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Comment on: Durability of antimicrobial activity of antibiotic-impregnated external ventricular drains: a prospective study

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Sir,

We read with interest the article by Mounier *et al.*[1] on antibiotic-impregnated external ventricular drains (AI-EVDs). We consider that their conclusions are weakened by their choice of methods and a lack of understanding of the intended purpose and mode of action of the devices.

Regarding their use of the zone-of-inhibition test to determine antimicrobial activity of removed AI-EVDs, this tests only diffusible activity from the catheter surface. Their method does not, as is claimed, test the inside surface as only the cut edges are in contact with the agar. This would be expected to give a larger zone of inhibition than the 'outer surface' version (their Figure 1). However, the legend for their Figure 1 might contain an error: 'In this example, "internal diameter" equals 3 mm (no inhibition) and "external diameter" equals 15 mm'. This statement is not borne out in subsequent text: 'The antimicrobial activity dropped faster for the external side, with no inhibition. . .' Also, the zone-of-inhibition test does not give relevant data as the authors appear to assume that the AI-EVDs depend on release of antibiotics into the CSF. This is not so: they depend on presenting an antimicrobial surface to bacteria that alight on it. The diffusible component is not relevant to their function and is intended to be as small as possible.

The tests for the type of antimicrobial activity are therefore also not useful. In line with the above paragraph, the AI-EVDs are not designed to release static or cidal concentrations of antimicrobials into the CSF, explaining their apparent 'failure' to inhibit a suspension of planktonic bacteria.

When an EVD catheter is removed from a patient, the intracerebral part passes through the skin tunnel and it usually becomes contaminated on the external surface. This is why it is important to sample only the inner surface (by sonication) to determine colonization, yet the authors sampled both surfaces together. This could explain their 'colonization' cases.

The protocol for quantitation of drug content in the AI-EVDs is incorrect. The 'extraction' method used cannot be expected to access drugs in the catheter matrix as a non-polar solvent such as chloroform or toluene is required for this. Methanol, a polar solvent, will not penetrate silicone sufficiently to access any drugs in the matrix and will solubilize only those on the surface. The authors say (in their Supplementary Methods) '. . .because the concentration of antibiotics in new EVD was unknown', yet this information is in the public domain.

The authors compare their protocols with other published methods and say that the difference in results is probably explained by short periods of exposure in others. They cite here three studies[2–4] (their references 15, 16 and 21) saying that exposure to challenge bacteria was between 5 min and 1 h. Only one technical paper[3] (their reference 16) used a 5 min exposure, but this was shown to be sufficient to induce consistent colonization of control catheters in a constant flow model. The other two[2,4] were much more rigorous as though the initial challenges were 1 h, they were followed by further challenges every 2 weeks with constant flow for 42 days without colonization of AI catheters, but consistent colonization of controls.

The authors also refer to three clinical trials of AI-EVDs and say that, of these, only one was in favour of AI-EVD.[5–7] Their reference 3 found in favour, their reference 4 had too few infections in either group to make it sufficiently powered and, in their reference 5, the antimicrobial catheters without additional systemic antibiotics gave a statistically comparable low infection rate to plain catheters with long-term systemic antibiotics, but without the cases of *Clostridioides difficile* infection reported. It would therefore, in our view, be misleading to say that there is 'lack of clinical efficiency'.

There are many misconceptions of the science and mode of action of AI-EVDs in this article. This might not be surprising as the technology is not widely used except in CSF shunts and EVDs. However, evaluation protocols, test methods and assays and their rationales are fully described in the literature cited and the differences in approach taken here explain why the data from Mounier *et al.*[1] are so at variance with most other published data on the topic.

The authors say that they cannot explain the two cases of ventriculitis due to Gram-negative bacteria. The Bactiseal formulation is aimed specifically at Gram-positive bacteria and any cases of ventriculitis in patients using this AI-EVD are expected to be due to Gram-negative bacteria. This same observation has been made by Ramirez *et al.*[8] and others.

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Transparency declarations

R.B. is the named inventor of Bactiseal, but has not received any royalties. He has received speaker fees from Codman, but these have been paid to his university and were not for personal gain. W.A.: none to declare.

References

1 Mounier R, Lang E, Hulin A *et al*. Durability of antimicrobial activity of antibiotic-impregnated external ventricular drains: a prospective study. *J Antimicrob Chemother* 2019; doi:10.1093/jac/dkz335.

2 Bayston R, Lambert E. Duration of protective activity of cerebrospinal fluid shunt catheters impregnated with antimicrobial agents to prevent bacterial catheter-related infection. *J Neurosurg* 1997; **87**: 247–51.

3 Bayston R, Grove N, Siegel J *et al*. Prevention of hydrocephalus shunt catheter colonisation in vitro by impregnation with antimicrobials. *J Neurol Neurosurg Psychiatr* 1989; **52**: 605–9.

4 Bayston R, Ashraf W, Bhundia C. Mode of action of an antimicrobial biomaterial for use in hydrocephalus shunts. *J Antimicrob Chemother* 2004; **53**: 778–82.

5 Zabramski JM, Whiting D, Darouiche RO *et al*. Efficacy of antimicrobial-impregnated external ventricular drain catheters: a prospective, randomized, controlled trial. *J Neurosurg* 2003; **98**: 725–30.

6 Pople I, Poon W, Assaker R *et al*. Comparison of infection rate with the use of antibiotic-impregnated vs standard extraventricular drainage devices: a prospective, randomized, controlled trial. *Neurosurgery* 2012; **71**: 6–13.

7 Wong GKC, Ip M, Poon WS *et al*. Antibiotics-impregnated ventricular catheter versus systemic antibiotics for prevention of nosocomial CSF and non-CSF infections: a prospective randomised clinical trial. *J Neurol Neurosurg Psychiatr* 2010; **81**: 1064–7.

8 Ramirez P, Gordon M, Soriano A *et al*. Assessment of the in vivo formation of biofilm on external ventricular drainages. *Eur J Clin Microbiol Infect Dis* 2013; **32**: 1437–43.

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