Authors: Silvestre Ortega-Peña, Mark Smeltzer, Kenneth Urish, Daniel G. Meeker, Jeffrey B. Stambough

QUESTION 1: What antiseptics can be used to prevent biofilm formation?

RECOMMENDATION: Although several studies have demonstrated the ability of certain antiseptic agents to prevent biofilm formation in vitro, the ability of antiseptics to provide prevention of biofilm formation in vivo is uncertain. They may have utility in the context of revision surgery due to existing infection, but this issue has not been adequately studied.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 2%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

It has not been established whether a specific antiseptic or a combination of agents is better to eradicate biofilms from an implant surface in vivo [1]. So far, almost all of the studies focused on the abilities of antiseptics to inhibit biofilm formation have been demonstrated in in vitro studies [2–5].

Santos et al. performed a crossover, randomized double-blind clinical trial to evaluate the effects of two chlorhexidine solutions (alcohol-containing 0.12% chlorhexidine solution and alcohol-free 0.12% chlorhexidine solution) against supra- and sub-gingival biofilm formation. The group found that both solutions had similar inhibitory effects on the formation of biofilms [6]. In addition, Quintas et al. performed an observer-masked, crossover, randomized clinical trial to evaluate the in situ antiplaque effect after four days of using twocommercial antimicrobial agents (essential oils and 0.2% chlorhexidine) in the short-term on undisturbed plaque-like biofilm [7]. Although the 0.2% chlorhexidine showed better results with regard to reducing the thickness and covering grade by the biofilm, both antiseptics had high and similar antiplaque effects.

The ability of acetic acid and polyhexanide to prevent biofilm formation has also been mentioned in the literature. Halstead et al. demonstrated that acetic acid at low concentrations of 0.16 to 0.31% was able to inhibit biofilm formation in vitro [8]. Lenselink et al. performed a cohort study to evaluate the clinical efficacy of the polyhexanide-containing bio cellulose dressing for the eradication of biofilms in non-healing wounds [9]. They suggested that continuous application of polyhexanide, using a bio cellulose wound dressing, reduced biofilm in the stagnating wounds treated, thus promoting healing.

Regarding the clinical use of povidone-iodine to prevent the formation of biofilms, there are limited studies in vitro. Hill et al. utilized a sophisticated in vitro biofilm model that was designed to closely mimic chronic wound biofilms and demonstrated the complete destruction of an established seven-day mixed Pseudomonas and *Staphylococcus* biofilm by iodine-based dressings [10]. Kanno et al. suggested that irrigation of wounds with 1% povidone-iodine was an effective way to reduce bacterial counts on the wound surface and prevent new biofilm formation by using a rat model of wound chronic biofilm infection [11]. However, Presterl et al. found that povidone-iodine was inferior to hydrogen peroxide and alcohol for the eradication of *Staphylococcus epidermidis* biofilms [12].

It is worth noting that many biofilm infections occur much later in the postoperative period, often due to the hematogenous dissemination of bacteria to the site of an implanted device from a breach in surface structures [13]. Indeed, this can occur months or even years after implantation and it is unlikely to prevent this mode of infection development with the use of antiseptic agents at the time of perioperative period. The role of antiseptics in various debridement protocols for the treatment of established periprosthetic joint infections (PJIs) remains controversial. Each clinical scenario is unique in terms of causative pathogen, host factors, local tissue viability, as well as the duration and virulence of the infection. If the surgeon is attempting to salvage the existing prosthesis through a debridement, antibiotics and implant retention (DAIR) protocol, it is imperative that all biofilm should be removed through mechanical and chemical disruption [14–16]. If a one-stage revision including component explantation, debridement and reimplantation of a new prosthesis is to be undertaken in a single surgical setting, the importance of debriding all infected tissue is vital. The role of antiseptics, in this case, is not to treat existing biofilm, as all prosthetic components will have been removed. Instead, the purpose is to aggressively treat the remaining bone and its soft tissue envelope to prevent recolonization. Antiseptics used for this purpose include acetic acid, Dakins solution (NaOCl), povidine-iodine and hydrogen peroxide [17]. In this situation, the volume of antiseptic solution may be more important than the combination and sequence of agents [17,18].

The use of antiseptic agents during the perioperative period has the potential to reduce the rate of surgical infection early in the postoperative period. Additionally, the use of certain antiseptic solutions for lavage, during primary and revision total joint arthroplasty operations, has the potential to reduce infection rates [19]. However, validated protocols do not exist for the use of such solutions in terms of concentration, volume and duration of exposure. More in vivo studies are needed to evaluate the use of various antiseptic agents for this purpose, such that direct comparisons between agents can be made.

Ultimately, although several studies have demonstrated the ability of certain antiseptic agents to prevent biofilm formation in vitro, the ability of antiseptics to provide protection against biofilm formation in vivo is uncertain. They may have utility in the context of revision surgery due to existing infection, but this issue has not been adequately studied.

REFERENCES

[1] Lora–Tamayo J, Murillo O, Iribarren JA, Soriano A, Sánchez–Somolinos M, Baraia–Etxaburu JM, et al. A large multicenter study of methicillin–susceptible and methicillin–resistant staphylococcus aureus prosthetic joint infections managed with implant retention. Clin Infect Dis. 2013;56:182–194. doi:10.1093/cid/cis746.

[2] Percival SL, Finnegan S, Donelli G, Vuotto C, Rimmer S, Lipsky BA. Antiseptics for treating infected wounds: efficacy on biofilms and effect of pH. Crit Rev Microbiol. 2016;42:293–309. doi:10.3109/1040841X.2014.940495.

[3] Ortega–Peña S, Hidalgo–González C, Robson MC, Krötzsch E. In vitro microbicidal, anti–biofilm and cytotoxic effects of different commercial antiseptics. Int Wound J. 2017;14:470–479. doi:10.1111/iwj.12625.

[4] Théraud M, Bédouin Y, Guiguen C, Gangneux JP. Efficacy of antiseptics and disinfectants on clinical and environmental yeast isolates in planktonic and biofilm conditions. J Med Microbiol. 2004;53:1013–1018. doi:10.1099/jmm.0.05474–0.

[5] Schmidt K, Estes C, McLaren A, Spangehl MJ. Chlorhexidine antiseptic irrigation eradicates staphylococcus epidermidis from biofilm: an in vitro study. Clin Orthop Relat Res. 2018;476:648–653. doi:10.1007/s11999.0000000000000052.

[6] Santos GOD, Milanesi FC, Greggianin BF, Fernandes MI, Oppermann RV, Weidlich P. Chlorhexidine with or without alcohol against biofilm formation: efficacy, adverse events and taste preference. Braz Oral Res. 2017;31:e32. doi:10.1590/1807–3107BOR–2017.vol31.0032.
[7] Quintas V, Prada–López I, Donos N, Suárez–Quintanilla D, Tomás I. Antiplaque effect of essential oils and 0.2% chlorhexidine on an in situ model of oral biofilm growth: a randomised clinical trial. PLoS One. 2015;10:e0117177. doi:10.1371/journal.pone.0117177.
[8] Halstead FD, Rauf M, Moiemen NS, Bamford A, Wearn CM, Fraise AP, et al. The antibacterial activity of acetic acid against biofilm–producing pathogens of relevance to burns patients. PLoS One. 2015;10:e0136190. doi:10.1371/journal.pone.0136190.
[9] Lenselink E, Andriessen A. A cohort study on the efficacy of a polyhexanide–containing biocellulose dressing in the treatment of biofilms in wounds. J Wound Care. 2011;20:534, 536–539. doi:10.12968/jowc.2011.20.11.534.
[10] Hill KE, Malic S, McKee R, Rennison T, Harding KG, Williams DW, et al. An in vitro model of chronic wound biofilms to test wound dressings and assess antimicrobial susceptibilities. J Antimicrob Chemother. 2010;65:1195–1206. doi:10.1093/jac/dkq105.
[11] Kanno E, Tanno H, Suzuki A, Kamimatsuno R, Tachi M. Reconsideration of iodine in wound irrigation: the effects on pseudomonas aeruginosa biofilm formation. J Wound Care. 2016;25:335–339. doi:10.12968/jowc.2016.25.6.335.
[12] Presterl E, Suchomel M, Eder M, Reichmann S, Lassnigg A, Graninger W, et al. Effects of alcohols, povidone–iodine and hydrogen peroxide on biofilms of staphylococcus epidermidis. J Antimicrob Chemother. 2007;60:417–420. doi:10.1093/jac/dkm221.
[13] Zimmerli W. Clinical presentation and treatment of orthopaedic implant–associated infection. J Intern Med. 2014;276:111–119. doi:10.1111/joim.12233.
[14] Qasim SN, Swann A, Ashford R. The DAIR (debridement, antibiotics and implant retention) procedure for infected total knee replacement – a literature review. SICOT J. 2017;3:2. doi:10.1051/sicotj/2016038.
[15] Schwechter EM, Folk D, Varshney AK, Fries BC, Kim SJ, Hirsh DM. Optimal irrigation and debridement of infected joint implants: an in vitro methicillin–resistant staphylococcus aureus biofilm model. J Arthroplasty. 2011;26:109–113. doi:10.1016/j.arth.2011.03.042.
[16] Jiranek WA, Waligora AC, Hess SR, Golladay GL. Surgical treatment of prosthetic joint infections of the hip and knee: changing paradigms? J Arthroplasty. 2015;30:912–918. doi:10.1016/j.arth.2015.03.014.
[17] Williams RL, Ayre WN, Khan WS, Mehta A, Morgan–Jones R. Acetic acid as part of a debridement protocol during revision total knee arthroplasty. J Arthroplasty. 2017;32:953–957. doi:10.1016/j.arth.2016.09.010.
[18] Haddad FS, Sukeik M, Alazzawi S. Is single–stage revision according to a strict protocol effective in treatment of chronic knee arthroplasty infections? Clin Orthop Relat Res. 2015;473:8–14. doi:10.1007/s11999–014–3721–8.
[19] Ruder JA, Springer BD. Treatment of periprosthetic joint infection using antimicrobials: dilute povidone–iodine lavage. J Bone Jt Infect. 2017;2:10–14. doi:10.7150/jbji.16448.