

# Systemic plus topical antibiotic prophylaxis reduced acquired infections and organ dysfunction in critically ill adults

Krueger WA, Lenhart FP, Neeser G, et al. **Influence of combined intravenous and topical antibiotic prophylaxis on the incidence of infections, organ dysfunctions, and mortality in critically ill surgical patients: a prospective, stratified, randomized, double-blind, placebo-controlled clinical trial.** *Am J Respir Crit Care Med.* 2002;166:1029-37.

## QUESTION

Does a regimen of systemic and topical antibiotic prophylaxis prevent infections, organ dysfunction, and mortality in critically ill patients?

## DESIGN

Randomized {allocation concealed\*}†, blinded (clinicians, patients, data collectors, and outcome assessors),\* placebo-controlled trial with follow-up until discharge from the intensive care unit (ICU).

## SETTING

ICUs in 2 large tertiary care hospitals in Germany.

## PATIENTS

546 patients  $\geq$  18 years of age who were in the ICU > 48 hours and had at least 1 of the following: expected intubation > 24 hours, thoracic or abdominal surgery in the preceding 24 hours, severe organ dysfunction, swallowing disorder, chronic obstructive lung disease, immunosuppressive therapy, or age > 70 years. Exclusion criteria were expected death within 48 hours, inability to randomize within 12 hours of admission, intolerance of study medications, gastrointestinal bleeding in the past month, or pregnancy. 527 patients (97%) were included in the analysis (mean age 53 y, 62% men).

## INTERVENTION

Patients were stratified by disease severity according to Acute Physiology and Chronic Health Evaluation (APACHE) II scores (< 20, 20 to 29, and  $\geq$  30). 273 patients were allocated to prophylaxis, which comprised intravenous ciprofloxacin, 400 mg every 12 hours for 4 days, and a mixture of topical antibiotics (gentamicin, 80 mg, and polymyxin B, 50 mg dissolved in 10 mL sterile saline, which also contained vancomycin, 125 mg) every 6 hours during the ICU stay. 1 mL of the topical solution was applied into each nostril, and 3 and 5 mL were given into the oral cavity and stomach, respectively, after the oropharynx was suctioned. 273 patients were allocated to placebo and received intravenous 0.9% NaCl, 200 mL, twice daily, and NaCl as placebo for topical administration. All patients received sucralfate suspension, 1.5 g, 4 times per day into the stomach 3 hours after administration of the topical study drugs for stress ulcer prophylaxis.

## MAIN OUTCOME MEASURES

Incidence and time of onset of infection, severe organ dysfunction, and mortality.

## MAIN RESULTS

On admission, 211 patients (40%) had infections and 339 (64%) had severe dysfunction of  $\geq$  1 organ. Fewer patients in the prophylaxis group than in the placebo group developed infections or severe organ dysfunction (Table). The groups did not differ for ICU mortality (Table).

## CONCLUSION

In critically ill patients, a regimen of systemic and topical antibiotic prophylaxis reduced acquired infections and organ dysfunction.

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\*See Glossary.

†Information provided by author.

## Ciprofloxacin plus topical antibiotics (prophylaxis) vs placebo for critically ill adults‡

Outcomes	Prophylaxis	Placebo	RRR (95% CI)	NNT (CI)
Infection	34%	57%	52% (38 to 63)	4 (3 to 5)
Organ dysfunction	24%	37%	36% (13 to 54)	8 (6 to 22)
ICU mortality	20%	29%	24% (-9 to 47)	Not significant

‡Abbreviations defined in Glossary; NNT (CI) calculated from relative risks (CIs) and control event rates reported in article.

## COMMENTARY

The trial by Krueger and colleagues is one of the largest studies of selective digestive decontamination (SDD), and its findings are consistent with those of a systematic review (1). Krueger and colleagues found no differences in overall mortality or length of stay, but did find reduced mortality in patients with APACHE II scores between 20 and 29, which corresponded to a predicted mortality risk of about 25% to 60%. Critically ill patients are heterogeneous, and the APACHE score identified patients most likely to benefit from the intervention. Patients in the middle stratum of mortality risk are at increased risk for nosocomial infection yet do not have the profound physiologic derangements that make survival improbable. Krueger and colleagues thus focused on patients most likely to benefit from the intervention, while potentially minimizing the theoretical risk for resistance associated with the use of prophylactic antibiotic therapy for all ICU patients.

In the entire study population, SDD reduced organ failure and infection, which was defined clinically. Interestingly, the use of SDD did not substantially reduce subsequent use or the expense of antibiotics: 68%

of patients in the prophylaxis group and 75% of patients in the placebo group received antibiotics for suspected or proven infection during their ICU stay. Although a concern about the use of SDD is the potential development of antibiotic resistance, patients in this study remained liberally exposed to antibiotics.

Assuming that a clinically important reduction in mortality for this population would be 5%, this trial seems to be underpowered to detect such a benefit. Nonetheless, the results are consistent with meta-analyses of SDD, which suggest that, on balance, it reduces infection and improves survival (1). Curiously, clinicians have been slow to adopt this intervention, which is one of the best-studied prophylactic methods in critical care.

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## Reference

1. D'Amico R, Pifferi S, Leonetti C, et al. *BMJ.* 1998;316:1275-85.