Original Article

DOI: 10.7860/NJLM/2019/36849:2338

Pathology Section

A Retrospective Analysis of the Efficacy of Ceftriaxone-Sulbactam-EDTA Combination for Suspected Biofilm Infections

SUNITA GUPTA[1], TARANPREET KAUR[2]

ABSTRACT

Introduction: Bacterial biofilms are highly recalcitrant to antibiotic treatment and thus carry important clinical repercussions. In view of rising biofilm-forming pathogens, new antibacterial approaches aimed at disrupting biofilms are needed.

Aim: To determine the clinical utility of CSE-1034 (Ceftriaxone-Sulbactam-EDTA) therapy in suspected biofilm infections.

Materials and Methods: Subjects with Urinary Tract Infections (UTIs) or Intra-Abdominal Infections (IAIs) with in-vivo devices (catheters, stents, etc.,) and suspected of biofilm-related infections and who received CSE-1034 as 2nd line therapy were included in this study. Based on susceptibility report, CSE-1034 therapy was started in these patients and continued or discontinued based on improvement in clinical symptoms.

Results: Thirty culture-positive adult patients were included in this study. All the patients had received Pipericillin-Tazobactam (Pip-Taz) or Cefaperazone-Sulbactam empirically but none of them responded clinically. Culture susceptibility results available on day 3 have shown that isolates from 40% patients started with Pip-Taz were reported susceptible to Pip-Taz and 45% of patients started with Cefaperazone-Sulbactam were reported susceptible to antibiotic used. 100% of the isolates were susceptible to CSE-1034, 90% to Meropenem and susceptibility to Colistin was 80%. Based on culture susceptibility report and further treatment modifications done, all the patients were switched over to CSE-1034 as 2nd line treatment. A total of 27 patients responded to CSE-1034 and were cured. However, 3 patients who did not respond to CSE-1034 for 48 hour were switched over to Meropenem and reported to be cured.

Conclusion: From this study, it can be suggested that CSE-1034 should be a choice of treatment over beta-lactam/beta-lactam inhibitor combinations for patients suspected of biofilm infections.

Keywords: Antibiotic resistance, Beta-lactam Inhibitors, Intra-abdominal infections, Urinary tract infections

INTRODUCTION

During the past few years, the field of medical science has made great strides and more and more medical devices are being used in the treatment of various conditions. Though the extensive use of medical devices has improved the quality of life in critically ill patients, however these medical devices have come at the increased risk of biofilm related infections [1]. The process of device-related infections begins with colonisation of foreign material by the microorganisms, followed by a complex metamorphosis and finally leading to biofilm formation [1]. It has been reported that not all, but most of the medical devices result in biofilm infections [2]. Biofilms are heterogeneous structures formed of bacterial cells surrounded by the self-produced polymeric matrix and attached to solid surfaces. A range of infections including chronic tissue infections to those related to exogenous devices, such as catheters or prosthetic joints are associated with bacterial biofilms [2,3]. UTIs and IAIs are one of the most common bacterial infections acquired in hospital settings through biofilm producing pathogenic organisms.

Normally, the most important way to control bacterial infections are antibiotics, however, antibiotics fail to eradicate biofilm infections. Various in vivo and in vitro studies have demonstrated that bacterial biofilm cells are 100 to 1000 fold more resistant to antibiotics than their planktonic cells [4]. The altered gene expression of bacteria in biofilm structure which amounts up to 20% of all bacterial genes leads to their better protection against antibiotics compared to planktonic cells [5]. Bacteria once organised in the form of biofilms become highly recalcitrant to antibiotic agents, which holds serious consequences for these infections and thus, requires a more elaborate strategy for successful treatment [5]. EDTA, a known divalent metal ion chelator is demonstrated to have numerous antimicrobial and anti-biofilm properties by chelating various metal ions that have been implicated in maintaining matrix integrity of biofilms, microbial adherence and biofilm formation [6], in particular tetrasodium EDTA (tEDTA) [7]. Recently, EDTA has been reported a part of various antibiotics to increase the overall efficacy of the drug [8,9]. CSE-1034, a combination of Ceftriaxone-Sulbactam-disodium edetate is a novel drug approved by Drug Controller General India [10,11]. Various studies have demonstrated that EDTA when used in combination with Ceftriaxone and Sulbactam enhances the activity of Ceftriaxone-Sulbactam combination and is also reported to break biofilms and inhibit curli formation [12]. This retrospective study is aimed to explore the potential of CSE-1034 in the management of Chronic Urinary Tract Infections (cUTI) or IAI patients suspected of biofilm related infections by Gram negative pathogens. The evaluation has been carried out on the basis of clinical response, microbiological response, duration and cost of antibiotic treatment.

MATERIALS AND METHODS

Study Design and Study Population: This retrospective study was conducted on patients admitted to the hospital for treatment between June 2016 to June 2017 in the Department of Medicine, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mulana, Ambala. The case history sheets of all the patients admitted to the hospital for treatment between June 2016 to June 2017 were analysed. Patients in the age group of ≥18 years and suffering from cUTI and IAIs and suspected of biofilm infections by Gram-negative pathogens were included in this study.
The inclusion criteria were: 1) Patients diagnosed with cUTI or IAI based on various lab parameters and relevant signs and symptoms with presence of relevant device in-vivo; 2) Isolation of Gram-negative pathogen at the base-line; 3) Patients who received CSE-

1034 at least for a period of ≥48h; 3) Patients who received CSE-1034 as 2nd line of therapy.

The exclusion criteria were: 1) Patients who received CSE-1034 for a period of <48h; 2) Patients diagnosed with cUTI or IAI but tested culture positive in blood samples.

Patient Analysis, Antibiotic Usage and Outcomes: The information regarding the demographic and clinical characteristics including sex, age, infection type, microbiology, laboratory investigations, etc., for all the patients were retrieved from the case sheets of the patients.

Among all the 235 cases analysed, 30 patients who received CSE-1034 as second line of treatment and fulfilled the other above mentioned inclusion criteria were analysed further.

The dose of CSE-1034 used was 3.0g/12 hour (2000 mg Ceftriaxone/1000 mg - Sulbactam/74 mg - EDTA) given intravenous. The progress of the therapy was evaluated in terms of improvement in clinical parameters on daily basis and at the end of treatment.

Various haematological and biochemical investigations done for the patients included Complete Blood Count (CBC), Liver Function Test (LFT), Urine analysis. Specimens of urine or blood were used for the isolation of baseline pathogens.

In vitro Microbial Antibiotic-Susceptibility Testing (AST): AST of test antibiotics was done using Kirby–Bauer disk diffusion method [13]. Different discs of various antibiotics were used in the study. A single colony of pathogen was picked up from 18-24 hours agar plates to prepare the inoculum with a standard turbidity of 0.5 MacFarland in a Mueller-Hinton broth (MHB, Hi-media, Mumbai, India). A sterile cotton swab was dipped into inoculum suspension and streaked on Mueller-hinton agar (MHA) plate two to three times to ensure even distribution of inoculum. After sometime, antibiotic discs are implanted into inoculated agar plates ensuring complete contact with agar surface. The discs were distributed evenly ensuring a minimum distance of 24 m from center to center. After 15 minutes of inoculation, the plates were inverted and incubated in an incubator for 16-18 hours aerobically at 37°C.

Using breakpoints provided by manufacturer, AST for CSE-1034 was performed. Criteria was >21 mm-susceptible (S), 14-20-Intermediate (I), ≤13-Resistant (R). AST for other agents were done as per CLSI guidelines (2015) [13].

Diagnosis Criteria: The patients included in this study were suffering from Catheter-associated-UTI (CA-UTI) or IAI associated with stents or drains.

The criteria for the diagnosis of CA-UTI were localised signs or symptoms such as catheter obstruction, supra-pubic pain, costo-vertebral angle pain or tenderness, acute haematuria and fever without localised findings.

CA-UTIs were defined by the presence of UTI signs and symptoms with a culture growth of ≥105 colony-forming units/mL in urine specimen from a patient with indwelling catheter, indwelling supra-pubic, or intermittent catheterisation or from a person whose catheter has been removed within previous 48 hour [14].

IAIs were diagnosed based on h/o previous or current device placement and presenting with signs/symptoms of infection such as fever, abdominal pain, tenderness, guarding, rigidity. Radiological investigations e.g., USG, CT Abdomen are suggestive of intra-abdominal collections.

STATISTICAL ANALYSIS

The statistical analysis was performed using Chi-square test. The p-value of <0.05 was considered as statistically significant.

RESULTS

Subjects and their Baseline Characteristics: A total of 105 patients suffering from cUTI and IAIs who received CSE-1034 as 2nd line of treatment were screened. Thirty patients meeting in the present study inclusion criteria were included. Female patients were little more compared to males although not significantly. For details on other demographic and baseline characteristics, refer to [Table/Fig-1]. Overall, cUTI cases were more compared to IAIs. Diabetes mellitus and hypertension were the most common co-morbidities followed by hepatic disorders and Chronic Kidney Disease (CKD) [Table/Fig-1]. The predominant pathogens isolated were *Escherichia coli* (40%) followed by *Klebsiella pneumoniae* (20%) and *Acinetobacter baumannii* (15%). For further details, refer to [Table/Fig-2].

Characteristics		(n=30)
Gender	Male, n (%)	13 (43)
	Female, n (%)	17 (57)
Age (year)	Mean±SD	69±15.65
Height (Cm)	Mean±SD	164±4.88
Weight (Kg)	Mean±SD	72±12.6
Temperature (°F)	Mean±SD	99±2.14
BP (mmHg)	Systolic (Mean±SD)	128±12.36
	Diastolic (Mean±SD)	78±7.60
Pulse (beats/min)	Mean±SD	100±16.05
Respiratory rate (/min)	Mean±SD	23±8.51
Diagnosis n (%)	Chronic urinary tract infection	17 (57)
	Intra-abdominal infections	13 (43)
Co-morbidities n (%)		
	Diabetes mellitus	18 (60)
	Hypertension	17 (56)
	Hepatic disorders	10 (33)
	Chronic kidney disease	07 (23)
	Others	04 (13)

[Table/Fig-1]: Characteristics of the study population (n=30).

Antibiotics	Susceptibility	*E. coli* (12)	*K. pnuemoniae* (8)	*P. mirabilis* (6)	*A. baumannii* (4)
Ceftriaxone	Susceptible	0	0	0	0
	Resistant	12 (100)	8 (100)	6 (100)	4 (100)
Cefipime	Susceptible	1 (8.3)	0	1 (16.6)	1 (25)
	Resistant	11 (91.6)	8 (100)	5 (83.3)	3 (75)
Levofloxacin	Susceptible	0	1 (12.5)	1 (16.6)	0
	Resistant	12 (100)	7 (87.5)	5 (83.3)	4 (100)
Pip-taz	Susceptible	7 (58.3)	3 (37.5)	3 (50)	2 (50)
	Resistant	5 (41.6)	5 (62.5)	3 (50)	2 (50)
Cefaperazone/ sulbactam	Susceptible	6 (50)	4 (50)	2 (33.3)	2 (50)
	Resistant	6 (50)	4 (50)	4 (66.6)	2 (50)
Meropenem	Susceptible	12 (100)	7 (87.5)	6 (100)	3 (75)
	Resistant	0	1 (12.5)	0	1 (25)
CSE-1034	Susceptible	12 (100)	8 (100)	6 (100)	4 (100)
	Resistant	0	0	0	0
Colisitin	Susceptible	12 (100)	8 (100)	0	4 (100)
	Resistant	0	0	6 (100)	0

[Table/Fig-2]: In vitro microbial susceptibility evaluation towards various antibiotics.

E. coli: Escherichia coli; K. pnuemoniae: Klebsiella pneumoniae; P. mirabilis: Proteus mirabilis; A. baumannii: Acinetobacter baumannii

Antibiotic Susceptibility Analysis (AST): In vitro AST to various antibiotics including Ceftriaxone, Cefipime, Levofloxacin, Piperacillin-Tazobactam (Pip-Taz), Meropenem, Colistin and CSE-1034 are presented in [Table/Fig-2]. Culture susceptibility results available on day 3 have shown isolates from 40% patients started with Pip-Taz were reported susceptible to Pip-Taz and isolates from 45% patients started with Cefaperazone-Sulbactam were reported susceptible to the antibiotic used.

Overall, 15/30 (50%) isolates were susceptible to Pip-Taz, 14/30 (46.6%) to Cefaperazone-Sulbactam, 100% to CSE-1034 and 90% to Meropenem. The susceptibility to Colistin was 100% except Proteus species which was 100% (6/6) resistant to Colistin bringing the overall susceptibility of Colistin to 80% [Table/Fig-2].

Although, isolates from almost all the patients were both Meropenem and CSE-1034 susceptible, but based on hospital antibiotic stewardship policy, CSE-1034 is preferred as 2nd choice for suspected biofilm infections over Meropenem.

Antibiotic Outcome: On getting admitted to the hospital, all patients received either Pip+Taz or Cefoperazone-Sulbactam as per standard protocol and relevant culture specimens were sent before starting antibiotics. Clinical evaluation of patients and device was being done daily. Culture susceptibility results available at day 3 have shown that they were not in line with clinical response. Urinary catheter was replaced in 13 patients whose isolates were reported susceptible to 1st line of treatment and continued with same therapy. But none of the patients responded clinically and were shifted to CSE-1034 as 2nd line of treatment. The remaining 17 patients who were reported resistant to 1st line of treatment were directly shifted to CSE-1034, based on literature, previous experience and culture susceptibility results [15,16]. A total of 27 of the patients responded to CSE-1034 as 2nd line of treatment and were cured. However, three patients who did not respond to CSE-1034 as 2nd line of treatment after 48 hour, were switched over to Meropenem and were reported cured. Overall clinical assessment has shown that CSE-1034 monotherapy cured 27/30 (90%) patients suffering from biofilm related infections.

Laboratory parameters	Screening	Completion	p-value
T.L.C (/mm^3)	11231.2±2867.11	7809.81±2761.01	0.015
Hb (g%)	14.12±1.28	12.19±1.32	0.0589
E.S.R (mm/h)	39.5±14.56	17.52±10.46	0.592
S. Creatinine (mg/dL)	1.19±0.39	0.87±0.43	0.0008
International normalised ratio (INR)	0.8±0.17	0.97±0.08	0.085
Prothrombin time	12.0±1.04	11.9±1.28	0.508

[Table/Fig-3]: Laboratory parameters (mean) of study subjects before and after treatment.

The mean of laboratory parameters of all study subjects at the beginning and the end of treatment is given in [Table/Fig-3].

DISCUSSION

Although, medical devices improve the quality of life in critically ill patients, but on the other side these devices put them at an increased risk of nosocomial infections [7]. Around 50% of the nosocomial infections are associated with indwelling devices and 65% of them are caused by biofilm forming pathogens [17]. Bacterial biofilms carry important clinical repercussions as biofilm-embedded organisms exhibit increased capacity to with stand host immune defenses and resistance to anti-microbial therapy [1]. Various innate and induced mechanisms through which biofilm antibiotic resistance is exhibited include decreased/delayed antibiotic diffusion, decreased oxygen and nutrient supply, increased efflux pump expression, genetic spread of resistance markers within the community, and formation of metabolically dormant persister cells [5,18]. In view of the rising biofilm associated infections, new anti-bacterial approaches aimed at disrupting biofilms and killing the constituent bacteria are needed. We here in the present study report a successful treatment of biofilm suspected infections with CSE-1034. In the present study, the data sheets of 30 patients diagnosed with CA-UTI and IAI associated with biliary stents and suspected of biofilm infections were retrospectively analysed. The data analysis has shown the use of BL+BLI combinations as the empirical therapy in these patients. The present results demonstrated that these patients did not respond to the empirical treatment. In 13 patients, reported to be susceptible to first line of treatment, we tried removing/replacing catheters, but still the clinical response was not up to the mark. This might be due to the fact that biofilm migrates to bladder in 2-3 days time and can cause ascending UTI [19]. Hence, all such patients with device (19/30) and replaced/removed device (11/30) were switched over to second line therapy of AAE. A total of 3/30 patients who did not respond to CSE-1034 although culture-susceptible, were switched over to Meropenem and reported to be cured.

The susceptibility of these suspected biofilm pathogens to CSE-1034 can be attributed to different mechanisms through which CSE-1034 functions. This was possibly due to chelation of divalent ions present in EPS (Extracellular Polymeric Substances) layer thus making it more porous and facilitating the penetration of Ceftriaxone/Sulbactam and reducing the viable number of bacterial cells [6]. Donlan PM, reported that EPS contributes to the resistance properties of biofilms by binding to the antibiotics and impeding the transportation of antibiotics through biofilm [4]. Moreover, lot of studies have demonstrated that EDTA also enhances the penetration of drugs into sessile bacterial cells by enhancing the membrane porosity resulting in increased susceptibility of drugs which in turn decreased Minimum Inhibitory Concentration (MIC) [6,20]. Thus, this combination works through synergistic effect by acting into two different components of the biofilm namely the matrix and the cellular content. Chaudhary M and Payasi A, have reported that the use of Ceftriaxone/Sulbactam or EDTA individually were ineffective against biofilm infections [12]. Minimum Bactericidal Concentration (MBC) values of Ceftriaxone alone were 16 to 256 times higher than CSE-1034 in ESBL producing strains [12].

The treatment currently suggested for biofilm infections is a combination therapy of antibiotics with macrolides being one of the common antibiotics chosen. The most common antibiotic combinations of macrolides cited in literature are Clarithromycin or Azithromycin in combination with Vancomycin [21]. Another combination known to work against biofilm infections is Roxithromycin plus Imipenem which destabilizes the biofilm by enhancing a higher penetration of neutrophils into its structure [22]. This antibiotic combination is reported to possess in vivo activity against biofilms formed by *S. aureus*, *P. aeruginosa* and *S. epidermidis* [22,23]. Moreover, combination treatments of azithromycin and fluoroquinolones; and N-acetylcysteine with Vancomycin are also reported to be promising against biofilm-associated infectious diseases [24,25]. However, the drawbacks of these treatment options are that, many of them have not been extrapolated to in vivo level and are majorly focused towards limited types of pathogens. Moreover, culture susceptibility reports have shown complete susceptibility of pathogen isolates to Meropenem also, however based on the hospital records, CSE-1034 is a preferred treatment regimen in patients suspected of biofilm infections.

Hence, the present study suggests that CSE-1034, a novel combination of ceftriaxone, sulbactam and antibiotic adjuvant entity EDTA should be the choice of empiric treatment for the patients suspected of biofilm infections. The present study also highlights an important fact that combining antibiotic adjuvant entities with the existing old antibiotics can help to revive and broaden their anti-microbial spectrum and curb the pressure on the currently available antibiotic resources. Even though the culture susceptibility results showed susceptibility to BL/BLIs, however no response to BL/BLIs was reported clinically. However, it becomes imperative to mention that non-confirmation of biofilm infection can be limitation of this study.

CONCLUSION

In conclusion, the results of the present study show excellent activity of CSE-1034 against Gram-negative biofilm infections. The results

indicate that this drug can be ideal therapeutic choice over BL/BLIs for infections caused by Gram-negative pathogens especially by strains able to form biofilm on biotic or abiotic surfaces.

REFERENCES

[1] Singh S, Singh SK, Chowdhury I, Singh R. Understanding the mechanism of bacterial biofilms resistance to antimicrobial agents. Open Microbiol J. 2017;11:53-62.
[2] Bjarnsholt T. The role of bacterial biofilms in chronic infections. APMIS Suppl. 2013;01-51.
[3] Jamal M, Ahmad W, Andleeb S, Jalil F, Imran M, Nawaz MA, et al. Bacterial biofilm and associated infections. J Chin Med Assoc. 2018;81:07-11.
[4] Donlan RM. Biofilm elimination on intravascular catheters: important considerations for the infectious disease practitioner. Clin Infect Dis Off Publ Infect Dis Soc Am. 2011;52:1038-45.
[5] Hall CW, Mah T-F. Molecular mechanisms of biofilm-based antibiotic resistance and tolerance in pathogenic bacteria. FEMS Microbiol Rev. 2017;41:276-301.
[6] Finnegan S, Percival SL. EDTA: An antimicrobial and antibiofilm agent for use in wound care. Adv Wound Care. 2015;4:415-21.
[7] Percival SL, Suleman L, Vuotto C, Donelli G. Healthcare-associated infections, medical devices and biofilms: risk, tolerance and control. J Med Microbiol. 2015;64:323–34.
[8] Yoshizumi A, Ishii Y, Livermore DM, Woodford N, Kimura S, Saga T, et al. Efficacies of calcium-EDTA in combination with imipenem in a murine model of sepsis caused by Escherichia coli with NDM-1 β-lactamase. J Infect Chemother Off J Jpn Soc Chemother. 2013;19:992-95.
[9] Lebeaux D, Leflon-Guibout V, Ghigo J-M, Beloin C. In vitro activity of gentamicin, vancomycin or amikacin combined with EDTA or l-arginine as lock therapy against a wide spectrum of biofilm-forming clinical strains isolated from catheter-related infections. J Antimicrob Chemother. 2015;70:1704-12.
[10] Chaudhary M, Mir MA, Ayub SG. Safety and efficacy of a novel drug elores (ceftriaxone + sulbactam + disodium edetate) in the management of multi-drug resistant bacterial infections in tertiary care centers: a post-marketing surveillance study. Braz J Infect Dis. 2017;21:408-17.
[11] Chaudhary M, Ayub SG, Mir MA. Comparative efficacy and safety analysis of CSE-1034: An open labeled phase III study in community acquired pneumonia. J Infect Public Health. 2018;11(5):691-97.
[12] Chaudhary M, Payasi A. Comparative efficacy of antibiotics in biofilms eradication formed by ESBL and non ESBL producing micro-organisms. Int J Drug Dev Res 2012, 4(2): 138-147.
[13] CLSI Publishes New Antimicrobial Susceptibility Testing Standards-CLSI [Internet]. [cited 2016 Sep 6]. Available from:http://clsi.org/blog/2015/01/08/clsi-publishes-new-antimicrobial-susceptibility-testing-standards/
[14] Catheter-associated Urinary Tract Infections (CAUTI) | HAI | CDC [Internet]. 2017 [cited 2018 Sep 21]. Available from: https://www.cdc.gov/hai/ca_uti/uti.html
[15] Chaudhary M, Ayub SG, Mir MA. Post-marketing safety and efficacy evaluation of a novel drug cse-1034: a drug-use analysis in paediatric patients with hospital- acquired pneumonia. J Clin Diagn Res. 2018;12(9):25-28.
[16] Chaudhary M, Ayub G, Payasi A. Advancing in the Direction of Right Solutions: Treating Multidrug-Resistant Pneumonia. Contemp Top Pneumonia [Internet]. 2017 [cited 2018 Aug 31]; Available from: https://www.intechopen.com/books/contemporary-topics-of-pneumonia/advancing-in-the-direction-of-right-solutions-treating-multidrug-resistant-pneumonia
[17] Soto SM. Importance of biofilms in urinary tract infections: new therapeutic approaches. Adv Biol. 2014:543974.
[18] Joo H-S, Otto M. Molecular basis of in-vivo biofilm formation by bacterial pathogens. Chem Biol. 2012;19:1503-13.
[19] Guggenbichler JP, Assadian O, Boeswald M, Kramer A. Incidence and clinical implication of nosocomial infections associated with implantable biomaterials – catheters, ventilator-associated pneumonia, urinary tract infections. GMS Krankenhaushygiene Interdiszip. 2011;6(1):18.
[20] Cavaliere R, Ball JL, Turnbull L, Whitchurch CB. The biofilm matrix destabilizers, EDTA and DNaseI, enhance the susceptibility of nontypeable Hemophilus influenzae biofilms to treatment with ampicillin and ciprofloxacin. Microbiology Open. 2014;3:557-67.
[21] Presterl E, Hajdu S, Lassnigg AM, Hirschl AM, Holinka J, Graninger W. Effects of azithromycin in combination with vancomycin, daptomycin, fosfomycin, tigecycline, and ceftriaxone on staphylococcus epidermidis biofilms. Antimicrob Agents Chemother. 2009;53:3205-10.
[22] Yamasaki O, Akiyama H, Toi Y, Arata J. A combination of roxithromycin and imipenem as an antimicrobial strategy against biofilms formed by Staphylococcus aureus. J Antimicrob Chemother. 2001;48:573-77.
[23] Furuhata M, Iwamura M, Baba S, Inoue M. Combined effect of clarithromycin and imipenem/cilastatin against urinary biofilm infection after pyeloplasty. Int J Urol. 2003;10:228-30.
[24] Leite B, Gomes F, Melo P, Souza C, Teixeira P, Oliveira R, et al. N-acetylcysteine and vancomycin alone and in combination against staphylococci biofilm. Rev Bras Eng Bioméd. 2013;29:184-92.
[25] Wang A, Wang Q, Kudinha T, Xiao S, Zhuo C. Effects of fluoroquinolones and azithromycin on biofilm formation of stenotrophomonas maltophilia. Sci Rep. 2016;6:29701.

PARTICULARS OF CONTRIBUTORS:
1. Consultant, Department of Medicine, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mulana, Ambala, Haryana, India.
2. Senior Resident, Department of Medicine, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mulana, Ambala, Haryana, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Sunita Gupta,
Department of Medicine, Maharishi Markandeshwar Institute of Medical Sciences and Research,
Mulana, Ambala-133207, Haryana, India.
E-mail: sanjeevguptadr@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Apr 18, 2018**
Date of Peer Review: **Jun 02, 2018**
Date of Acceptance: **Oct 25, 2018**
Date of Publishing: **Jan 01, 2019**