patients in each unit were observed for 1 year in each branch of the crossover study. Twelve beds multiplied by 365 days is 4,380 bed-days; so they had 4,380 bed-days as a maximum (we do not know if the units were consistently fully occupied). Their reported infection rates are approximately 1 to 4 infections per 1,000 bed-days. This means that they observed approximately 4 to 16 infections over the entire year of the intervention for each arm of the study. This range represents a very small number of infections, and without getting into the details of the underlying Poisson regression model, the inherent variability on these numbers will be relatively high.

So, what does this mean? It means that the data are very noisy, and the study is unlikely to be able to demonstrate an effect even if it is there. Rough calculations suggest that even if improvements in hand hygiene adherence were able to decrease infection rates by 50%, then this study would have only roughly a 20% chance of demonstrating the effect.

Another issue important to this data set is whether the infections themselves are independent or whether they occurred in clusters (clumped in time). If they were clustered (which would mean that they were not statistically independent), then this analysis would be weakened even more, because ignoring the clustering would give a false sense of the amount of information contained in the data. If the infections are clustered in time, then the analysis is inappropriate.

To the authors' credit, they do acknowledge that the study is "underpowered to detect small differences in rates of infection,"[1] but it may be underpowered to demonstrate larger differences, too. The reviewers of this article should have noted to the authors that this is a good article but requested that they leave out the comments on "detectable changes in the incidence of healthcare-associated infection," because there does not appear to be enough information to generate a reliable conclusion.

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Trial of Alcohol-Based Hand Gel in Critical Care Units

To the Editor—We congratulate Rupp et al.[1] for their well-designed and well-performed study. However, we have some concerns. In contrast to the findings of several studies,[2-7] this study did not find an association between increased hand hygiene adherence and a reduction in nosocomial infections in intensive care units. The authors reported the incidence of 3 types of medical device–related infections (central venous catheter–related bacteremia, urinary catheter–associated urinary tract infection, and ventilator-associated pneumonia) and 3 types of infections associated with multidrug-resistant pathogens (methicillin-resistant *Staphylococcus aureus* [MRSA], vancomycin-resistant enterococci [VRE], and *Clostridium difficile*). Our major concern is that active surveillance cultures were not performed to identify patients colonized with MRSA or VRE. This is an important shortcoming, because the rate of importation of MRSA or VRE into intensive care units and the proportion of ICU patients colonized with such organisms ("colonization pressure") are factors shown to affect the rate of transmission and, most likely, the incidence of infection.[8] Because no surveillance cultures were performed, the present study was not able to assess the impact of hand hygiene on nosocomial transmission of these organisms.

The study was statistically underpowered to show a difference in the measured outcomes, and in fact no formal power analysis was conducted. With detection of such low rates of nosocomial infections, the findings can be explained by chance variability, regression to the mean, and, because nosocomial infections tend to cluster, overdispersion of infection rates relative to chance variation. The authors might consider pooling the data on the incidence of infections due to MRSA, VRE, *C. difficile,* and *Pseudomonas aeruginosa* to ascertain if there was a difference in the total number of infections caused by these pathogens during the periods under study, but it is unclear if this would overcome the above-mentioned problems. In addition, the study compares infection rates aggregated by time period. As stated in gold standard guidelines for the reporting of intervention studies of nosocomial infections,[9] measurement at regular intervals (weekly or monthly) would have better demonstrated trends.

Two of the device-related infections selected as outcomes—namely, catheter-related bloodstream infections and ventilator-associated pneumonia—often necessitate a combination ("bundle") of preventive measures, not just hand hygiene alone, to achieve substantial reductions in incidence. However, the authors did not mention if bundles were used during any of the study periods and, if they were, the degree of compliance with the bundles or other interventions that may have confounded the results.

The authors noted that their inability to demonstrate an association between hand hygiene adherence levels and rates of nosocomial infections may have been due to a failure to

achieve a sufficiently high adherence level. The highest level of hand hygiene adherence in their study was 69%. A study of the relation between MRSA prevalence and hand hygiene compliance conducted in a rehabilitation hospital found that wards with compliance greater than 70% had a lower prevalence of MRSA than wards with less compliance.[5] Additionally, there is ongoing debate about the efficacy of alcohol-based hand rub formulations with an ethyl alcohol content lower than 80%, in particular with gels and foam formulations.[7] The liquid formulations have achieved greater log reductions in the concentration of pathogens in in vivo laboratory-based studies of hand antisepsis. To our knowledge, however, to date no randomized clinical trials or epidemiologic data have demonstrated that the liquid formulations reduce transmission of pathogens to a greater degree than gel formulations.

Moreover, we would like to emphasize that what the authors have clearly designed and conducted, and what their results support, is a successful multimodal hand hygiene promotion campaign modeled on various experiences.[2,3,6,7] Their intervention included most key components of such a strategy[7]: education of healthcare staff by using various tools, face-to-face meetings with nursing staff, reminders in the workplace, monitoring of compliance, monitoring of the rate of nosocomial infections, surveillance feedback, and the introduction of alcohol-based hand rub at the point of care in 2 units at different time periods. The last, referred to as "system" change,[7] is the prerequisite for successful hand hygiene promotion (as clearly apparent from the study results[1]), but it is not sufficient in itself when introduced as a unique component of promotion.[7] In this regard, we believe that the abstract is somewhat misleading, as the authors and hospital healthcare staff efforts are insufficiently recognized.

Perhaps because of restrictions in the length of the article, the results were not compared with those of studies that showed a reduction in the transmission of nosocomial infections following promotion of alcohol-based hand hygiene.[2-7] In an intervention conducted in a neonatal unit, investigators monitored hand hygiene compliance, alcohol-based hand rub consumption, and nosocomial infections at the individual patient level.[8] Improved compliance was independently associated with a decreased risk of nosocomial infections and reduced cross-transmission of genotypically related bloodstream pathogens. Other researchers using quasi-experimental designs reported reduced MRSA infection acquisition following implementation of hand hygiene campaigns that included promotion of alcohol-based hand hygiene.[3,5,7]

We believe that it is important to evaluate further the impact of hand hygiene and other infection control interventions on the incidence of nosocomial infections. We are surprised by the tremendous attention that this article has drawn in the lay press with the take-home message that hand hygiene has no impact on nosocomial infections, a message that we consider harmful to the international patient safety movement. Of note, the World Health Organization World Alliance for Patient Safety has designated hand hygiene promotion as the cornerstone of the First Global Patient Safety Challenge, which is dedicated to tackling nosocomial infections as a worldwide priority.[7,10] To contribute to this field of endeavor in a meaningful way, future investigations must be carried out with appropriate statistical power and scientific rigor. Inappropriate interpretation of the study results by nonscientific experts is a disservice to the authors and the healthcare community, as it is of seminal importance for such a study to be fully understood.

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Alcohol-Based Hand Hygiene and Nosocomial Infection Rates

To the Editor—I read with great interest the study by Rupp et al., describing a crossover trial of alcohol hand gel use in critical care units.[1] I was surprised that the significant increase in compliance observed in this study did not appear to be associated with a decrease in nosocomial infection rates. I am concerned that superficial readers may conclude that alcohol-based hand hygiene does not provide a benefit in the healthcare environment compared with hand washing.

The causal role of microorganisms on hands in the pathogenesis of nosocomial infections is extremely well established.[2] However, the interplay between various factors involved in clinical practice (eg, availability of appropriate hand hygiene agents, correctness of their use, compliance with hand hygiene recommendations) and the outcome in terms of nosocomial infection rates is highly complex and multifactorial. Apart from the question of whether the study by Rupp et al.[1] had patient numbers sufficient in size and observation periods sufficient in length to demonstrate a difference, the authors apparently have not considered one factor that I think is important: the antimicrobial activity of a product used for hand hygiene.

The hand gel chosen by the authors has an ethanol content of only 62%. To determine the implications of this, it is necessary to look at some facts about alcohol-based hand hygiene. First, the published useful range of antimicrobial activity of alcohols is about 60%–80% for most microorganisms, with ethanol the least potent, followed by isopropanol and *n*-propanol.[2,3] The triclosan component (0.3%) of the gel used in the study has very negligible immediate antimicrobial activity.[4] With an ethanol content of 62%, this gel is at the very low end of the published range of activity. In addition, gel formulations often have considerably less antimicrobial activity (about 10-fold; ie, 1 log less) than do liquid alcohol hand rubs.[5] This has 2 implications: the antimicrobial activity is very low to start with, and it is further compromised by the gel formulation. The consequences are that there is no safety margin against handborne microbial contamination and that minor amounts of other liquids on the hands (eg, sweat, water) will render the agent inactive by dilution. Such issues have been addressed by the European EN testing standards. Hand rubs that pass EN 1500 typically produce a reduction in microbial contamination of about 4 log (about 10,000-fold) on hands within 30 seconds.[3,5] Very few gels pass EN 1500, and the ones that do typically contain 80% or more ethanol.[6] The World Health Organization's standardized hand hygiene solutions contain either 75% isopropanol or 80% ethanol, and each of these formulations pass EN 1500.[2]

Why is the antimicrobial activity of a hand hygiene agent important? First, it is beyond doubt that microorganisms on hands are responsible for nosocomial infections and that it is the killing or elimination of microorganisms on hands that prevents these infections[2]; it is not the act of performing hand hygiene per se. Second, although the relationship is not a formal mathematical one, there is a quantitative dose-response relationship between microorganisms eliminated from hands and infections prevented.[7] Third, there is no established "threshold" of microbial elimination beyond which hands can be considered "safe" from the risk of transmitting infections, such that lesser microbial reduction may be considered equally good. Fourth, with regard to user acceptability and compliance, it is important to bear in mind that antimicrobial activity per se has no negative impact on either; instead, user acceptability and compliance are influenced by overall hand rub composition and emollient additives.[8] As a consequence, it is necessary to choose hand hygiene products that have both significant antimicrobial activity and optimized composition for the users.

Finally, we can learn from history. It is now 160 years since Semmelweis made his seminal observations.[9] He showed clearly that soap-based handwashing—which is now known to cause only a minimal reduction in the number of microbial pathogens on hands—did not have the same beneficial effect in preventing puerperal sepsis as did hand treatment with chlorinated lime, which is now known to kill microorganisms very effectively. In essence, this study by Rupp et al.[1] appears to underline the observation by Semmelweis that very potent antimicrobial agents are most beneficial in reducing the incidence of nosocomial infections. Even high compliance with products that have limited activity may not sufficiently decrease the rate of nosocomial infections.

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