Another issue for interpretation of the Schortgen and colleagues study (1) was that the study's primary outcome variable was the number of patients reaching a 50% decrease in the dose of vasopressors within 48 hours; mortality was a secondary endpoint. Some would argue that this lessens credibility of the beneficial effect of cooling on mortality.

Importantly, there were significant imbalances at baseline in the cumulative dose of vasopressors (significantly higher in the no-cooling group). This maldistribution is an important confounder because the no-cooling group had higher total vasopressors dose at baseline and so would be predicted to take longer to wean vasopressors. This renders the unadjusted analysis very difficult or even impossible to interpret. I was pleased to see a specific adjustment of the primary and all secondary outcomes for the cumulative dose of vasopressors at baseline. The adjusted analyses confirmed the benefit of cooling; however, there is always concern about adequacy and accuracy of *post hoc* adjustment of differences at baseline between study groups that could confound interpretation of RCTs.

There are minor concerns about the inclusion criteria such as the time window for inclusion: was there a maximum time for how long patients had SIRS criteria, vasopressors, and ventilation? Also, the authors state that during the 48 hours of study treatment, the initiation of fluids for shock stabilization was similar between groups. However, the fluids reported in Table 3 do not include "fluids for hydration." It would be relevant to know the total volumes of fluids of each group because fluid volume differences between groups could alter ability to wean vasopressors.

The Schortgen and coworkers study (1) was a relatively small RCT and requires validation in a subsequent RCT. Furthermore, many of the potential benefits of control of fever that I summarized above were not addressed by Schortgen and colleagues (1) but would be useful to understand in future studies.

And so back to the bedside and a clinical recommendation in this era of evidence-based medicine. Schortgen and coworkers (1)—whose study may be the first RCT that directly addressed the effects of cooling on outcomes (including mortality) in septic shock—recommended that more larger studies are needed to validate their positive findings. Cooling is simple, safe, and easily implemented. Therefore, I suggest that cooling of febrile patients who have septic shock should be considered especially in patients who are on high doses of vasopressors, who require inotropic agents (e.g., dobutamine [14]), who have marked tachycardia, or who have progressive secondary organ dysfunction.

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Behind the Mask: Overdue Evidence

The article in this issue of the *Journal* by Dharmadhikari and colleagues (pp. 1104–1109) provides long-overdue data to support an iconic practice in tuberculosis (TB) infection control: the use of surgical masks on TB patients to prevent transmission (1). This practice appears to have been first recommended by the U.S. CDC in its 1979 "Guidelines for Prevention of TB Transmission in Hospitals" (2), but only for those who were considered to be "high transmitters." There were no supporting data as references. The latest CDC document from 2005 recommends more widespread use of surgical masks for TB patients outside of airborne infection isolation rooms (3). Although references were provided, they did not contain primary data. The current World Health Organization Policy on TB Infection Control includes the use of surgical masks as a component of cough etiquette but acknowledges the lack of data supporting the practice (4).

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The use of surgical masks to prevent spread of infection by transmissible aerosols was first suggested in 1897 (5), based largely on the work of Carl Flugge, who had suggested that TB was spread by airborne respiratory droplets (6). In 1905, Hamilton advocated for the use of masks in surgery to prevent transmission of streptococcal infection from "invisible sputum" (7), and she was the first to suggest a "mouth guard" to prevent communicable diseases, including TB (8). In 1918, Capps was the first to document the effectiveness of masking patients as well as medical practitioners to prevent spread of infection from measles and scarlet fever on hospital wards (9).

Dharmadhikari and colleagues used an innovative research design to study the intervention of having TB patients wear surgical masks (1). Their experimental TB ward in South Africa is modeled after that of Richard Riley and William F. Wells, whose classic studies firmly established the airborne transmission of TB (10). South Africa is an ideal setting for such a study, as it is suffering from the devastating impact of nosocomial transmission of multidrug-resistant and extensively drug-resistant TB (11, 12). They exposed guinea pigs, an established animal model of experimental TB, to the air from a six-bed TB ward, and they used appropriate positive and negative controls. The outcome was infection in the exposed guinea pigs assessed by monthly tuberculin skin testing. Although this design did not allow for the differentiation of exposures from individual patients, studying the airborne exposure from the pooled sample of patients on alternating days of intervention versus no intervention is very reasonable and efficient.

Purists might argue that the investigators should have continued the intervention for a full 24 hours, but we concur with the authors' implementation of the intervention only during daytime hours. To expect patients to wear masks while sleeping would be both cruel and potentially dangerous. Health care workers (HCWs) tolerate wearing a surgical mask only slightly better than a respirator over an 8-hour period with breaks (13), and approximately one-half of HCWs are not willing to wear any type of mask for an 8-hour shift (14). We are impressed that the patients complied with wearing the masks for 12 hours except for short breaks. Future operational studies might evaluate compliance without incentives and for shorter periods.

These issues speak to the external validity of this study. Should TB patients be expected to wear surgical masks for long periods while they are awake to protect HCWs and other patients? We think not, and we agree with the authors that short-term use, such as during transport, is most appropriate.

An aspect of surgical mask use not addressed by the authors is the potential effect of surgical masks on patients in protecting HCWs or others who may be in close proximity to them, e.g., while performing a medical procedure. It is likely that surgical masks can decrease or divert the concentration of infectious aerosols close to a coughing patient, that is, in the "near field," as described in studies of other occupational exposures (15). The design of this study effectively studied the "far field" effect of the intervention, that is, the concentration at a considerable distance away from the patient. It is possible that the effect on more proximal exposures could be even greater, but further research will be required to assess this.

We were frankly surprised by the magnitude of the efficacy of the use of surgical masks in preventing transmission. Although one could argue that a 56% reduction in infections is not a large magnitude, we find it impressive given the use of the loose-fitting masks used in this study. There appears to be considerably more leakage of cough aerosols from subjects wearing surgical masks compared with N95 respirators (16), so a slightly tighter-fitting mask may be even more effective. One problem with studying surgical masks is the large variation in design features, from little more than a tissue with ear loops to a mask similar to a tight-fitting respirator. Although the authors seemed skeptical that other mask types would be appropriate for TB patients, some designs might be more effective and tolerable, especially for short-term use.

The research design may have also underestimated the true efficacy of the intervention. The small numbers of TB patients likely resulted in only a few of them being infectious given the known variability of infectiousness (17). In a follow-up to the study by Escombe and colleagues cited by Dharmadhikari and colleagues (18), the average infectiousness of the ward air was 8.2 quanta per hour, but only 8.5% of the 118 ward admissions by TB patients caused 98% of the guinea pig TB cases (19). As exposure misclassification usually biases results toward the null hypothesis, a larger number of highly infectious patients may have demonstrated an even greater magnitude of effect.

The authors compared the infectiousness of the ward air in their study to those of others, but readers should be reminded that the population in this study was selected with a bias toward infectiousness, unlike the other studies cited, and there were other methodological differences that may have influenced the results. Although it might appear that the patients in the study from Escombe and colleagues were less infectious, one multidrug-resistant TB patient in that study produced 226 infectious quanta (units) per hour (19). We suspect that the target populations of TB patients in these studies were more similar than not.

Dharmadhikari and colleagues are to be congratulated for this seminal study. We can now be confident that the use of surgical masks on TB patients is supported by scientific evidence, but we should be mindful that this intervention is only one of several control measures that should be implemented to prevent the transmission of TB to our patients and to our colleagues.

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