Chlorhexidine-Based Antiseptic Solution vs Alcohol-Based Povidone-Iodine for Central Venous Catheter Care

Olivier Mimoz, MD, PhD; Stéphanie Villeminey, MD; Stéphanie Ragot, PharmD, PhD; Claire Dahyot-Fizelier, MD; Leila Laksiri, MD; Franck Petitpas, MD; Bertrand Debaene, MD, PhD

Background: Although chlorhexidine-based solutions and alcohol-based povidone-iodine have been shown to be more efficient than aqueous povidone-iodine for skin disinfection at catheter insertion sites, their abilities to reduce catheter-related infection have never been compared.

Methods: Consecutively scheduled central venous catheters inserted into jugular or subclavian veins were randomly assigned to be disinfected with 5% povidone-iodine in 70% ethanol or with a combination of 0.25% chlorhexidine gluconate, 0.025% benzalkonium chloride, and 4% benzylic alcohol. Solutions were used for skin disinfection before catheter insertion (2 consecutive 30-second applications separated by a period sufficiently long to allow for dryness) and then as single applications during subsequent dressing changes (every 72 hours, or earlier if soiled or wet).

Results: Of 538 catheters randomized, 481 (89.4%) produced evaluable culture results. Compared with povidone-iodine, the chlorhexidine-based solution was associated with a 50% decrease in the incidence of catheter colonization (11.6% vs 22.2% [P = .002]; incidence density, 9.7 vs 18.3 per 1000 catheter-days) and with a trend toward lower rates of catheter-related bloodstream infection (1.7% vs 4.2% [P = .09]; incidence density, 1.4 vs 3.4 per 1000 catheter-days). Independent risk factors for catheter colonization were catheter insertion into the jugular vein (adjusted relative risk, 2.01; 95% confidence interval, 1.24-3.24) and use of povidone-iodine (adjusted relative risk, 1.87; 95% confidence interval, 1.82-2.96).

Conclusion: Chlorhexidine-based solutions should be considered as a replacement for povidone-iodine (including alcohol-based) formulations in efforts to prevent catheter-related infection.

Trial Registration: clinicaltrials.gov Identifier NCT00259350

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IN THE UNITED STATES, PHYSICIANS INSERT MORE THAN 5 MILLION CENTRAL VENOUS CATHETERS EACH YEAR.1 UNFORTUNATELY, THE USE OF CENTRAL VENOUS CATHETERS IS ASSOCIATED WITH ADVERSE EVENTS THAT ARE HAZARDOUS TO PATIENTS AND EXPENSIVE TO TREAT. CATHETER-RELATED BLOODSTREAM INFECTIONS HAVE BEEN REPORTED TO OCCUR IN 3% TO 8% OF CATHETERS INSERTED AND ARE THE PREDOMINANT CAUSE OF NOSOCOMIAL BACTEREMIA IN INTENSIVE CARE UNITS (ICUS), WITH 80 000 CASES ANNUALLY AT A COST OF $300 MILLION TO $2.3 BILLION.2 THE ADDITIONAL FINANCIAL COSTS MAY BE AS HIGH AS $30 000 PER SURVIVOR, INCLUDING 1 EXTRA WEEK IN THE ICU AND 2 TO 3 ADDITIONAL WEEKS IN THE HOSPITAL.3 ATTRIBUTABLE MORTALITY HAS RANGED FROM NO INCREASE TO 35%, DEPENDING ON ADEQUATE CONTROL FOR SEVERITY OF ILLNESS.3,4 THE CENTERS FOR DISEASE CONTROL AND PREVENTION IDENTIFIES CATHETER-ASSOCIATED ADVERSE EVENTS, INCLUDING BLOODSTREAM INFECTIONS, AS ONE OF ITS 7 HEALTH CARE SAFETY CHALLENGES, WITH A GOAL TO REDUCE SUCH COMPLICATIONS BY 50% IN 5 YEARS.5 RECOGNIZED PREVENTIVE MEASURES FOR CATHETER-RELATED INFECTIONS INCLUDED MAXIMAL PRECAUTIONS DURING CATHETER INSERTION AND CAREFUL ASEPTIC TECHNIQUES DURING SUBSEQUENT MANIPULATIONS OF CATHETERS.6 USE OF AN ANTISEPTIC SOLUTION FOR SKIN DISINFECTION AT THE CATHETER INSERTION SITE HELPS PREVENT CATHETER-RELATED INFECTION. UNFORTUNATELY, IT REMAINS UNCLEAR WHICH ANTISEPTIC SOLUTION IS BEST. CHLORHEXIDINE-BASED SOLUTIONS ARE SU-

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prior to aqueous povidone-iodine in reducing the risk for catheter colonization and catheter-related bloodstream infection, and their use as first-line antiseptic agents is now recommended. In a recent study performed in adult ICUs, the use of alcohol-based povidone-iodine was associated with a lower incidence of catheter colonization compared with use of aqueous povidone-iodine. Chlorhexidine-based solutions and alcohol-based povidone-iodine have never been compared directly. We therefore compared a chlorhexidine-based solution with alcohol-based povidone-iodine for skin antisepsis in terms of rates of catheter colonization and bloodstream infection in severely ill patients.

METHODS

CATHETERS

The trial was conducted from May 14, 2004, through June 29, 2006, at a surgical ICU of a university-affiliated hospital after its approval by the institutional review board. All consecutively scheduled nontunneled central venous catheters expected to remain in place for 3 or more days were eligible for the study. Catheters inserted outside the ICU, in patients with a history of allergy to any of the antiseptic agents studied, at an existing site over a guidewire, via the femoral route, or for hemodialysis were not included. Ultrasound guidance was not used to help catheter insertion. All enrolled patients or their legal guardians gave written informed consent.

ANTISEPTIC SOLUTIONS

Catheters were randomly assigned by attending physicians to 5% povidone-iodine in 70% ethanol (Betadine Alcoolique; Via-tris Pharmaceuticals, Me´rignac, France) or a combination of chlorhexidine gluconate, 0.25% benzalkonium chloride, and 4% benzyl alcohol (Biseptine; Bayer HealthCare, Gaillard, France). The same antiseptic solution was used for skin antisepsis before catheter insertion and during subsequent dressing changes. Both types of antiseptic solution are approved for clinical use in this setting, and their retail prices per milliliter of solution are virtually identical.

RANDOMIZATION

Randomization was stratified according to catheter insertion site (ie, the jugular or the subclavian vein) and equilibrated in blocks of 8. The randomization sequences were generated by attending physicians to 5% povidone-iodine in 70% ethanol (Betadine Alcoolique; Via-tris Pharmaceuticals, Me´rignac, France) or a combination of chlorhexidine gluconate, 0.25% benzalkonium chloride, and 4% benzyl alcohol (Biseptine; Bayer HealthCare, Gaillard, France). The same antiseptic solution was used for skin antisepsis before catheter insertion and during subsequent dressing changes. Both types of antiseptic solution are approved for clinical use in this setting, and their retail prices per milliliter of solution are virtually identical.

INSERTION AND MAINTENANCE OF CATHETERS

Trained physicians inserted the catheters using maximal sterile barrier precautions. Before catheter insertion, the skin was disinfected twice (once before and once after placement of large sterile disposable drapes) with the assigned solution for at least 30 seconds and allowed to dry between each antiseptic application. The 20-cm-long, 7F, triple-lumen, unimpregnated polyurethane central venous catheters ( Edwards Lifesciences Corp, Irvine, California) were placed percutaneously using the Seldinger technique. After insertion, catheters were dressed with sterile gauze (Mepore; Mölnlycke Health Care, Göteborg, Sweden). Every 72 hours (or earlier if soiled or wet), the dressing was removed by a nurse wearing a cap, a surgical mask, and sterile gloves. The catheter insertion site was then inspected for signs of infection or inflammation and disinfected with the assigned antiseptic solution, and a new sterile gauze was applied. Topical antimicrobial or antiseptic ointments and antimicrobial filters were not used on any catheter in this study. The potentially confounding effect of health care provider bias was minimized by using a written protocol for catheter care. The catheters could be used for any purpose. Blood samples obtained through the line were not permitted. The decision to remove the catheter was made solely by the patient's physician, who kept the catheter in place until it was no longer needed or until an adverse event, such as catheter-related infection or catheter occlusion, necessitated its removal.

CULTURES

Catheters were removed aseptically. The distal 5 cm of the catheter was sectioned with sterile scissors and placed in a sterile tube, which was immediately carried to the microbiology laboratory. Catheters were cultured using a simplified technique of quantitative broth dilution. This technique was previously reported to have 97.5% sensitivity and 80% specificity for the diagnosis of catheter-related sepsis when the catheter tip culture yielded at least 1000 colony-forming units (cfu) per milliliter.

Sets of aerobic and anaerobic blood cultures (Bact/Alert FA and FN; bioMérieux, Durham, North Carolina) were routinely obtained when a patient had a fever (body temperature > 38.3°C), hypothermia (body temperature < 36.5°C), or other indications (chills or sudden shock). In patients in whom catheter-related infection was suspected on clinical grounds, 2 or more peripheral blood samples were collected for culture before or immediately after catheter removal. All cultures were processed by the clinical microbiology laboratory according to standard methods.

DEFINITIONS

Catheter colonization was defined as a quantitative culture of a catheter tip showing at least 1 microorganism at a concentration of 1000 cfu/mL or greater. Catheter-related bloodstream infection was defined as the isolation of the same organism (ie, the same species with identical antimicrobial susceptibility) from the colonized catheter and from at least 1 cultured peripheral blood sample drawn 48 hours before or after catheter removal in a patient with clinical manifestations of infection and no other apparent source except the catheter. When a patient had coagulase-negative staphylococcal bacteremia, at least 2 cultures with positive results obtained from separate blood samples were mandatory.

STATISTICAL ANALYSIS

The number of catheters that would be required for an adequate examination of the hypothesis that catheters inserted after skin disinfection with the chlorhexidine-based solution are significantly less likely to be colonized than catheters inserted after skin disinfection with alcohol-based povidone-iodine was estimated before undertaking the study. On the basis of previous reports and our own clinical experience, we estimated that 8% of catheters in the chlorhexidine-based solution protocol and 16% of catheters in the povidone-iodine protocol yielded at least 1 microorganism at a concentration of 1000 cfu/mL or greater.
protocol would be colonized. Randomly assigning approximately 260 catheters that could be evaluated to each group would have allowed us to detect with 80% power a significant difference of 30% in the rates of colonization between the 2 antiseptic solutions at a 2-tailed significance level of 5%.

We performed an intention-to-treat analysis. The significance of the differences between the 2 study groups was determined with use of the t test for continuous variables and the χ² test (or the Fisher exact test if necessary) for categorical variables. All P values were based on 2-tailed tests of significance. The proportions of catheters that were free of colonization as a function of the length of time they had been in place were compared between the groups with use of a log-rank test. A Cox proportional hazards model was used to estimate relative risk (RR) (with 95% confidence intervals [CIs]) for microbial colonization or bloodstream infection between groups, adjusting for catheter insertion site and other potential confounding factors in the estimates of treatment effects. Potential quantitative confounding factors were modeled as continuous variables. To avoid rejecting variables that might have influenced the risk of catheter colonization or catheter-related bloodstream infection, variables that were significant at a P<.20 in the univariate analysis were included in a maximal model. A backward-elimination approach was then performed. In this model, variables were removed one at a time, starting with the variable that had the largest P value, until all remaining variables had a 2-sided P<.10. All computations were performed with StatView statistical software (SAS Institute Inc, Cary, North Carolina). An independent study monitoring board reviewed all study findings.

RESULTS

CHARACTERISTICS OF PATIENTS AND CATHETERS

A total of 538 catheters were randomized to the 2 antiseptic groups. Complete data could be evaluated for 481 of them (89.4%) (Figure 1). The remaining 57 catheters (with similar patient and catheter characteristics) could not be inserted (n=17) or were not cultured (n=34), or informed consent was withdrawn (n=6), and therefore they were excluded from further analysis. Characteristics of patients (Table 1) and catheters (Table 2) were similar between the 2 groups except for sex, with more male patients in the povidone-iodine protocol. At least 1 blood culture was performed for 403 study catheters (83.8%). The number of sets of blood cultures obtained per study catheter (median; 6; interquartile range, 2-11) was comparable between the 2 groups.

COLONIZATION OF CATHETERS

Catheters assigned to the chlorhexidine group were less frequently colonized than those assigned to the povidone-iodine group (28 of 242 [11.6%] vs 53 of 239 [22.2%] [P=.02]; incidence density of 9.7 vs 18.3 per 1000 catheter-days). Comparable results were observed when the length of time the catheters were in place was taken into account (Figure 2). The difference was significant only for catheters inserted in the subclavian vein (19 of 198 [9.6%] vs 38 of 188 [20.2%]; RR, 0.47; 95% CI, 0.28-0.79) but not in the jugular vein (9 of 44 [20.5%] vs 15 of 51 [29.4%]; RR, 0.69; 95% CI, 0.34-1.43). Similar findings were observed for the 415 catheters being in place for more than 3 days (28 of 204 [13.7%] vs 52 of 211 [24.6%] [P=.005]).

Catheters assigned to the chlorhexidine group were significantly less frequently colonized with gram-positive cocci (6.2% vs 12.6% [P=.02]), coagulase-negative staphylococci (6.2% vs 8.8% [P=.04]), or gram-negative bacilli (5.8% vs 10.5% [P=.05]) than those assigned to the povidone-iodine group (Table 3).

Table 1. Patients’ Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Chlorhexidine-Based Solution</th>
<th>Alcohol-Based Povidone-Iodine</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of catheters/patient</td>
<td>242/215</td>
<td>239/204</td>
<td>.94</td>
</tr>
<tr>
<td>Men</td>
<td>163 (67.4)</td>
<td>181 (75.7)</td>
<td>.04</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>57 (18)</td>
<td>58 (19)</td>
<td>.76</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>27 (5)</td>
<td>27 (6)</td>
<td>.47</td>
</tr>
<tr>
<td>SAPS II, mean (SD)</td>
<td>42 (17)</td>
<td>43 (16)</td>
<td>.73</td>
</tr>
<tr>
<td>Admission type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operative emergency</td>
<td>146 (60.3)</td>
<td>140 (58.6)</td>
<td>.66</td>
</tr>
<tr>
<td>Operative elective</td>
<td>27 (11.2)</td>
<td>21 (8.8)</td>
<td>.66</td>
</tr>
<tr>
<td>Nonoperative</td>
<td>69 (28.5)</td>
<td>78 (32.6)</td>
<td></td>
</tr>
<tr>
<td>Risks factors for infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inotropes</td>
<td>69 (28.5)</td>
<td>83 (34.7)</td>
<td>.15</td>
</tr>
<tr>
<td>Urinary catheter</td>
<td>237 (97.9)</td>
<td>229 (95.8)</td>
<td>.19</td>
</tr>
<tr>
<td>Thoracic or abdominal drainage</td>
<td>62 (25.6)</td>
<td>71 (29.7)</td>
<td>.32</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>225 (93.0)</td>
<td>214 (89.5)</td>
<td>.20</td>
</tr>
<tr>
<td>Other intravascular catheter</td>
<td>216 (89.3)</td>
<td>223 (93.3)</td>
<td>.12</td>
</tr>
<tr>
<td>Cancer</td>
<td>22 (9.1)</td>
<td>29 (12.1)</td>
<td>.28</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); SAPS II, Simplified Acute Physiology Score II.

a Unless otherwise indicated, data are expressed as number (percentage) of catheters.

b The 2-sided test was used for quantitative data and the χ² test or Fisher exact test was used for categorical data.

c Existing at any time of catheter placement.
of colonization of catheters with Staphylococcus aureus (2.1% vs 3.8%) and yeasts (0.8% vs 1.3%) did not differ significantly between groups.

Independent predisposing factors of catheter colonization were insertion of the catheter into the jugular vein (adjusted RR [ARR], 2.01; 95% CI, 1.24-3.24), use of povidone-iodine (ARR, 1.87; 95% CI, 1.18-2.96), and time to ICU admission (ARR, 1.02; 95% CI, 1.00-1.04).

CATHETER-RELATED BLOODSTREAM INFECTION

In 14 cases, bloodstream infection was attributed to a study catheter (Table 4). These catheters had been in place for a median of 16 days (interquartile range, 8-23 days). Four cases of catheter-related bloodstream infection occurred among catheters assigned to the chlorhexidine group (1.7%; 1.4 per 1000 catheter-days), compared with 10 cases among catheters assigned to the povidone-iodine group (4.2%; 3.4 per 1000 catheter-days) (P = .09). Sepsis resolved spontaneously without antibiotic therapy after the catheter was removed in 6 cases and the patients survived. In the remaining episodes, patients required antibiotic or antifungal therapy. Three patients died, but the medical staff did not consider any death to be unequivocally linked to catheter-related sepsis.

Independent predisposing factors of catheter-related bloodstream infections were patient severity at ICU admission assessed by the Simplified Acute Physiology Score II13 (ARR for 1 point, 1.05; 95% CI, 1.01-1.09) and use of povidone-iodine (ARR, 2.94; 95% CI, 0.90-9.61).

RESULTS FOR FIRST CATHETER INSERTION

Analysis of data for only the first catheter insertion (399 catheters [83.0%]) showed that the use of a chlorhexidine-based solution remained associated with lower rates of catheter colonization (19 of 195 [9.7%] vs 43 of 204 [21.1%]; ARR, 0.51; 95% CI, 0.30-0.87) and a trend toward a lower risk of catheter-related bloodstream infection (1.0% vs 3.9% [P = .09 by log-rank test]) than did povidone-iodine. There were no significant differences between the 2 groups in patients’ characteristics and risk factors for catheter infection.

ADVERSE EFFECTS

Arterial puncture occurred in 31 patients (6.4%) (Table 2) and was never associated with hemorrhage that required blood products or surgery. Pneumothorax developed in 7 cases (1.5%) and always required the insertion of a chest tube. Skin inflammation at catheter insertion sites were observed with similar
The use of a chlorhexidine-based solution for central venous catheter care was associated with a lower rate of colonization and a trend toward a lower rate of bloodstream infection than the use of alcohol-based povidone-iodine. It was estimated that for every 1000 catheter-days when sites are disinfected with a chlorhexidine-based solution rather than povidone-iodine, 9 episodes of catheter colonization and 2 episodes of catheter-related bloodstream infection would be prevented, with the latter reduction not statistically significant. The benefit was observed against both gram-positive and gram-negative microorganisms.

Our findings of remarkably low incidence densities of catheter colonization and catheter-associated bloodstream infection associated with the use of a chlorhexidine-based solution (9.7 and 1.4 per 1000 catheter-days, respectively) were similar to rates previously reported with the same antiseptic solution (8 and 2 per 1000 catheter-days, respectively). By contrast, incidence densities of catheter colonization and bloodstream infection with povidone-iodine (18.3 and 3.4 per 1000 catheter-days, respectively) were slightly higher than those previously reported with the same method of catheter culture (15.2 and 1.1 per 1000 catheter-days, respectively).

The superiority of the chlorhexidine-based solution may have several potential explanations. First, despite an apparent low amount of chlorhexidine, its concentration of 2500 µg/mL is 50-fold higher than the minimum inhibitory concentrations against nearly all nosocomial bacteria and yeasts, and the combinations with benzalkonium chloride and with benzyl alcohol are synergistic against virtually all gram-positive and gram-negative bacteria and yeasts. Second, blood, serum, and other protein-rich biomaterials can deactivate the microbicidal effect of povidone-iodine but not that of chlorhexidine. Third, the residual effect of chlorhexidine, defined as the long-term antimicrobial suppressive activity, is prolonged (≥ 6 hours), whereas that of povidone-iodine is minimal.

Two additional issues should be considered regarding the use of chlorhexidine-based solutions for catheter insertion site care. Hypersensitivity reactions have been reported with the use of central venous catheters impregnated by chlorhexidine and silver sulfadiazine and with the use of chlorhexidine for bathing. However, no hypersensitivity reactions were reported in clinical studies using antiseptic solutions containing chlorhexidine on intact skin. Moreover, other antiseptics including povidone-iodine have also been incriminated in contact dermatitis after therapy-related or work-related exposure. Bacterial resistance is another potential concern when a choice among different antiseptic solutions is being made. Because reports of primary or acquired nosocomial resistance to chlorhexidine are rare, despite widespread use for decades, the effect on antimicrobial resistance is likely to be small, unless multiple-dose bottles of antiseptic are used. However, continued surveillance for resistance is required as part of the further clinical use of such antiseptic solutions.

Our results are likely to be generalizable to a variety of chlorhexidine-based solutions and clinical settings according to the results of a meta-analysis comparing chlorhexidine and povidone-iodine for vascular catheter-site care. This meta-analysis included a variety of patient populations in different types of medical centers requiring peripheral, arterial, or central venous catheters and using different types of chlorhexidine-based solution for catheter care, including 0.5% or 1% chlorhexidine alcoholic solution, 2% chlorhexidine aqueous solution, and the mixture used in the present study. The magnitude of risk reduction for catheter colonization and catheter-related bloodstream infection was consistent across studies, regardless of the type of
chlorhexidine-based solutions used or the setting in which care was provided.\(^9\)

Some limitations should be acknowledged. First, the study could not be conducted in a blinded manner because the 2 antiseptic solutions have different colors. However, the use of strictly defined end points and the review of all outcomes by an independent study monitoring board should have minimized any possible biases. Second, despite randomization at the time of study inclusion, the 2 groups of patients were not equally distributed with regard to sex. However, in the multivariate analysis, sex was not an independent factor for catheter colonization or infection. Third, using the chlorhexidine-based solution, we found a reduction of catheter colonization and of catheter-related bloodstream infection, the latter not statistically significant mainly because our study was not designed (and thus was underpowered) to demonstrate this difference. However, we used a quantitative technique for culture of catheters and a threshold of 1000 cfu/mL to diagnose significant catheter colonization. This relatively high count has previously been correlated with catheter-related sepsis with or without bacteremia and ensures that catheter contamination was not taken into account in the analysis.\(^12\) Moreover, catheter colonization is considered an acceptable first-step surrogate end point for catheter-related bloodstream infection because both are highly correlated statistically \((r=0.69 \ [P < .001])\) and clinically.\(^27\)

We report, to our knowledge, the first study with only short-term central venous catheters inserted in fresh sites and compare a chlorhexidine-based solution with an alcohol-based povidone-iodine formulation for skin antisepsis before catheter insertion and during subsequent dressing changes. Our results demonstrate that the use of a chlorhexidine-based solution rather than povidone-iodine is likely to result in decreased catheter colonization. Given the extent of the benefit and the absence of incremental cost, chlorhexidine-based solutions should be considered as a replacement for povidone-iodine (including alcohol-based formulations) in efforts to prevent catheter-related infection. Indeed, their use in combination with 4 evidence-based procedures recommended by the Centers for Disease Control and Prevention (hand washing, using full-barrier precautions during catheter insertion, avoiding the femoral site if possible, and removing unnecessary catheters) resulted in a large and sustained reduction (≈66\%) in rates of catheter-related bloodstream infection in a recent cohort study performed in 103 US ICUs.\(^28\)

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Correspondence: Oliver Mimoz, MD, PhD, Département d’Anesthésie Réanimation, Centre Hospitalier et Universitaire de Poitiers, 86021 Poitiers, France (o.mimoz@chu-poitiers.fr).

Author Contributions: Dr Ragot had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Mimoz, Ragot, and Debaene. Acquisition of data: Mimoz, Villedumey, Dahyot-Fizelier, Laksiri, Petipas, and Debene. Analysis and interpretation of data: Mimoz and Ragot. Drafting of the manuscript: Mimoz and Ragot. Critical revision of the manuscript for important intellectual content: Villedumey, Dahyot-Fizelier, Laksiri, Petipas, and Debene. Statistical analysis: Ragot. Obtained funding: Mimoz. Administrative, technical, and material support: Mimoz. Study supervision: Mimoz and Debene.

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