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Selective Decontamination of the Digestive Tract and Ventilator-Associated Pneumonia (Part 1)

We read with interest the article "The Pathogenesis of Ventilator-Associated Pneumonia: Its Relevance to Developing Effective Strategies for Prevention," by Safdar et al.[1] We were surprised by 3 completely misleading statements: (1) most but not all selective digestive decontamination (SDD) meta-analyses have found a beneficial effect on ventilator-associated pneumonia (VAP), (2) they found an inconsistent effect on mortality, and (3) recent studies have justified the concern relating to the potential for promoting antimicrobial resistance with long-term use of SDD. We cannot let this misinformation go uncorrected.

SDD is the best ever evaluated manoeuvre in intensive care medicine.[2] Twenty years of clinical research have generated 55 randomized controlled trials (RCTs) and 10 meta-analyses, half of which are from Europe, invariably from Italy, and half from North America, of which two are from Canada and three are from the United States.[3–12] One of the American meta-analyses[9] was produced by Safdar, the author of the article to which we are responding here. All but one meta-analysis assessed the efficacy of SDD in mixed intensive-care-unit (ICU) populations.

Out of the 10 meta-analyses, the main end point was pneumonia in 7.[3–8,10] The end points of 2 meta-analyses were yeast carriage and infections[11] and bloodstream infections,[12] and the end point of Safdar's meta-analysis was overall infection and Gram-negative infections in liver-transplant patients.[9] Table 1 summarizes the morbidity results of these meta-analyses. The 7 meta-analyses with the end point of pneumonia consistently demonstrated a significant reduction in pneumonia. The most recent Cochrane meta-analysis, published in 2004, with 6,922 patients, showed that SDD using parenteral and enteral antimicrobials reduces the odds ratio for pneumonia to 0.35 (95% confidence interval [CI] 0.29–0.41).[10] On average, 5 patients need to receive SDD to prevent one pneumonia. A total of 9,230 patients were available for the first meta-analysis of RCTs that reported bloodstream infections[12] (Luciano Silvestri MD, unpublished data). SDD using parenteral and enteral antimicrobials significantly reduced the odds ratio for bloodstream infections, to 0.63 (95% CI 0.46–0.87). Additionally, a protective effect against bloodstream infections due to aerobic Gram-negative bacilli (AGNB) was found, with an odds ratio of 0.44 (95% CI 0.27–0.73). These findings are in strong contrast with Safdar's claim that not all meta-analyses have found a beneficial effect.

Mortality was the outcome measure in 8 meta-analyses (Table 2).[3–7,9,10,12] There was a consistent survival benefit in all but 2 meta-analyses.[4,9] The most recent Cochrane meta-analysis of RCTs demonstrated that SDD using parenteral and enteral antimicrobials reduces the odds ratio for mortality to 0.78 (95% CI 0.68–0.89).[10] The systematic review of RCTs that reported bloodstream infections and mortality in 9,230 patients[12] showed that SDD using parenteral and enteral antimicrobials significantly reduced the odds ratio for mortality, to 0.74 (95% CI 0.60–0.91) (Luciano Silvestri, unpublished data). The number of patients to be treated with SDD to save one life is 21 in the pneumonia meta-analysis.[10] Kollef's meta-analysis of 2,270 surgical/medical patients[4] and Safdar's meta-analysis of 259 liver-transplant recipients[9] did show an impact on mortality, but the impact was not significant, as the sample size was too small.[13]

Safdar's claim that there is a very real concern relating to the potential of SDD for promoting antimicrobial resistance is based on 2 editorials, written by the groups of Bonten[14] and Daschner,[15] who openly oppose SDD. Remarkably, Safdar ignores the largest individual RCT, which had about 1,000 patients, and the primary end point was antimicrobial resistance among AGNB, the target microorganisms of SDD.[16] This RCT, published in 2003, and conducted over the years 1999–2001, demonstrated that carriage of AGNB resistant to imipenem, ceftazidime, ciprofloxacin, tobramycin, and polymyxins occurred in 16% of SDD patients, compared with 26% in control patients, with a relative risk of 0.6 (95% CI 0.5–0.8). Fair enough; at this point in time there is no meta-analysis on antimicrobial resistance during SDD available. However, as RCTs have predefined study periods, in general a few years, this type of meta-analysis, although valuable, will not address Safdar's justified concern with regard to antimicrobial resistance over the long term. The long-term use of SDD has been evaluated in 10 SDD studies, which monitored it between 2 and 9 years, and resistance associated with SDD has not been a clinical problem.[17–26] There are 4 possible explanations why SDD reduces resistance among the target bacteria. First, in eradicating abnormal carriage and overgrowth, SDD prevents increased spontaneous mutation. Second, very high topical bactericidal levels in throat and gut eradicate resistant mutants already present. Third, polymyxin E and tobramycin are a synergistic mixture. Fourth, the administration of parenteral antimicrobials is lower in successfully decontaminated patients. These observations are in sharp contrast with the common experience that the introduction of any new potent parenteral antibiotic is associated with superinfections within 2 years.[27] We believe that the addition of enteral to parenteral antimicrobials is a promising practice to maintain the usefulness of antimicrobials.

Finally, Safdar refers to the latest fad of SDD antagonists, concerning the relative contribution of the parenteral and enteral components to the reduction of morbidity and mortality.[28] The 55 RCTs were not designed to assess the relative effect of the 2 major components of SDD. However, uncertainty of the weight of the parenteral and enteral contribution does not justify withholding a treatment that, in its entirety, has been shown consistently to save lives.

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Table 1. Main Morbidity Results of the 10 Meta-Analyses of Randomized Controlled Trials of Selective Digestive Decontamination

Author(s)	Year	Number of RCTs	Aggregate Number of Patients	End Points	Odds Ratio	95% Confidence Interval
SDD Trialists Collaborative Group[3]	1993	22	4,142	Pneumonia		
				Parenteral/enteral	0.33	0.27–0.40
				Enteral	0.43	0.33–0.56
Kollef[4]	1994	16	2,270	Pneumonia	0.145*	0.116–0.174
Heyland et al[5]	1994	25	3,395	Pneumonia	0.46†	0.39–0.56
D'Amico et al[6]	1998	33	5,727	Pneumonia		
				Parenteral/enteral	0.35	0.29–0.41
				Enteral	0.56	0.46–0.68
Nathens et al[7]	1999	11	NR (surgical)	Pneumonia	0.19	0.15–0.26
				Bacteremia	0.51	0.34–0.75
		11	NR (medical)	Pneumonia	0.45	0.33–0.62
				Bacteremia	0.77	0.43–1.36
Redman et al[8]	2001	NR	NR	Pneumonia		
				Parenteral/enteral	0.31	0.20–0.46
				Enteral	0.40	0.29–0.55
Safdar et al[9]	2004	4	259 (liver transplant)	Infection overall	0.88†	0.73–1.09
				Infection due to AGNB	0.16†	0.07–0.37
Liberati et al[10]	2004	36	6,922	Pneumonia		
				Parenteral/enteral	0.35	0.29–0.41
				Enteral	0.37	0.29–0.48
Silvestri et al[11]	2005	42	6,075	Fungal carriage	0.32	0.19–0.53
				Fungal infections	0.30	0.17–0.53
				Fungaemia	0.89	0.16–4.95
Silvestri et al[12]	2005	51	9,230	Bloodstream infections	0.63	0.46–0.87
				Bloodstream infections due to AGNB	0.44	0.27–0.73
				Bloodstream infections due to Gram-positives	0.92	0.59–1.44

RCTs = randomized controlled trials
SDD = selective decontamination of the digestive tract
NR = not reported
AGNB = aerobic Gram-negative bacilli
*Risk difference
†Relative risk
Data from Reference 12 include unpublished data from Luciano Silvestri MD.

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Table 2. Mortality Results of 10 Meta-Analyses of Randomized Controlled Trials of Selective Digestive Decontamination*

Author(s)	Year	Number of RCTs	Aggregate Number of Patients	Odds Ratio	95% Confidence Interval
SDD Trialists Collaborative Group[3]	1993	22	4,142	0.80	0.67–0.97
Kollef[4]	1994	16	2,270	0.051†	0.015–0.089
Heyland et al[5]	1994	25	3,395	0.87‡	0.79–0.97
D'Amico et al[6]	1998	33	5,727	0.80	0.69–0.93
Nathens et al[7]	1999	11	NR (surgical)	0.60	0.41–0.88
		11	NR (medical)	0.75	0.53–1.06
Redman et al[8]	2001	NR	NR	NR	NR
Safdar et al[9]	2004	4 (liver transplant)	259	0.82†	0.22–2.45
Liberati et al[10]	2004	36	6,922	0.78	0.68–0.89
Silvestri et al[11]	2005	42	6,075	NR	NR
Silvestri et al[12]	2005	51	9,230	0.74	0.60–0.91

*Only data on the effect of the combination of parenteral and enteral components of SDD are shown, where possible,[3,5,7,10,12]
RCTs = randomized controlled trials
SDD = selective decontamination of the digestive trace
NR = not reported
†Risk difference for mortality related to acquired nosocomial infections
‡Relative risk
Data from Reference 12 include unpublished data from Luciano Silvestri MD.

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