

## **Bölüm 4**

# **BİYOFİLM, KLİNİK ÖNEMİ, KONTROLÜ ve TEDAVİSİ**

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### **GİRİŞ**

Biyofilm, birbirlerine ve bir yüzeye geri dönüşümsüz bağlanmış, hücre dışı polimerik madde (EPS) üreten ve ürettikleri bu maddenin içine gömülüp çoğalan, planktonik hücrelere kıyasla değişmiş ve gelişmiş bir fenotip sergileyen ve birbirleriyle etkileşime giren mikroorganizmalar topluluğu olarak tanımlanabilir <sup>(1-4)</sup>. Biyofilm, tek türden veya farklı türlerden mikroorganizmalardan meydana gelebilir. Biyofilmi oluşturan hücre toplulukları, tutundukları yüzeye geri dönüşümsüz bağlanırlar ve tutundukları bu çevrede hayatta kalmalarını sağlayan kendi ürettikleri matriks tarafından sarılırlar <sup>(5-7)</sup>. EPS, besin maddeleri için bir depolama tesisi görevi gören ve diğer mikroorganizmaları ve hücresel olmayan mineraller, kristaller ve korozyon ürünler gibi malzemeleri hapsedebilen, yüksek oranda hidratlanmış ve kimyasal olarak karmaşık bir matrikstir <sup>(1,3)</sup>. Bakteriler mantarlar, protozoonlar ve mikroalgler biyofilm oluşturabilir <sup>(7,8)</sup>.

Biyofilmlerdeki bakteri hücreleri, fizyolojik olarak karşılıklı gelen planktonik emsallerinden farklıdır ve koordineli bir şekilde işlev görürler. Biyofilm bazı yönlerden çok hücreli organizmaların davranışını taklit eder <sup>(3, 9, 10)</sup>. Bakteriler arasındaki işbirliği koordine gen ekspresyonu ve düzenlenmiş hücre farklılaşmasıyla sağlanır <sup>(11, 12)</sup>. Koloni, her türlü olumsuz koşula karşı iyi adapte olabilen esnekliğe ve yüksek gelişmişliğe sahip bir topluluk gibi davranır <sup>(13)</sup>. Biyofilm oluşturma yeteneği prokaryotların eşsiz bir özelliğidir. Biyofilmler; aşırı sıcaklık, uygunsuz pH, UV'ye maruziyet gibi sert koşullarda hemostaz sağlarlar ayrıca olumsuz koşullarda dayanıklılığı sağlamak için hücreler arasında kemotaksisi kolaylaştırarak ve sinyal yollarını geliştirerek kompleks bir etkileşim sağlarlar <sup>(3, 14)</sup>.

EPS'lerin oluşumu, biyofilmin yüzeye bağlanma aşamasında meydana gelir. Biyofilmin cansız veya katı bir yüzeyde oluşup oluşmayacağı, biyofilmdeki mik-

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## KAYNAKÇA

1. Donlan, R. M. Biofilms: microbial life on surfaces. *Emerg Infect Dis*, 2002; 8 (9), 881. Doi: 10.3201/eid0809.020063
2. Donlan, R. M., Costerton, J. W. Biofilms: survival mechanisms of clinically relevant microorganisms. *Clin Microbiol Rev*, 2002; 15 (2), 167-193. Doi: 10.1128/CMR.15.2.167-193.2002.
3. Hall-Stoodley, L., Costerton, J. W., Stoodley, P. Bacterial biofilms: from the natural environment to infectious diseases. *Nature reviews microbiology*, 2004; 2 (2), 95-108. Doi: 10.1038/nrmicro821.
4. Pantanella, F., Valenti, P., Natalizi, T., et al. Analytical techniques to study microbial biofilm on abiotic surfaces: pros and cons of the main techniques currently in use. *Ann Ig*, 2013; 25 (1), 31-42. Doi: 10.7416/ai.2013.1904
5. Prakash, B., Veeregowda, B., Krishnappa, G. Biofilms: a survival strategy of bacteria. *Current science*, 2003; 1299-1307.
6. Smith, A. W., Biofilms and antibiotic therapy: is there a role for combating bacterial resistance by the use of novel drug delivery systems? *Advanced drug delivery reviews*, 2005; 57 (10), 1539-1550. Doi: 10.1016/j.addr.2005.04.007.
7. Fanning, S., Mitchell, A.P. Fungal biofilms. *PLoS Pathog*, 2012; 8 (4), e1002585. Doi: 10.1371/journal.ppat.1002585.
8. Ji, C., Wang, J., Liu, T. Aeration strategy for biofilm cultivation of the microalga *Scenedesmus dimorphus*. *Biotechnology letters*, 2015; 37 (10), 1953-1958. Doi: 10.1007/s10529-015-1882-5.
9. Davey, M. E., O'toole, G. A., Microbial biofilms: from ecology to molecular genetics. *Microbiology and molecular biology reviews*, 2000; 64 (4), 847-867. Doi: 10.1128/MMBR.64.4.847-867.2000.
10. Parsek, M. R., Fuqua, C. Biofilms: emerging themes and challenges in studies of surface-associated microbial life. *Journal of bacteriology*, 2004; 186 (14), 4427-4440. Doi: 10.1128/JB.186.14.4427-4440.2004.
11. Gualdi, L., Tagliabue, L. and Landini, P. Biofilm formation-gene expression relay system in *Escherichia coli*: modulation of  $\sigma^S$ -dependent gene expression by the CsgD regulatory protein via  $\sigma^S$  protein stabilization. *J Bacteriol*, 2007; 189 (22), 8034-8043. Doi: 10.1128/JB.00900-07.
12. Tolker-Nielsen T. Biofilm Development. *Microbiol Spectr*. 2015; 3 (2), 1-2014. Doi: 0.1128/microbiolspec.MB-0001-2014.
13. Marlow, V. L., Porter, M., Hogley, L., et al., Phosphorylated DegU manipulates cell fate differentiation in the *Bacillus subtilis* biofilm. *Journal of bacteriology*, 2014; 196 (1), 16-27. Doi: 10.1128/JB.00930-13.
14. Stoodley, P., Sauer, K., Davies, D. G., et al., Biofilms as complex differentiated communities. *Annual Reviews in Microbiology*, 2002; 56 (1), 187-209. Doi: 10.1146/annurev.micro.56.012302.160705.
15. Branda, S., Vik Å Friedman, L., Kolter, R. Biofilms: the matrix revisited. *Trends Microbiol*, 2005; 13, 20-26. Doi: 10.1016/j.tim.2004.11.006.
16. Miron, J., Ben-Ghedalia, D., Morrison, M., Invited review: adhesion mechanisms of rumen cellulolytic bacteria. *Journal of dairy science*, 2001; 84 (6), 1294-1309. Doi: 10.3168/jds.S0022-0302(01)70159-2.
17. Sun, D., Accavitti, M., Bryers, J. Inhibition of biofilm formation by monoclonal antibodies against *Staphylococcus epidermidis* RP62A accumulation-associated protein. *Clinical and diagnostic laboratory immunology*, 2005; 12 (1), 93-100. Doi: 10.1128/CDLI.12.1.93-100.2005.
18. Lu, T. K., Collins, J. J. Dispersing biofilms with engineered enzymatic bacteriophage. *Proceedings of the National Academy of Sciences*, 2007; 104 (27), 11197-11202. Doi: 10.1073/pnas.0704624104.
19. Sauer, K. The genomics and proteomics of biofilm formation. *Genome biology*, 2003; 4 (6), 1-5. Doi: 10.1186/gb-2003-4-6-219.

20. Sutherland, I. W. The biofilm matrix—an immobilized but dynamic microbial environment. *Trends in microbiology*, 2001; 9 (5), 222-227. Doi: 10.1016/s0966-842x(01)02012-1.
21. Federle, M. J., Bassler, B. L. Interspecies communication in bacteria. *The Journal of clinical investigation*, 2003; 112 (9), 1291-1299. Doi: 10.1172/JCI20195.
22. Shaw, T., Winston, C., Rupp, J. C., et al., Commonality of elastic relaxation times in biofilms. *Physical review letters*, 2004; 93 (9), 098102. Doi: 10.1103/PhysRevLett.93.098102.
23. Bakker, D., Postmus, B., Busscher, H., et al., Bacterial strains isolated from different niches can exhibit different patterns of adhesion to substrata. *Applied and Environmental Microbiology*, 2004; 70 (6), 3758-3760. Doi: 10.1128/AEM.70.6.3758-3760.2004.
24. Korber, D. R., Lawrence, J. R., Lappin-Scott, H. M. Growth of Microorganisms on. *Microbial biofilms*, 2003; 5, 15.
25. Garrett, T. R., Bhakoo, M., Zhang, Z. Bacterial adhesion and biofilms on surfaces. *Prog Natl Sci*, 2008; 18 (9), 1049-1056.
26. Renner, L. D., Weibel, D. B. Physicochemical regulation of biofilm formation. *MRS Bull*, 2011; 36 (5), 347.
27. Vu, B., Chen, M., Crawford, R. et al., Bacterial extracellular polysaccharides involved in biofilm formation. *Molecules*, 2009; 14 (7), 2535-2554. Doi: 10.3390/molecules14072535.
28. Tribedi, P., Sil, A. Cell surface hydrophobicity: a key component in the degradation of polyethylene succinate by *Pseudomonas* sp. AKS 2. *J Appl Microbiol*, 2014; 116 (2), 295-303. Doi: 10.1111/jam.12375.
29. Flemming, H., Wingender, J. The biofilm matrix. *Nat Rev Microbiol*, 2010; 8, 623–633.
30. Borlee, B. R., Goldman, A. D., Murakami K., et al. *Pseudomonas aeruginosa* uses a cyclic di-GMP regulated adhesin to reinforce the biofilm extracellular matrix. *Mol Microbiol*, 2010; 75 (4), 827-842. Doi: 10.1111/j.1365-2958.2009.06991.x.
31. Smirnova, T., Didenko, L. V., Azizbekyan, R. R., et al. Structural and functional characteristics of bacterial biofilms. *Microbiol*, 2010; 79 (4), 413-423. Doi: 10.1134/S0026261710040016.
32. Dubey, G. P., Ben-Yehuda, S. Intercellular nanotubes mediate bacterial communication. *Cell*, 2011; 144 (4), 590-600. Doi: 10.1016/j.cell.2011.01.015.
33. Dunne, W. M. Bacterial adhesion: seen any good biofilms lately? *Clin Microbiol Rev*, 2002; 15 (2), 155-166. Doi: 10.1128/CMR.15.2.155-166.2002.
34. Kokare, C., Chacabarty, S., Khopade, A. N., et al. Biofilm: *Importance and applications*, 2009; 8, 159-168.
35. Kreft, J. U. Biofilms promote altruism. *Microbiol*, 2004; 150 (8), 2751-2760. Doi: 10.1099/mic.0.26829-0.
36. O'Toole, G. A., Stewart, P. S. Biofilms strike back. *Nat Biotechnol*, 2005; 23 (11), 1378-1379. Doi: 10.1038/nbt1105-1378.
37. Le Magrex-Debar, E., Lemoine, J., Jacquelin, L. F., et al. Evaluation of biohazards in dehydrated biofilms on foodstuff packaging. *Int J Food Microbiol*, 2000; 55 (1-3), 239-243. Doi: 10.1016/s0168-1605(00)00177-x.
38. Espeland, E., Wetzel, R. Complexation, stabilization, and UV photolysis of extracellular and surface-bound glucosidase and alkaline phosphatase: implications for biofilm microbiota. *Microb Ecol*, 2001; 42 (4), 572-585. Doi: 10.1007/s00248-001-1023-7.
39. McNeill, K., Hamilton, I. Acid tolerance response of biofilm cells of *Streptococcus mutans*. *FEMS Microbiol Lett*, 2003; 221(1), 25-30. Doi: 10.1016/S0378-1097(03)00164-2.
40. Yin, W., Wang, Y., Liu, L., et al. Biofilms: The Microbial “Protective Clothing” in Extreme Environments. *Int. J. Mol. Sci*, 2019; 20, 3423. Doi:10.3390/ijms20143423.
41. Teitzel, G. M., Parsek, M. R. Heavy metal resistance of biofilm and planktonic *Pseudomonas aeruginosa*. *Appl Environ Microbiol*, 2003; 69 (4), 2313-2320. Doi: 10.1128/AEM.69.4.2313-2320.2003.
42. Sakarya, S., Gunay, N., Karakulak, M., et al. Hypochlorous Acid: An Ideal Wound Care Agent With Powerful Microbicidal, Antibiofilm, and Wound Healing Potency. *Wounds*, 2014; 26 (12), 342-350. PMID:25785777.

43. Donlan, R. Biofilms on central venous catheters: is eradication possible?, *Curr Top Microbiol Immunol*, 2008; 322, 133-61.
44. Donlan, R. M. Biofilms and device-associated infections. *Emerging infectious diseases*, 2001; 7 (2), 277. Doi: 10.1007/978-3-540-75418-3\_7.
45. Donlan, R. M. Biofilm formation: a clinically relevant microbiological process. *Clin Infect Dis*, 2001; 33 (8), 1387-1392. Doi: 10.1086/322972.
46. Douglas, L. J. Candida biofilms and their role in infection. *Trends Microbiol*, 2003; 11 (1), 30-36. Doi: 10.1016/s0966-842x(02)00002-1.
47. Ramage, G., Martínez, J. P., López-Ribot, J. L. Candida biofilms on implanted biomaterials: a clinically significant problem. *FEMS Yeast Res*, 2006; 6 (7), 979-986. Doi: 10.1111/j.1567-1364.2006.00117.x.
48. Bielecki, P., Glik, J., Kawecki, M., et al. Towards understanding Pseudomonas aeruginosa burn wound infections by profiling gene expression. *Biotechnol Lett*, 2008; 30 (5), 777-790. Doi: 10.1007/s10529-007-9620-2.
49. Neethirajan, S., Clond, M. A., Vogt, A. Medical biofilms—nanotechnology approaches. *J Biomed Nanotechnol*, 2014; 10 (10), 2806-2827. Doi: 10.1166/jbn.2014.1892.
50. Saarela, M., Alakomi H. L., Suihko M. L., et al. Heterotrophic microorganisms in air and biofilm samples from Roman catacombs, with special emphasis on actinobacteria and fungi. *Int Biod. Biodeg*, 2004; 54 (1), 27-37.
51. Kumamoto, C. A. A contact-activated kinase signals Candida albicans invasive growth and biofilm development. *Proc Natl Acad Sci*, 2005; 102 (15), 5576-5581. Doi: 10.1073/pnas.0407097102.
52. Laffey, S. F., Butler, G. Phenotype switching affects biofilm formation by Candida parapsilosis. *Microbiology*, 2005; 151 (4), 1073-1081. Doi: 10.1099/mic.0.27739-0.
53. Richard, M. L., Nobile, C. J., Bruno, V. M., et al. Candida albicans biofilm-defective mutants. *Eukaryotic Cell*, 2005; 4 (8), 1493-1502. Doi: 10.1128/EC.4.8.1493-1502.2005.
54. Gulati, M., Nobile C. J. Candida albicans biofilms: development, regulation, and molecular mechanisms. *Microbes Infect*, 2016; 18 (5), 310-21. Doi: 10.1016/j.micinf.2016.01.002.
55. Trizna, E. Y., Khakimullina, E. N., Latypova, L. Z., et al. Thio derivatives of 2 (5H)-furanone as inhibitors against Bacillus subtilis biofilms. *Acta Naturae*, 2015; 7 (2), 102-107. PMID:26085951.
56. Mah, T. F. C., O'Toole, G. A. Mechanisms of biofilm resistance to antimicrobial agents. *Trends Microbiol*, 2001; 9 (1), 34-39. Doi: 10.1016/s0966-842x(00)01913-2.
57. Gilbert, P., Allison, D., McBain, A. Biofilms in vitro and in vivo: do singular mechanisms imply cross-resistance? *J Appl Microbiol*, 2002; 92, 98-110. PMID:12000619.
58. Chen, M., Yu, Q., Sun, H. Novel strategies for the prevention and treatment of biofilm related infections. *International journal of molecular sciences*, 2013; 14 (9), 18488-18501. Doi: 10.3390/ijms140918488.
59. Walters, M. C., Roe, F., Bugnicourt, A., et al. Contributions of antibiotic penetration, oxygen limitation, and low metabolic activity to tolerance of Pseudomonas aeruginosa biofilms to ciprofloxacin and tobramycin. *Antimicrob Agents Chemother*, 2003; 47 (1), 317-323. Doi:10.1128/AAC.47.1.317-323.2003
60. Anderl, J. N., Zahller, J., Roe, F., et al. Role of nutrient limitation and stationary-phase existence in Klebsiella pneumoniae biofilm resistance to ampicillin and ciprofloxacin. *Antimicrob Agents Chemother*, 2003; 47 (4), 1251-1256. Doi: 10.1128/AAC.47.4.1251-1256.2003
61. Davies, D. Understanding biofilm resistance to antibacterial agents. *Nature Reviews Drug Discovery*, 2003; 2 (2), 114-122.
62. Percival, S. L., Vuotto, C., Donelli, G., et al. Biofilms and Wounds: An Identification Algorithm and Potential Treatment Options. *Adv Wound Care*, 2015; 4 (7), 389-397. Doi:10.1089/wound.2014.0574
63. Rhoads, D. D., Wolcott, R. W., Cutting, K. F., et al. Evidence of biofilms in wounds and potential ramifications. *BiofilmClub*, 2007; 8, 131-143.

64. Anwar, H., Strab, J. L., Chen, K., et al. Dynamic interactions of biofilms of mucoid *Pseudomonas aeruginosa* with tobramycin and piperacillin. *Antimicrob Agents Chemother*, 1992; 36 (6), 1208-1214. Doi:10.1128/aac.36.6.1208
65. Fux, C.A. et al. Survival strategies of infectious biofilms. *Trends Microbiol*, 2005; 13 (1), 34-40. Doi: 10.1016/j.tim.2004.11.010.
66. Lewis, K. Persister cells and the riddle of biofilm survival. *Biochemistry*, 2005; 70 (2), 267-274. Doi: 10.1007/s10541-005-0111-6.
67. Roberts, M. E., Stewart, P. S., Modelling protection from antimicrobial agents in biofilms through the formation of persister cells. *Microbiology*, 2005; 151 (1), 75-80. Doi: 10.1099/mic.0.27385-0.
68. Harrison, J. J., Turner, R. J., Ceri, H. Persister cells, the biofilm matrix and tolerance to metal cations in biofilm and planktonic *Pseudomonas aeruginosa*. *Environ Microbiol*, 2005; 7 (7), 981-994. Doi: 10.1111/j.1462-2920.2005.00777.x.
69. Percival, S., Kite, P. Intravascular Catheters and infection control. *J Vasc Access*, 2007; 2, 69-80. PMID:17534791.
70. Jacqueline, C., Caillon, J. Impact of bacterial biofilm on the treatment of prosthetic joint infections. *J Antimicrob Chemother*, 2014; 69, 37-40. Doi: 10.1093/jac/dku254.
71. Götz, F. Staphylococcus and biofilms. *Mol Microbiol*, 2002; 43(6), 1367-1378. Doi: 10.1046/j.1365-2958.2002.02827.x.
72. Lewis, K. Riddle of biofilm resistance. *Antimicrob Agents Chemother*, 2001; 45, 999e1007. Doi: 10.1128/AAC.45.4.999-1007.2001.
73. Darouiche, R. O. Treatment of infections associated with surgical implants. *N Engl J Med*, 2004; 350, 1422e9. Doi: 10.1056/NEJMra035415.
74. Campoccia, D., Montanaro, L., Arciola, C. R. The significance of infection related to orthopedic devices and issues of antibiotic resistance. *Biomaterials*, 2006; 27, 2331-2339. Doi: 10.1016/j.biomaterials.2005.11.044.
75. Tenke, P., Kovacs, B. Jäckel, M., et al. The role of biofilm infection in urology. *World J Urol.*, 2006; 24, 13-20. Doi: 10.1007/s00345-005-0050-2.
76. Donlan, R. M. Biofilms: a source of infection?. in: Rutala W. Disinfection, sterilisation and antiseptics: principles, practices and new research. Association for Professionals in Infection Control, Washington 2004; 219-226.
77. Lindsay, D., von Holy, A. What food safety professionals should know about bacterial biofilms. *Br Food J.*, 2006; 108, 27-37. Doi 10.1108/00070700610637616.
78. Marion-Ferey, K., Pasmore, M., Stoodley, P., et al. Biofilm removal from silicone tubing: an assessment of the efficacy of dialysis machine decontamination procedures using an in vitro model. *J Hosp Infect.*, 2003; 53, 64-71. Doi: 10.1053/jhin.2002.1320.
79. Ciofu, O., Rojo-Molinero, E., Macià, M. D., et al. Antibiotic treatment of biofilm infections. *Oliver A. APMIS*. 2017; 125 (4), 304-319. Doi: 10.1111/apm.12673
80. Percival, S. L., Kite, P. Intravascular catheters and biofilm control. *J Vasc Access*, 2008; 2, 69-80. PMID:17534791.
81. Harrison-Balestra, C., Cazzaniga, A. L., Davis, C. S., et al. A wound-isolated *Pseudomonas aeruginosa* grows a biofilm in vitro within 10 hours and is visualized by light microscopy. *Dermatol Surg*, 2003; 29, 631e635. Doi: 10.1046/j.1524-4725.2003.29146.x.
82. Tredget, E. E., Shankowsky, H. A., Rennie, R., et al. *Pseudomonas* infections in the thermally injured patient. *Burns*, 2004; 30:3e26. Doi: 10.1016/j.burns.2003.08.007.
83. Anaissie, E., Penzak, S., Dignani, C. The hospital water supply as a source of nosocomial infections. *Arch Intern Med*, 2002; 162, 1483e1492. Doi: 10.1001/archinte.162.13.1483.
84. Exner, M., Kramer, A., Lajoie, L., et al. Prevention and control of health care-associated waterborne infections in health care facilities. *Am J Infect Control*, 2005; 33, 26-40. Doi: 10.1016/j.ajic.2005.04.002.
85. Rutala, W. A., Weber, D. J., Gergen, M. F., et al. Efficacy of a washer/pasteurizer for disinfection of respiratory care equipment. *Infect Control Hosp Epidemiol*, 2000; 21, 333-6. Doi: 10.1086/501767.

86. Pajkos, A., Vickery, K., Cossart, Y. Is biofilm accumulation on endoscope tubing a contributor to the failure of cleaning and decontamination? *J Hosp Infect*, 2004; 58, 224e229. Doi: 10.1016/j.jhin.2004.06.023.
87. Nelson, D. B. Recent advances in epidemiology and prevention of gastrointestinal endoscopy related infections. *Curr Opin Infect Dis*, 2005; 18, 326e330. Doi: 10.1097/01.qco.0000171925.47452.8f.
88. Vickery, K., Pajkos, A., Cossart, Y. Removal of biofilm from endoscopes: evaluation of detergent efficiency. *Am J Infect Control*, 2004; 32, 170e176. Doi: 10.1016/j.ajic.2003.10.009.
89. Aumeran, C., Thibert, E., Chapelle, F. A., et al. Assessment on experimental bacterial biofilms and in clinical practice of the efficacy of sampling solutions for microbiological testing of endoscopes. *J Clin Microbiol*, 2012; 50, 938-42. Doi: 10.1128/JCM.06221-11.
90. Pajkos, A., Vickery, K., Cossart, Y. Is biofilm accumulation on endoscope tubing a contributor to the failure of cleaning and decontamination? *J Hosp Infect*, 2004; 58, 224-9.
91. Vickery, K., Ngo, Q.-D., Zou, J., et al. The effect of multiple cycles of contamination, detergent washing, and disinfection on the development of biofilm in endoscope tubing. *Am J Infect Control*, 2009; 37, 470-5. Doi: 10.1016/j.ajic.2008.09.016.
92. Bagge, N., Schuster, M., Hentzer, M., et al. *Pseudomonas aeruginosa* biofilms exposed to imipenem exhibit changes in global gene expression and beta-lactamase and alginate production. *Antimicrob Agents Chemother*, 2004; 48 (4), 1175-87. Doi: 10.1128/AAC.48.4.1175-1187.2004.
93. Hoffman, L. R., D'Argenio, D. A., MacCoss, M. J., et al. Aminoglycoside antibiotics induce bacterial biofilm formation. *Nature*, 2005; 436(7054), 1171-5. Doi: 10.1038/nature03912
94. Simões, M. Antimicrobial strategies effective against infectious bacterial biofilms. *Curr Med Chem*, 2011; 18 (14), 2129-45. Doi: 10.2174/092986711795656216.
95. Francolini, I., Donelli, G. Prevention and control of biofilm-based medical-device-related infections. *FEMS Immunol Med Microbiol*, 2010; 59 (3), 227-38. Doi: 10.1111/j.1574-695X.2010.00665.x.
96. Ofek, I., Hasty, D. L., Sharon, N. Anti-adhesion therapy of bacterial diseases: prospects and problems. *FEMS Immunol Med Microbiol*, 2003; 38 (3), 181-91. Doi: 10.1016/S0928-8244(03)00228-1.
97. Bavington, C., Page, C. Stopping bacterial adhesion: a novel approach to treating infections. *Respiration*, 2005; 72 (4), 335-44. Doi: 10.1159/000086243.
98. Kasimanickam, R. K., Ranjan, A., Asokan, G. V., et al. Prevention and treatment of biofilms by hybrid- and nanotechnologies. *Int J Nanomedicine*, 2013; 8, 2809-19. Doi: 10.2147/IJN.S44100.
99. Alfa, M.J., Howie, R. Modeling microbial survival in buildup biofilm for complex medical devices *BMC Infect Dis*, 2009; 9, 56. Doi:10.1186/1471-2334-9-56.
100. del Pozo, J. L., Rouse, M. S., Mandrekar, J. N., et al. The electricidal effect: reduction of *Staphylococcus* and *pseudomonas* biofilms by prolonged exposure to low-intensity electrical current. *Antimicrob Agents Chemother*, 2009; 53 (1), 41-5. Doi: 10.1128/AAC.00680-08.
101. Pickering, S. A., Bayston, R., Scammell, B. E. Electromagnetic augmentation of antibiotic efficacy in infection of orthopaedic implants. *J Bone Joint Surg Br.*, 2003; 85 (4), 588-93 Doi: 10.1302/0301-620x.85b4.12644.
102. Rajesh, S., Koshi, E., Philip, K., Mohan, A. Antimicrobial photodynamic therapy: An overview. *J Indian Soc Periodontol*, 2011; 15 (4), 323-327. Doi: 10.4103/0972-124X.92563.
103. Rai, M., Yadav, A., Gade, A. Silver nanoparticles as a new generation of antimicrobials. *Biotechnol Adv*. 2009; 27 (1), 76-78. Doi: 10.1016/j.biotechadv.2008.09.002.
104. Shrivastava, S., Bera, T., Roy, A., et al. Characterization of enhanced antibacterial effects of novel silver nanoparticles. *Nanotechnology*, 2007; 18, 225103. Doi:10.1088/0957-4484/18/22/225103.
105. Ramasamy, M., Lee, J. Recent Nanotechnology Approaches for Prevention and Treatment of Biofilm-Associated Infections on Medical Devices. *Biomed Res Int*, 2016; 1-17. Doi: 10.1155/2016/1851242.