii	35	MDS	2
		MDR sensitive to Carbapenem	4
		XDR sensitive to Colistin	29
Pseudomonas aeruginosa	32	MDS	20
		MDR sensitive to Carbapenem	3
		XDR sensitive to Colistin	9
Escherichia coli	7	MDS	1
		ESBL	3
		PCP	2
		AmPC	1
Serratia marcescens	4	XDR	4
Elizabethkingia meningoseptica	3	XDR	3
Enterobacter sps	2	MDS	2
Stenotrophomonas maltophilia	1	XDR	1
Morganella morganii	1	MDS	1
Burkholderia cepacia	1	MDS	1
Citrobacter koseri	1	MDS	1

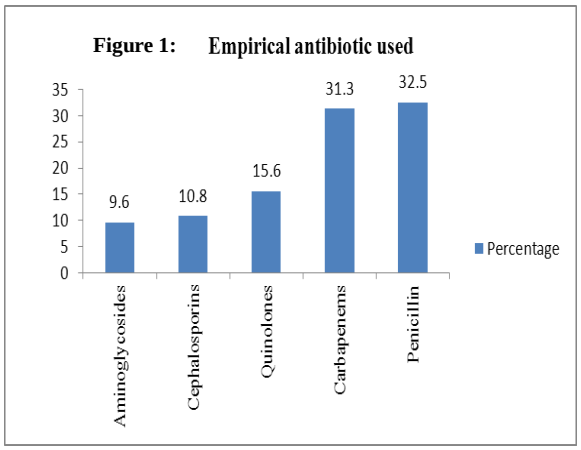
MDS – Multi Drug Sensitive, ESBL – Extended Spectrum Beta Lactamase, KPC – Klebsiella Carbapenamase Producer, XDR – Extensively Drug Resistant, MDR - Multi Drug Resistant, AmPC – AmPC beta lactamases.

Rationale for nebulized colistin:

In the 53 patients of sensitive strain group 62.5% of initial *Pseudomonas aeruginosa* isolates were susceptible to all anti-pseudomonal antibiotics and 28.1% were resistant to Carbapenems. 82.8% of *Acinetobacter baumannii*, 69 % of *Klebsiella pneumoniae* and 28.5% of *Escherichia coli* were sensitive only to Polymyxin. Most patients in our study received atleast 4 different classes of antibiotics (Figure 1) prior initiating colistin therapy. The most commonly prescribed empirical antibiotics were Penicillins 32.5% followed by Carbapenems 31.3% and Quinolones 15.6% which were subsequently escalated to Polymyxin E nebulization (Figure 2). Of the 53 patients requiring therapy with nebulized colistin all of them had growth of atleast one bacteria that is considered pathogenic.

Post treatment microbial documentation:

Post treatment relapse of pneumonia caused by other organism were more predominant in *Klebsiella*



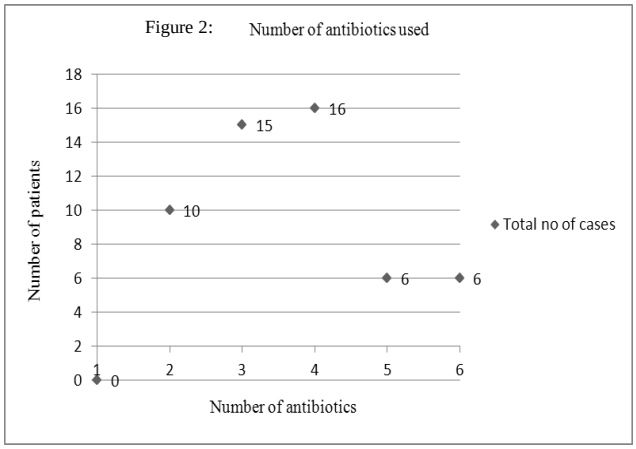


Table 2: Persistance of infection at Day 7 of therapy with nebulized colistin.

Pneumonia caused by		MDS (n=22)	XDR (n=37)
Klebsiella pneumoniae	Cure at Day 7	5	14
	Persisting at day 7	2	4
Acinetobacter baumannii	Cure at Day 7	4	10
	Persisting at day 7	2	7
Pseudomonas aeruginosa	Cure at Day 7	5	2
	Persisting at day 7	4	0

pneumoniae group where patients had super-infection with multiple organisms as *Elizabeth kingia, staphylococcus aureus, Pseudomonas aeruginosa, Acinetobacter baumannii* 2/25 whereas *Pseudomonas aeruginosa* group did not have much super-infections. Patients infected primarily with *Acinetobacter baumannii* had super infection with *Pseudomonas aeruginosa* 6/11 as the most common super-infection followed by *Klebsiella pneumoniae* 4/11. In such cases either nebulization was continued for another 7 days or an additional antibiotic was started as dual therapy. Patients with pneumoniae caused by susceptible strains are treated with combination of Penicillin and Aminoglycoside. Nebulized colistin was considered as a cure to MDR organisms and prevents lung infections. Recurrence after initial cure of VAP was not considered as failure of antimicrobial therapy, instead the persisting reservoirs are inaccessible to IV or Nebulized colistin.

Based on the primary culture for initiation of nebulized colistin we took most common isolates as *Klebsiella pneumoniae* (25), *Acinetobacter baumannii* (23), *Pseudomonas aeruginosa* (11) for future analysis. These organisms were divided as MDS and XDR based on the resistance pattern for microbial documentation, cure at day 7 was analyzed in both the groups. About 14/22 (63.6%) of MDS organism and 26/37 of XDR organism had cure at day 7 (Table 2). The remaining required further more treatment extension of 14 days or an add-on antibiotic therapy.

IV. Discussion

Aerosolized colistin is an effective adjunctive intervention for pneumonia caused by MDR organisms mainly for gram-negative bacteria in patients without cystic fibrosis . Once banned, colistin came back to practice just few years ago for the use in multi-drug resistant gram-negative bacteria in case of resistance to available broad spectrum antibiotics. Drug delivery mechanism using aerosols are the major part of therapy in

Respiratory Tract Infections (RTI)[15]. Nebulised colistin have certain concerns related to adverse effects such as broncho constriction, cough and IV colistin has dose dependent nephrotoxicity, CNS toxicity with associated symptoms as dizziness, pruritis, slurred speech and vertigo. Once mixed colistimethate begins its conversion to colistin - component that causes severe pulmonary toxicity. There are certain qualities of ideal inhaled antibiotics such as penetrance to the actual site of action, concentration in sputum, thermal stability during aerosolization, minimal local toxic effects (bronchospasm, cough)[16].

Lu Q et al conducted a four year study in patients with VAP caused by *Pseudomonas aeruginosa* and *Acinetobacter baumannii.* Among them, 43 had MDR strains and treated with nebulized colistin and showed a clinical response of 67%[7]. *Levin et al* reported 60 patients who had pneumonia caused by MDS *Pseudomonas aeruginosa* and MDR *Acinetobacter baumannii* and observed a cure rate of 60%. Whereas in our study we had a cure of 51.3% in MDR *Pseudomonas aeruginosa* and *Acinetobacter baumannii*[17]. A 2 year study conducted by Naesens *R et al* showed inhaled colistin had 100% response, 40% in intravenous route and 78% in combinational therapy for MDR *Pseudomonas aeruginosa* which is in accordance with our study, MDR *Pseudomonas aeruginosa* showed 100% response in inhaled route[18].

Michalopoulos *et al.* revealed the responsible pathogen for nosocomial pneumonia 87.5% by *Acinetobacter baumannii* and 12.5% *Pseudomonas aeruginosa* whereas in our study predominant was with *Klebsiella pneumoniae* (42 cases) followed by *Acinetobacter baumannii* (25 cases) and *Pseudomonas aeruginosa* (32 cases)[6]. Abdellatif *et al.* assessed therapeutic efficacy of aerosolized colistin in 49 patients with MDR VAP showed 72.3% favourable outcomes and most common pathogen causing VAP in were *Acinetobacter baumanni*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*[19]. Ratjen F *et al* evaluated colistin pharmacokinetics in patients with cystic fibrosis which states single dose of Colistimethate sodium (CMS) 2MIU reaches significant higher concentration in the sputum even after 12 hours with low levels in urine and serum[14].

V. Conclusion:

Gram-negative bacteria mainly *Klebsiella pneumoniae* 32.5% (42 cases) was the most common organism causing pneumonia followed by *Acinetobacter baumannii* 35 (27.1%) and *Pseudomonas aeruginosa* 32 (24.8%). *Acinetobacter baumannii* 82.8% (29/35), *Klebsiella pneumoniae* 69% (29/42), *Escherichia coli* 28.5% (2/7) and *Pseudomonas aeruginosa* 28.1% (9/32) were carbapenemase producers. The least isolated organisms *Citrobacter koseri*, *Burkholderia cepacia*, *Morganella morganii*, *Stenotrophomonas maltophilia* were XDR requiring colistimethate sodium. Extensive drug resistance was noted in 59.6% of the isolates. Antibiotic resistance is increasing in an alarming rate and irrational use of antibiotics remains a major contributor. Judicious use of antibiotics are mandated to reduce overuse and misuse of antibiotics.

METHODOLOGICAL LIMITATIONS

Since this study is conducted in a single center we were not able to analyze the therapeutic options implemented in other health care centers. Because of unavailability of control group we couldnot accurately assess the efficacy of nebulized colistin. As with any retrospective study the number of days for microbial eradication, normalization of infectious markers and side effects cause by inhalational therapy were not analyzed. A prospective study in a larger population is warranted to assess efficacy and better safety outcomes.

CONFLICT OF INTEREST

The authors have no conflict of interest in this work.

Acknowledgment

The authors are thankful to Dr. Nalla G Palaniswami, Chairman and Managing Director of Kovai Medical Center and Hospital, Coimbatore, Dr. Thavamani D Palaniswami, Vice Chairman, Kovai Medical Center Research Cancer and Educational Trust and Dr. Arun N Palaniswami, Executive Director, Kovai Medical Center and Hospital, Coimbatore for providing necessary facilities and continuous encouragement.

References

[1]. Dhar R. Pneumonia: Review of guidelines. J Assoc Physicians India.2012;60:25-28.
[2]. https://www.who.int/news-room/fact-sheets/detail/pneumonia.
[3]. https//www.thehindu.com/sci-tech/health/india-saw-2nd-highest-number-of-pneumonia-deaths-of-children-under-age-five-un/article29980164.ece/amp/
[4]. Mandell LA, Wunderink RG, Anzueto A et al. Infectious Diseases Society of America/ American Thoracic Society Consensus Guidelines on the Management of Community Acquired Pneumonia in Adults. Clin Infectious Disease.2007;44:S27-72.
[5]. Burnham JP, Kollef MH, Louis St. CAP, HCAP, HAP, VAP. Chest.2017;5:909-10.
[6]. Michalopoulos A, Kasiakou SK, Mastora Z et al. Aerosolized colistin for treatment of nosocomial pneumoniae due to multidrug resistant gram negative bacteria in patient without Cystic Fibrosis. Criti Care.2005;9(1):R53-59.
[7]. Lu Q, Luo R, Bodin L et al. Efficacy of High dose nebulized colistin in Ventilator Associated Pneumonia caused by multidrug

Resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Anesthesiology.2012;117(6):1335-47.
[8]. Linden PK, Paterson DL. Parenteral an Inhaled colistin for treatment of ventilator associated pneumonia. Clin Infectious Disease.2006;43(2):S89-94.
[9]. Gurjar M. Colistin for lung infection: an update. J Intensive Care.2015;3(3):1-12.
[10]. Antoniu SA, Cojocaru L. Inhaled colistin for lower respiratory tract infections. Expert Opin. Drug Deliv.2012;9(3):333-42.
[11]. Colistimethate sodium.In: Lexi-drugs online. Hudson (OH): lexicomp Inc.;2020.Updated on February 2020, Cited on April 2020. Available from:http://online.lexi.com. Subscription required to view.
[12]. Lu Q, Girardi C, Zhang M et al. Nebulized and intravenous colistin in experimental pneumonia caused by *Pseudomonas aeruginosa*. Intensive care med.2010;36:1147-55.
[13]. Sanford guide (2019). Antimicrobial Therapy, Inc.Mobile Application Software.
[14]. Ratjen F, Rietschel E, Kaseel D et al. Pharamacokinetics of inhaled colistin in patients with cystic fibrosis. J antimicrob Chemother.2006;57:306-11.
[15]. Athanassa Z.E, Markantonis S.L, Fousteri M,F et al. Pharmacokinetics of inhaled colistimethate sodium(CMS) in mechanically ventilated critically ill patients. Inten Care Med.2012;2628-7.
[16]. Honore PM, Jacobs R, Hendrickx I et al. Nebulized colistin for treatment of ventilator-associated pneumonia caused by multidrug-resistant Gram-negative bacteria: We still need to straighten out the dose! Criti Care.2015;19:265.
[17]. Levin AS, Barone AA, Penco J et al. Intravenous colistin as therapy for Nosocomial infection caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Clin Infect Dis.1999;28:1008-11.
[18]. Naesens R,Vlieghe E, Verbrugghe W et al. A retrospective observational study on the efficacy of colistin by inhalation as compared to parenteral administration for the treatment of nosocomial pneumoniae associated with multidrug-resistant *Pseudomonas aeruginosa*. BMC inf dis.2011;11:317-25.
[19]. Abdellatif S, Trifi A, Daly F et al. Efficacy and toxicity of aerosolized colistin in ventilator-associated pneumonia: a prospective, randomised trial. Ann. Inten Care.2016;6(26):1-11.

Govindaraju Gayathiri, et. al."Aerosolized Polymyxin-E for the Treatment of Multidrug Resistant Respiratory Tract Infections." *IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS)*, 15(5), (2020): pp. 52-57.