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Selective Decontamination in Critical Care
Interpreting the Synthesized Evidence

Similar to the experience accumulated with topical intestinal antibiotics for prevention of febrile episodes during neutropenia,1 selective decontamination of the digestive tract (SDD) appeared as a controversial issue when proposed 15 years later to critical care physicians.2 The value of SDD remains debated, mainly because of limited evidence of patient benefit and of the risk for emergence of infection due to (the often more difficult-to-treat) organisms intrinsically resistant to the topical antibiotics used in decontamination regimens.1,3-5 It is important to note, however, that the proposed use of the so-called SDD in critically ill patients extends far beyond the administration of oral non-absorbable antibiotics for prophylaxis of "translocation" of bacteria from the digestive tract during episodes of neutropenia.6,7 Proponents of SDD in the ICU actually recommend a triple (synergistic) combination designed for the ambitious goal of preventing ICU-acquired infections, especially of the lower respiratory tract (LRT), by adding two more components to the traditional former component: oropharyngeal topical antibiotics and a short course of systemic antibiotics, administered for the first few days in the ICU, and expected to prevent/treat early occurring LRTI largely due to community-acquired organisms.7

A number of uncontrolled trials show dramatic reductions in the incidence of LRTI with such prophylactic regimens, as compared with historic controls receiving no prophylaxis, and many small-sized randomized controlled trials show similar (although less impressive) results, with no effect on other major outcomes, such as mortality and length of hospital stay (LOS) or duration of mechanical ventilation. These studies, however, individually lacked statistical power to adequately address clinically important outcome measures. Even the largest published randomized double-blind placebo-controlled trials of SDD in ICU patients have only included 322 and 445 patients respectively.8,9 Meta analysis (or quantitative overviews), by analyzing with adequate statistical modeling the pooled results of a number of randomized controlled trials, is one approach to overcome this power problem, provided that the design and setting of trials surveyed are close enough that their aggregation is sensible. In this issue of Chest (see page 1221), Heyland et al present the results of one such methodologically rigorous overview of 25 controlled trials including 3,395 patients. Their results confirm that, although SDD appears to substantially reduce LRTI rates (RR=0.46), this does not translate into what they believe would be a meaningful impact on mortality (RR=0.87, 95% CI 0.79, 0.97) or LOS. It is worthwhile noting that another quantitative overview of SDD10 has recently appeared.11 This overview, based on an analysis of 23 trials including 4,142 patients, showed results similar to that of the Canadian group, with a quantitative assessment of the RR of LRTI in treated patients of 0.37 (95% CI 0.31 to 0.43), but no significant reduction in mortality (RR = -0.90, 95% CI 0.79 to 1.04). While a large proportion of both overviews is composed of the same trials, it is worth noting the consistency of overall results, and the fact that the 700 additional patients included in the Italian group's overview did not alter the results on mortality.

The discrepancy between effects of SDD on pneumonia rates and outcome of patients is striking and raises major concerns. While the Italian group concluded that respiratory tract infections do not substantially impact on mortality (an hypothesis also suggested by Heyland et al), an alternative explanation to these findings is that the reduction of respiratory tract infections might have been grossly overestimated in many trials because of the lack of
specific criteria used to diagnosis pneumonia. That prevention of upper airways colonization or tracheobronchitis does not result in substantial reduction of mortality of LOS of patients is not unexpected. Pneumonia can be difficult to diagnose in mechanically ventilated patients and even more so when oropharyngeal topical antibiotics are administered. Spillover of antibiotics into the trachea may then obscure the interpretation of bacteriologic data, which in turn induces physicians into using clinical criteria only for the diagnosis of infections. It is now well recognized that such clinical criteria are nonspecific in the critically ill ventilated patient. Conversely, pneumonia rates in nontreated patients may have been overestimated in many SDD trials, because of the widespread colonization of the upper and even lower respiratory tract in intubated patients, and no serious attempt had been made to distinguish between colonization and infection. Indeed, LRTI or pneumonia rates in the control groups of trials included in these overviews range from 9 percent to as much as 100 percent. It is, therefore, not surprising that both overviews found statistically significant heterogeneity between studies with regard to effects of SDD on LRTI. Heyland et al have explored the potential role of some predefined factors to explain this heterogeneity, such as criteria used for defining pneumonia, design of studies, and differing types of regimens used across them (Heyland, this issue). Interestingly, they point out that studies including a more rigorous definition of pneumonia show significantly less treatment effect (RR = -0.49) than other studies (RR = 0.19). As emphasized by the authors, given this heterogeneity between studies, results on respiratory tract infections should be interpreted cautiously. In addition to the above-mentioned problems with diagnosing pneumonia, several other potential causes for heterogeneity between studies may exist and influence pneumonia rates and/or outcome of prophylaxis. Cointerventions (e.g., stress-ulcer prophylaxis), or the case-mix of patients and admission categories, which varies widely across trials included in the overview (whether surgical, trauma, or medical patients, and whether patients are admitted from the community or from the hospital), are among other important factors that may largely influence the epidemiology of LRTI. Accounting for the latter factor would have required individual patient’s assessment of outcome (as opposed to trial-based assessment). There is general agreement that “medical” patients do not benefit from SDD; this may also be the case for mixed populations of medical-surgical patients, but this has not been formally tested. Which specific population, if any, would show substantial benefits from SDD, with limited associated risk of long-term ecologic problems (i.e., of antimicrobial resistance), should be the next question addressed by trials of SDD.

The variety of regimens used in trials included in the overview is another cause of concern, making any recommendations difficult. Both the Canadian and the Italian group found that regimens using the full (triple) regimen including systemic antibiotics were more effective than those using only topical antibiotics. Caution, however, must again be expressed in view of the nonsignificant difference of treatment effect between the two categories of trials. It is interesting to note, however, that the two large double-blind randomized trials alluded to above, which have tested only the topical components of SDD, were negative both in terms of effects on respiratory tract infections and on mortality. Besides, in a mixed medical-surgical population, as well as in the subgroup of trauma patients, systemic and topical antibiotics were not more effective than systemic antibiotics alone. Given the greater effect of systemic and topical antibiotics combined as opposed to topical agents only, an interesting hypothesis that remains to be tested is: if these results are confirmed in specific subgroups of patients, (e.g., trauma patients or complicated surgery), will such patients benefit from a short course of systemic antibiotics alone as compared with placebo or usual surgical prophylaxis.

The relationship between ICU-acquired infections and mortality in critically ill patients is a complex issue, and available data are conflicting. Although further studies in specific subgroups of patients are clearly needed in this area, recent studies on morbidity and mortality of nosocomial pneumonia in critically ill patients indicate that, when accurately diagnosed, pneumonia may significantly contribute to mortality, with an attributable mortality of one third of overall mortality of affected patients, as well as increased the LOS in the ICU by about 7 days. These results are similar to observations made in the general hospital population, where nosocomial pneumonia is usually easier to diagnose. With such data in mind, it should not be difficult to show a significant impact of a prophylactic measure, if effective, on patients’ outcome. Meanwhile, the conclusions by Heyland et al that the synthesis of evidence from SDD trials shows marginal benefit, if any, in the general ICU population, appears justified. Considering cost and adverse effects in the short and long term, SDD is probably not useful from a risk benefit point of view in mixed ICU populations, and this complex prophylaxis, which has profound impact on ecology of units, remains at this stage investigational in other categories of patients.
The differing interpretations of the two overviews conducted on SDD (Heyland, and ref 11) is worth a few comments. First, the efforts of groups conducting such overviews should be commended, given the amount of energy required to bring together reliable data on randomized trials from widely dispersed groups of investigations. Second, one would hope that collaboration between groups conducting overviews be established so that studies such as this one would be maximally efficient. Third, it also serves to emphasize that quantitative results of overviews should be examined cautiously, especially when significant heterogeneity between trials exists, such as in the case of SDD where trials have tested different (albeit related) hypotheses, using various therapeutic regimens, in different patients populations.19 In such cases, it should be emphasized that even when the quantitative assessment provides significant treatment effect, the overview itself may not provide definitive guidelines to therapeutic decisions.

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Iatrogenous Pneumothorax

The article by Despars and colleagues that appears in this issue of Chest (see page 1147), once again brings to our attention an increasingly important issue: that of iatrogenous complications and their inherent harm to the patient and resultant increased cost for the healthcare system. Of all the iatrogenous complications related to usual diagnostic or therapeutic procedures, pneumothorax is among the most common. Its incidence has been reported to be from <1 to over 13 percent with central venous cannulation,1-3 from 5 to 20 percent with thoracentesis and pleural biopsy,4-6 from <1 to 3 percent with transbronchial lung biopsies,7 from ≤10 percent to over 50 percent with transthoracic needle lung biopsy,8-10 and from 1 percent to over 40 percent with positive pressure mechanical ventilation.11 The extremely wide range of reported incidence with some of these procedures obviously reflects different patient populations, differences in technique, and/or different circumstances under which the data were collected. However, the article also strongly suggests that some standardization may be necessary to minimize the frequency with which this complication occurs under comparable clinical circumstances. Unfortunately, currently in many (most?) hospitals, exact concurrent information on the incidence resulting from a specific procedure is not readily