In vitro influence of vancomycin on adhesion of a *Staphylococcus epidermidis* strain encoding intercellular adhesion locus *ica* to intraocular lenses

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Purpose: To assess anti-adhesion and/or bactericidal properties of vancomycin in vitro and to determine when these effects are detectable to estimate its relevance to perioperative antibiotic prophylaxis and analyze the efficacy of a newly designed vancomycin insert prototype for endophthalmitis prevention.

Setting: University research laboratory, Lyon, France.

Methods: *Staphylococcus epidermidis* clinical strain N890074 containing the intercellular adhesion locus *ica* was used as the infectious agent. Vancomycin was used at 20 μg/mL. A sterile biocompatible, biodegradable vancomycin insert, releasing 230 μg of antibiotics over 100 minutes, was designed especially for this study. To obtain bacterial killing curves, experiments were first performed in a 103 colony-forming units (CFU/mL) bacterial suspension containing no intraocular lenses (IOL). Then IOLs were incubated in the suspension, and bacterial adherence was determined using bacterial counting with and without antibiotic.

Results: Vancomycin (solution and insert) had an anti-adhesion effect after 1 hour and a relevant bactericidal effect after 6 hours of incubation.

Conclusions: Vancomycin used with irrigating solutions does not remain in the anterior chamber long enough to develop bactericidal effect. Even if it initially reduces bacterial adhesion, used at a drug level dropping below the bacterial minimal inhibitory concentration, it could result in a secondary increase of the adhesion of slime-producing bacteria. A sufficiently high concentration was obtained in vitro by the new sustained-release system, thereby overcoming the theoretical drawback of a short half-life within the anterior chamber. Anti-adhesion and bactericidal action of vancomycin inserts remains to be confirmed in clinical studies.

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Postoperative endophthalmitis remains one of the most serious complications after cataract surgery with intraocular lens (IOL) implantation. The prevalence of postoperative endophthalmitis is estimated to be between 0.07% and 0.32%.[1–3] However, aqueous humor contamination appears to be relatively common after uneventful cataract surgery. The frequency of bacterial growth in anterior chamber aspirates ranges from 0% to 46%.[4–7] It has been shown that bacteria normally enter the anterior chamber during cataract extraction, carried into the eye by irrigation or adhering to the IOL during the implantation process.[6,8,9] Bacteria are known to adhere rather easily to biomaterials. Despite preoperative local ophthalmologic prophylaxis, a sterile IOL introduced through the conjunctival flap and section may result after as little as 5 seconds of contact in a bacterial contamination rate of 26% (mainly *Staphylococcus epidermidis*, 87%), proving the ability of bacteria to adhere instantaneously to IOLs.[9,10]

Bacterial adhesion to a solid substrate is followed by interbacterial adhesion, this 2-step process allowing

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bacterial biofilm formation.[11–14] For *S epidermidis*, the first phase is mediated by nonspecific physicochemical forces, capsular polysaccharide/adhesion (referred to as PS/A), and several surface proteins. The second phase is bacterial production of a polysaccharide glycocalyx (slime) on the IOL surface,[12,15] containing a bacterial antigen called polysaccharide intercellular adhesin (PIA). A recent study[13] has shown that the intercellular adhesion *ica* locus of *S epidermidis* encodes for the production of both PS/A and PIA.[13]

Bacterial adhesion to IOLs as they are inserted is a prominent etiological factor of endophthalmitis.[8,15–18] Polypropylene was the first biomaterial for which this relation of cause and effect was proven.[8,19,20] Thus, one might potentially decrease endophthalmitis incidence and clinical pathogenicity by reducing the adhesion of bacteria to intraocular implants, especially that of the most frequently involved germ, *S epidermidis*.[18]

Clinical findings on the prevention of endophthalmitis led to the current practice of adding filtered antibiotics (vancomycin 20 µg/mL and/or gentamicin 8 µg/mL) to the infusion bottle during cataract surgery, a practice popularized by J.P. Gills, MD, based on his surgical observations of more than 50 000 cases.[21] In his series, only 2 cases of endophthalmitis occurred. But the interpretation of these data is seriously restricted by the absence of a control group. Moreover, other authors failed to demonstrate that vancomycin prophylaxis significantly reduced residual bacteria from the anterior chamber.[22,23]

The purpose of the present in vitro study was to investigate the anti-adhesion and bactericidal properties of vancomycin using an *S epidermidis* strain carrying the *ica* locus and therefore producing a great amount of slime. By these means, we wanted to assess whether the use of antibiotic prophylaxis in the irrigation fluid effectively prevents bacterial adhesion and growth. The setup of our study using a slime-producing bacterial strain was carefully chosen to have a time delay that allowed us to differentiate between these 2 effects. We also designed and tested a biocompatible vancomycin insert prototype, which progressively released the antibiotic over time, thus allowing bacterium–antibiotic contact time long enough to be efficient. As far as we know, a similar attempt to avoid endophthalmitis by using a material that could progressively release an antibiotic into the anterior chamber has not been published before.

Patients and Methods

IOLs

Two hundred and seventy-three sterile (SM575) silicone IOLs with poly(methyl methacrylate) (PMMA) haptics provided by Corneal were used throughout this study. All of them had identical optical diameters (5.75 mm) and refractive power (22 diopters). In previous personal studies with this exact IOL (SM575), adhesion was high with these 2 biomaterials but without significant differences between them.[24,25]

Bacterial Strain

The microbiology department of Edouard Herriot Hospital (Staphylococci National Reference Centre, Lyon, France) provided a clinical isolate of *S epidermidis* (N890074). This strain was isolated from the infected cerebrospinal fluid of a hydrocephalic child following a ventriculoperitoneal shunt. The species was identified by colony and microscopic morphology by the lack of coagulase activity on rabbit plasma (BioMérieux) and by the absence of production of a clumping factor (Staphyslide, BioMérieux) and according to ID32 Staph gallery (BioMérieux). Using polymerase chain reaction (PCR) amplification[26] proved that this strain carried the *ica* locus,[27] which is known to encode production of *S epidermidis* polysaccharide antigens mediating adhesion to biomaterials (PS/A) and between bacteria (PIA). Previously, it was demonstrated that the environmental conditions used here were favorable for slime secretion.[16,24,26] This isolate was

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sensitive to vancomycin and methicillin, presenting a minimal inhibitory concentration (MIC) to vancomycin of 2 mg/mL and minimal bactericidal concentrations to vancomycin of 8 mg/mL. For the assays, the bacterial concentration was adjusted to 108 colony-forming units (CFU) per milliliter in a sterile 0.08 M phosphate-buffered (pH 7.8) saline solution (PBS buffer). Five further dilutions of this bacterial suspension in Trypticase-Soja bBroth (BioMérieux) yielded 103 CFU/mL of the organism.

Concentrations of Vancomycin

Vancomycin was used at the concentration recommended for perioperative irrigation fluids during cataract surgery in antibiotic prophylaxis, which is 20 μg/mL. The antibiotic solution was prepared using the injectable form.

Vancomycin Insert

A sterile biocompatible vancomycin insert (Figure 1) was especially designed for this study by Corneal. A biodegradable polymer (302 mg), polylactic-co-glycolic acid (50:50) (PLG, Boehringer, Inc.), was prepared and mixed with acetone to obtain a mass of 4 g, which was then made soluble by intense shaking. Vancomycin (50 mg) was added to this solution, which was then shaken continuously for 2 hours. Portions of 500 μL of the vancomycin–polymer mix were put in shells with a diameter of 27 mm before the solvent was removed by evaporation at room temperature under sterile conditions for 15 hours. A rigid film of vancomycin–PLG was thus obtained. In the presence of water, the translucent insert is degraded while releasing the antibiotic. By-products are easily eliminated because they are nontoxic (carbon dioxide and water essentially). The time course of antibiotic release was determined in vitro by spectrometry (l = 280 nm; Table 1); the release was complete after 100 minutes. Inserts were designed to have a diameter of 6 mm (by trephination), a weight of 1.210 mg, and a thickness of 400 μm and to contain 230 μg of vancomycin each (~20% wt/wt). The experiments were carried out 10 times, with an average release of 230 μg of vancomycin after 100 minutes. Inserts were sterilized using ethylene oxide, in accordance with IOL norms. One hundred sixty-one inserts were used.

Methods

Determining Bacteria-Killing Curves. To obtain bacteria killing curves, experiments were first carried out using the bacterial suspension (103 CFU/mL) containing no IOLs at 37°C for the 20 μg/mL vancomycin solution and the vancomycin insert. Half of the bacterial suspensions were exposed to the antibiotic, and the others were not (control curve) for 1, 3, 6, 11, 16, 21, and 24 hours. Testing was repeated 10 times for each group and each incubation period. Samples were centrifuged at 2000 rpm for 20 minutes, and the supernatant was carefully decanted. Quantitative cultures were then made.

Bacterial Adhesion Studies. Complete IOLs (including haptics) were incubated at 37°C in a freshly prepared bacterial suspension (103 CFU/mL), which was constantly gently shaken for 1, 3, 6, 11, 16, 21, and 24 hours before being washed 3 times in sterile 0.08 M PBS (pH 7.8) solution to remove unbound bacteria. Testing was repeated 10-fold for each group and each incubation period. The IOLs were either immersed without antibiotic or, from the start (to reproduce in vivo prophylactic conditions as much as possible), in the presence of 20 μg/mL vancomycin solution or a vancomycin insert. Bacterial adherence was then investigated using bacterial counting (plate count agar method). Washed lenses were soaked in PBS buffer (1 mL), and bound bacteria were then dispersed by sonication at 45 kHz for 5 minutes using a Bransonic device, that does not affect bacterial viability.[16] The resulting suspension was diluted and spread on a nutritive agar plate (Trypticase-Soja, BioMérieux). Colonies were counted after 24-hour incu-

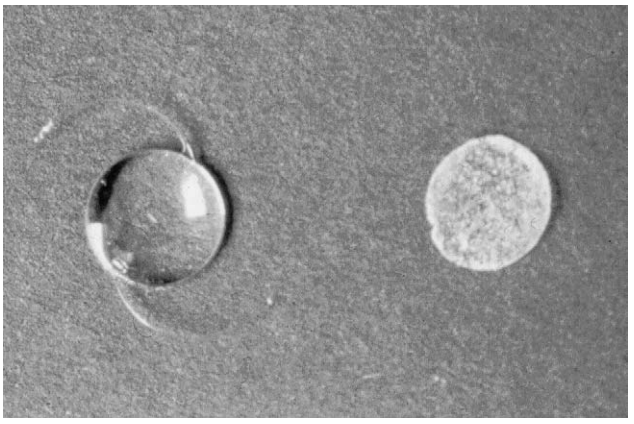

Figure 1. Biodegradable, biocompatible translucent insert of vancomycin with a diameter of 6 mm on the right side of the figure, next to an IOL (SM575, diameter 5.75 mm) on the left.

Table 1. Kinetic release of vancomycin from the vancomycin insert, obtained by spectrometry.*

Time (min)	Released Vancomycin (μg) (Cumulative Concentrations)
0	0
20	136
40	186
60	202
80	218
100	230

(λ = 280 nm)

*The experiments were carried out 10 times, with a mean release of 230 μg of vancomycin

bation at 37°C; bacteria density was displayed as CFU/mL or log10. To assess any anti-adhesion effect of an antibiotic, the presence of viable bacteria in broth suspension (and the absence of bacteria on IOL surface) after incubation with the antibiotic had to be detected.

Scanning electron microscopy was used to confirm the results, according to established standard protocols as previously described.[24] Three samples per incubation period were evaluated for each of the groups. The entire surface of each IOL was examined.

Statistical Analysis. The antibiotic effects were calculated using the established standard formula for bacterial reduction assays by comparing the number of CFU/mL in the control with the number of CFU/mL obtained in the presence of an antibiotic [(control-antibiotic)/control × 100]. A statistical analysis was made using appropriate software (SPSS for Windows, version 11.5; SPSS Inc.). The paired-sample *t*-test was used to compare the means of 2 variables that represent the same group at different times. A *P* value below 0.05 was considered significant.

Results

Bacterial growth results with and without vancomycin are presented in Figure 2. In the presence of vancomycin, bacterial counts decreased over time. A bactericidal effect of the vancomycin solution was found after 1 hour of incubation ($P = .005$), with a bacterial reduction of 13% (compared with control without vancomycin), progressing to a minimum of a 3 log reduction (99.9%) after 11 hours (Figure 2 and Table 2). Comparable effects were observed for the vancomycin insert (Figure 2 and Table 3).

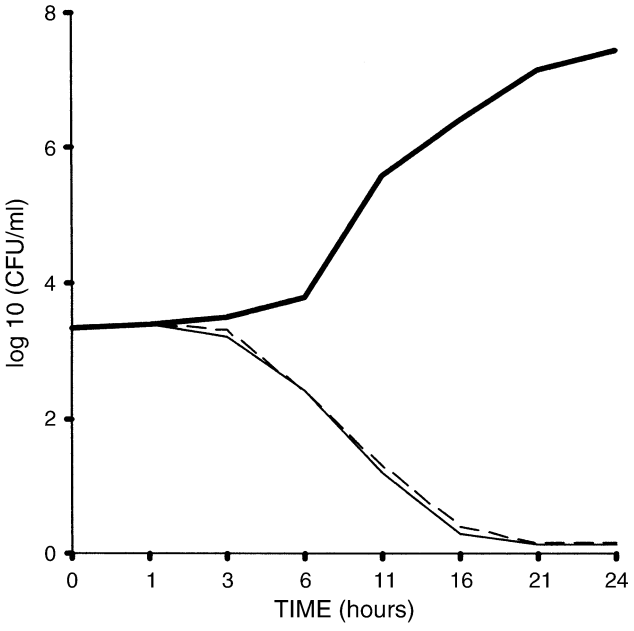

Figure 2. Bacterial killing curves with and without vancomycin. A mean of 10 experiments for each period of incubation was expressed in log10 (CFU/mL). Standard errors were always below 0.12.

Analysis of bacterial adhesion proved that vancomycin significantly reduced the counts of adhering bacteria after 1 hour of incubation ($P < .001$) (Figure 3 and Table 2).

At 1 and 3 hours, vancomycin reduced the quantity of bacteria adhering to IOLs by approximately 80%, whereas the number of bacteria present in suspension was reduced by only 13% and 36%, respectively ($P < .001$ and $P = .017$ at 1 and 3 hours). From 6 hours on, the anti-adhesion and bactericidal effects could not be discriminated from each other (Figure 4) because the difference between the 2 effects was too tiny. After 6 hours of incubation, no bacteria were found on IOL surfaces (Figure 3) and not enough bacteria were found in broth suspension (Figure 2). Indeed, the bactericidal effect of vancomycin became highly relevant by then (1 log of bacterial growth reduction in suspension at 6 hours, 3 log at 11 hours). The comparison between the vancomycin solution and the vancomycin insert revealed no difference regarding bactericidal and anti-adhesion effects at any point in time ($P > .05$).

Bacterial growth was identical in the solutions with and without IOL (data not shown), showing that the presence of an IOL had no effect on the planktonic bacteria.

Results were also confirmed by SEM. A few adhering bacteria per observation field at 1 and 3 hours only, with a decrease over time, but always were observed fewer than on control IOLs (data not shown).

Discussion

All published studies state that coagulase-negative *Staphylococcus* is the most common organism contaminating the anterior chamber after uneventful cataract surgery.[4,5,7,28] Not surprisingly, *S epidermidis* is also the most common germ found in acute endophthalmitis (50% to 60% of the cases).[1] Vancomycin, known to be highly effective against this group of bacteria, is the antibiotic most frequently added to the irrigation fluid. It is a glycopeptide antibiotic, which acts by inhibiting the polymerization of the peptidoglycan, an essential

Table 2. Time-dependent effect of vancomycin (20 μg/ml) on bacterial growth in suspension and on bacterial adhesion to intraocular lenses (IOLs).*

	Bacterial Growth in IOL-Free Suspension (Bactericidal Effect)		Bacterial Adhesion to IOL (Anti-Adhesion Effect)		Comparison of Reduction Percentages
Time (H)	Reduction of Bacterial Growth (%)	*P* Value	Reduction of Bacterial Adhesion (%)	*P* Value	*P* Value
1	13	.005	82	<.001	<.001
3	36	<.001	79	.002	.017
6	90	.002	94	.017	NS
11	99.9	<.001	99.7	.005	NS
16	≥99.9	<.001	≥99.9	<.001	NS
21	≥99.9	<.001	≥99.9	.002	NS
24	≥99.9	<.001	≥99.9	.01	NS

H = hours; NS = not significant
*Standard errors were always below 0.14.

Table 3. Time-dependent effect of vancomycin insert on bacterial growth in suspension and on bacterial adhesion to intraocular lenses (IOLs).*

	Bacterial Growth in IOL-Free Suspension (Bactericidal Effect)		Bacterial Adhesion to IOL (Anti-Adhesion Effect)		Comparison of Reduction Percentages
Time (H)	Reduction of Bacterial Growth (%)	*P* Value	Reduction of Bacterial Adhesion (%)	*P* Value	*P* Value
1	8	.007	83	<.001	<.001
3	33	<.001	81	.002	<.001
6	89	.002	91	.017	NS
11	99.9	<.001	99.6	.005	NS
16	≥99.9	<.001	≥99.9	<.001	NS
21	≥99.9	<.001	≥99.9	.002	NS
24	≥99.9	<.001	≥99.9	.01	NS

H = hours; NS = not significant
*Standard errors were always below 0.14.

constituent of the bacterial cell wall. Thereby it can reach the cellular targets of gram-positive[29] but not of gram-negative bacteria.[30] Vancomycin antibacterial activity is slow and time-dependent and is reported to begin in vitro only after 6 hours, becoming complete after 24 to 48 hours.[23] Moreover, 1 recent study demonstrated an anti-adhesion effect of vancomycin[31] using a concentration of 10 mg/mL, which is 500 times higher than that used in irrigating solutions; this factor might have distorted the results. Another recent study using the ATCC (American Type Culture Collection) 14 990 strain of *S epidermidis* also showed an anti-adhesion effect of vancomycin at the clinically used concentration of 20 μg/mL.[32] But PCR amplification revealed that this isolate did not contain the ica locus,[27] which encodes the production of polysaccharides mediating adherence to biomaterials and slime production. Slime, a virulence factor of staphylococci,[33,34] prevents the action of vancomycin, which may explain its incomplete effect in eradicating foreign-body infections (such as catheter infection) due to slime-producing coagulase-negative staphylococci.[35] It thus seemed important to us to study a strain carrying the ica locus and therefore produced a great amount of slime[16,24,26] in order to assess whether vancomycin also had an anti-adhesion effect in the presence of this genetic virulence determinant.

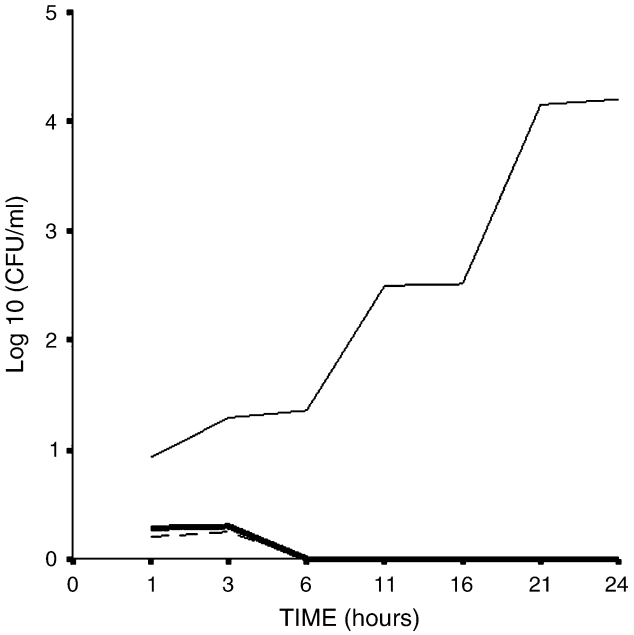

Figure 3. Curves of bacterial adhesion to IOLs with and without vancomycin. A mean of 10 experiments for each period of incubation was expressed in log10 (CFU/mL). Standard errors were always below 0.14.

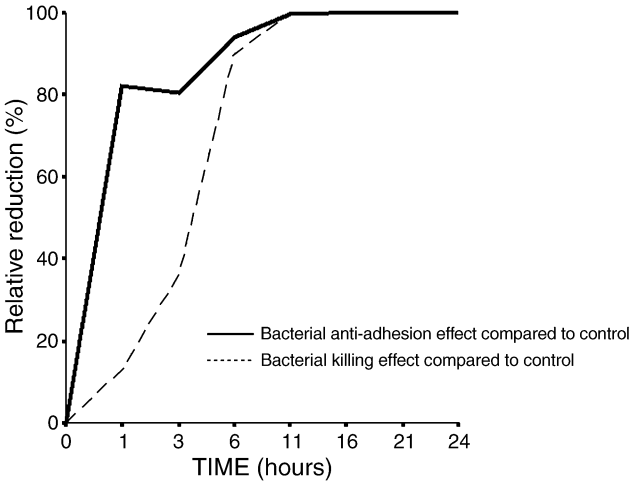

Figure 4. Time-dependent effect of vancomycin (20 μg/mL) on bacterial adhesion to IOLs and on bacterial growth in suspension compared with control. The relative reduction of bacterial growth as well as of bacterial adhesion with vancomycin, compared with the controls, was significant at each point of time. However, comparison of relative reduction between bacterial growth and bacterial adhesion with vancomycin showed significance only at 1 hour ($P < .001$) and 3 hours ($P = .017$). From 6 hours on, anti-adhesion and bactericidal effects could not be discriminated from each other. The area between the 2 curves represents the independent anti-adhesion effect of vancomycin. Curves were identical for vancomycin solution and vancomycin insert.

Consequently, this study attempted to analyze the ability of vancomycin, at concentrations normally used in the irrigating solutions, to reduce *S epidermidis* adhesion to IOLs and to eradicate this organism. To do this, we developed an in vitro model mimicking the in vivo situation that occurs when the patient has cataract surgery with an antibiotic-containing irrigating solution. An inoculum of 103 CFU/mL seemed appropriate in this situation. Indeed, estimated inocula from culture-positive anterior chamber aspirates after cataract surgery vary from 10 to 2.10^2 CFU/mL.[4,36,37] A minimum number of bacteria are necessary to provide significant differences between the groups with and without antibiotic. We did not use 10^5 to 10^8 CFU, as done in most previous studies, because these bacterial concentrations do not mirror the clinical situation.[30]

We proved for the first time that vancomycin had an early in vitro anti-adhesion effect on an *S epidermidis* strain carrying the ica locus and determined the point of time from which this effect is relevant, after only 1 hour of incubation. Furthermore, we confirmed the point of time from which vancomycin has a bactericidal effect (starting at 6 hours) and proved that it was complete after 11 hours, markedly earlier than the reported 24 to 48 hours.[23] One might speculate that, by inhibiting bacterial cell-wall synthesis, vancomycin induces some alteration of bacterial wall structures such as surface adhesions mediating bacterial adherence. This again argues in favor of studying bacterial isolates carrying the *ica* locus. The bactericidal activity of vancomycin is clearly delayed with respect to its anti-adhesion effect. This is not surprising because bacterial lysis is known to be a late result of the initial inhibitory effect of cell-wall active antibiotics.[38]

A current practice of many surgeons is to add vancomycin to the infusion during cataract surgery, despite its failure to reduce bacterial concentration in the aqueous humor (ie, the number of intraocular cultures positive for microorganisms), at the end of surgery[23] or at 2 hours postoperatively.[22] Our results, however, prove that the number of positive aqueous humor taps does not suitably measure the antibiotic prophylactic efficiency of vancomycin brought by irrigation. In fact, it only quantifies the early bactericidal activity, which may not be the only prophylactic effect of vancomycin.

Vancomycin is a time-dependent antibiotic. Its bactericidal effect begins, as confirmed by our results, in

vitro only after 6 hours of incubation. Because of this we were able to assess the anti-adhesion effect of vancomycin during the first 6 hours. It may be better to harbor bacteria in the anterior chamber than on the IOL surface where they are embedded within a slime layer. Indeed, host defenses and antibiotics have trouble penetrating this bacterial biofilm.[39,40] Therefore, bacteria suspended in aqueous humor are less critical to treat than those bound on an IOL surface. Nonetheless, intracameral vancomycin used in irrigating liquids shows a postoperative half-life of less than 2 hours,[22,41] which means that its concentration becomes theoretically inferior to the MIC after 4 to 6 hours[42] (the estimated MIC for most bacteria responsible for postoperative endophthalmitis is about 4 μg/mL).[41] Thus, in a clinical situation, the antibiotic concentration decreases over time, which differs from our in vitro model. Therefore, there is no evidence that contact time with vancomycin is long enough in vivo for the anti-adhesion effect to become clinically relevant. Moreover, it has even been shown that vancomycin could potentially increase bacterial adhesion if the drug concentration fell below the MIC for the infecting strain, by enhancing the biofilm matrix produced by slime-positive coagulase-negative staphylococci on the IOL surface.[43,44] This could eventually worsen the clinical situation. This absolutely merits further studies.

Because the contact time with the antibiotic contained in the irrigating solution is definitely not long enough to develop a relevant bactericidal effect, we designed a biodegradable, biocompatible sterile insert to overcome this drawback. Although only in vitro results are available for now, we believe that placing this insert in the capsular bag could, beyond its action closer to the site in which germs are most critical, progressively release the antibiotic, thus obtaining a longer and more efficient effect. This vancomycin insert obtained in vitro effects identical to those of a 20 μg/mL vancomycin solution. Because the carried dose is 230 μg, while the mean volume of the pseudophakic anterior chamber is 536 μL,[45] our insert would keep a local concentration above the MIC for at least 14 hours respecting a postoperative half-life of vancomycin of less than 2 hours.[22,41] Moreover, with the continuous curvilinear capsulorhexis and the posterior chamber IOL, the bag is widely isolated from the aqueous circulation by the implanted IOL, which might increase the calculated duration by a lower release into the anterior chamber.[46] This would also mean a weaker endothelial toxicity.[46] This expected time of at least 14 hours would be sufficient to develop a bactericidal effect as well as an anti-adhesion one. These hypotheses have to be assessed in vivo, using animal experiments in the future.

In conclusion, the risk–benefit ratio (ie, its effect on bacterial adhesion growth) of supplementing irrigating solutions with vancomycin seems very ambiguous. Nevertheless, a sustained-release system would principally overcome the drawbacks of vancomycin as used in addition to irrigating solutions by allowing both actions of the antibiotic to develop. Furthermore, we demonstrated that our in vitro model is suitable to study anti-adhesion and bactericidal effects of antibiotics.

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