ORIGINAL ARTICLE

Use of selective digestive tract decontamination in European intensive cares: the ifs and whys

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ABSTRACT

Background. Several studies have shown that the use of selective digestive tract decontamination (SDD) reduces mortality. However, fear for increasing multidrug resistance might prevent wide acceptance. A survey was performed among the units registered in the European Registry for Intensive Care (ERIC), in order to investigate the number of ICUs using SDD and the factors that prevented the use of SDD.

Methods. One invitation to the electronic survey was sent to each ERIC unit. The survey focused on department characteristics (intensive care type, local resistance levels), local treatment modalities (antibiotic stewardship) and doctors' opinions (collaborative issues concerning SDD). All ICU's in countries participating in the European Centre for Disease Prevention and Control resistance surveillance program were analysed.

Results. Seventeen percent of the ICUs registered in the ERIC database used SDD prophylaxis. Most of these ICUs were located in the Netherlands or Germany. ICUs using SDD were four times more likely to use antibiotic stewardship. Also larger ICUs were more likely to use SDD. On the contrary, resistance to antibiotics was not related to the use of SDD. Also the doctor's opinion that SDD is proven in cluster-randomized trials was not a determinant for not using SDD.

Conclusion. SDD is used in a minority of the European ICUs registered in the ERIC database. Larger ICUs and ICUs with a prudent antibiotic policy were more likely to use SDD. Neither antibiotic resistance nor the cluster randomized study design were determinants of the non-use of SDD. *(Minerva Anestesiol 2015;81:734-42)*

Key words: Anti-bacterial agents - Gastrointestinal trac

In an era of increasing antibiotic resistance, the use of prophylactic antibiotics in ICU patients, including selective digestive tract decontamination (SDD) is a controversial practice. SDD aims at prevention of secondary colonisation with Gram-negative bacteria, methicil-

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lin-sensitive *Staphylococcus aureus*, *Streptococcus pneumoniae* and yeasts through application of non-absorbable antimicrobial agents in the oropharynx and gastrointestinal tract. Classically, these non-absorbable antimicrobial agents consist of polymyxin E, amphotericin B and tobramycin accompanied by a short course of systemic antibiotics to prevent early infections with potentially pathogenic microorganisms which might be present in the patients commensal flora.

During the first three decades after SDD was defined, most studies performed were underpowered to detect an effect on mortality. However, these studies do show a decrease in infection rate due to Gram-negative bacteria.[1-5] Recently, several single or multi-centre studies showed that SDD leads to a reduction in mortality.[6-9] The German study by Krueger *et al*.[7] was a single-center trial, demonstrating a mortality effect only for patients with a midrange APACHE-II score of 20-29. A randomised trial performed by de Jonge *et al*.[8] showed an absolute intensive care mortality reduction of 8% (with a relative risk of 0.65; 95% CI 0.49-0.85). In addition, de Smet *et al*.[9] performed a large multicenter cluster-randomised trial including almost six thousand patients, comparing SDD and selective oral decontamination (SOD) with standard treatment. After correction for baseline imbalances, the odds ratio for death at day 28 in the SDD group was 0.83 (95% CI 0.72-0.97) compared with the standard care group. Furthermore, a meta-analysis showed a reduction in total mortality with an odds ratio of 0.75 (95% CI 0.65-0.87),[10] without including the latter study.

Despite the evidence, SDD has not gained wide acceptance. The main reluctance has been the perceived widespread use of antimicrobial drugs, potentially leading to an increase in multidrug resistance.[10-13] The main reason for this fear was that SDD is counterintuitive [10] and has been explored only in regions with low endemic resistance. On the other hand, SDD is one of the few strategies, which has been shown to reduce mortality in meta-analysis and large clustered studies.

Given its potential importance, and the expertise that exists within Europe, the European Society of Intensive Care Medicine (ESICM) has endorsed an initiative to address this key issue. During a European Critical Care Research Network (ECCRN) Trial group meeting in November 2011 it was discussed that the current position of SDD in Europe was still unclear, so the first step forward was to investigate this in European ICUs. Therefore, a survey was performed among the units registered in the European Registry for Intensive Care (ERIC) database, with the aim to assess the proportion of ICUs using SDD and gain more insight into the factors that promote or prevented the use of SDD.

Materials and methods

Survey development

The survey was developed by the ESICM SDD Trialist Group and was checked by a non-medical survey specialist. The survey (available as electronic supplement) was converted to an electronic document (SurveyMonkey), with a direct check whether the survey was completed adequately. An email invitation to participate in the survey was sent to the head of each ERIC unit, as the aim was to survey the policy of an entire ICU and not of individual doctors. An Internet link to the survey was included with the email. Participants could complete the survey from March 1, 2012 till April 15. At the end of March, a reminder was sent by email. The ESICM ERIC database is aimed at creating a platform for research collaboration. It contains data of 411 ICUs, 343 of which are from countries collaborating with the European Centre for Disease Prevention and Control and 89 ICUs are from countries that do not have this collabora-

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tion. All answers were included automatically in an Excel spreadsheet.

Three categories of potential determinants of the use of SDD were studied: 1) department characteristics; 2) local treatment modalities; and 3) doctors' opinions. Department characteristics included hospital/intensive care type, total number of operational beds and local antimicrobial resistance patterns. Questions focussing on local treatment modalities included standard treatment to prevent ventilator associated pneumonia and antibiotic stewardship. Antibiotic stewardship contained questions such as if there was an "intensivist with a formal infectious disease background", "routine surveillance of resistant micro-organism", "resistance monitoring on ICU level" and "starting and stopping of antimicrobial drugs based on a written protocol". If all of the points above were answered positive, the ICU was considered to have an antibiotic stewardship protocol. Questions on doctors' opinion focused on collaborative issues concerning SDD, perceived available evidence and costs-effectiveness. These latter questions were assessed on a 5-point scale.

The national resistance pattern

National resistance patterns were obtained from the Surveillance report "Antimicrobial resistance surveillance in Europe 2010" issued by the European Centre for Disease Prevention and Control (ECDC) (www.ecdc.europa.eu). For this survey, all countries associated with the European Centre for Disease Prevention and Control were labelled as "European countries".

Statistical analysis

As the aim of this survey was to investigate the use of SDD in European countries, statistical analysis were only performed on the "European" countries. Univariate regression analysis and multivariate regression analysis were used to investigate which items were independently associated with the use of SDD. Items that had achieved a P<0.20 for the use of SDD in the univariate analysis, entered the multivariate analysis. Items entered the multivariate model in a forward logistic regression mode. The results of the regression analysis are expressed as odds ratio (OR) with the 95% confidence interval (CI) to predict the use of SDD. An OR>1 predicts the use of SDD.

Doctors' opinions were assessed in a 5-point scale. However, as only 15% of the respondents used SDD, several items on the 5-point scale resulted in no score of the respondents. To avoid miscalculations in the odds ratio, the "disagree" and "mostly disagree" answers were merged into "disagree". Also the "agree" and "mostly agree" answers were merged into "agree". This resulted in a 3-point scale: "disagree", "partly disagree/partly agree" and "agree" and at least one answer for each item.

To address the potential effect of non-response on our findings, we contacted 10% of the non-respondents by emailing the nominated head of the ICU. In case of no response, we contacted the attending intensivist by telephone. Non-response bias for using SDD of the unadjusted respondent mean was calculated by the difference between the use of SDD in the respondent group and the non-respondent group, times the total number of non-respondents divided by the total number of ICUs in the ERIC database.[14] Whether respondents differed in their use of SDD compared to non-respondents was tested using ANOVA.

Results

Of the 411 ICUs, 232 (57%) ICUs responded. Overall, 15% of the responding ICUs stated that they used SDD. 63% of the ICUs who used SDD, applied oral and enteral antibiotics with a short course of systemic antibiotics, 26% applied only oral and enteral antibiotics. 3% applied oral antibiotics and a short course of systemic antibiotics and 3% applied only oral antibiotics. In Europe, 17% of the responding ICUs and in non-European countries 10% of the responding ICUs applied SDD (Table I). The highest prevalence of uptake of SDD was found in The Netherlands (13/23; 57%), Russia (2/3; 67%) and Germany (6/21; 29%) (Figure 1). Of the European ICUs using SDD, 63% were located in the Netherlands or Germany.

TABLE I.—*Geographic distribution of the use of SDD.*

Western Europe			Non-Western Europe		
Country	No SDD	SDD	Country	No SDD	SDD
Austria	3	0	Argentina	1	0
Belgium	9	1	Australia	6	0
Denmark	4	1	Montenegro	1	0
Finland	7	0	Brazil	2	0
France	15	1	Switzerland	5	0
Germany	15	6	Ecuador	1	0
Greece	6	1	Egypt	1	0
Ireland	3	0	Georgia	1	0
Italy	11	2	India	5	1
Luxembourg	1	0	Iran	1	0
Czech Rep	4	0	Israel	1	0
Netherlands	10	13	Japan	2	0
Norway	1	0	Jordan	1	0
Portugal	9	0	Kazachstan	1	0
Spain	17	2	Macedonia	0	1
Sweden	6	0	Russia	3	2
Croatia	1	0	Saudi Arabia	3	0
Turkey	4	0	Serbia	3	0
UK	21	3	Singapore	1	0
Bosnia & Herzegovina	1	0	U.A.E	0	1
Hungary	2	0	USA	1	0
Poland	4	0	Montenegro	1	0
Romania	1	0	Ukraine	1	0
Total	155 (83%)	30 (17%)		42 (90%)	5 (10%)

This table shows the number of responding ICU's which use or do not use selective digestive tract decontamination, categorised per country.

Figure 1.—Units using SDD as percentage per country in Europe. Light greyshade represents no SDD use, dark greyshade represents high SDD use.

Fourteen percent of the responding European ICUs were ICUs in a secondary hospital, 41% were ICUs in a teaching hospital and 45% in a university hospital. In 81% of the secondary hospitals, an intensivist covered all shifts, versus 73% of the responding ICU in teachings hospitals and 90% for university ICUs. The mean total operational beds were 15.5±12 and in 21% of the European ICUs, the total operational beds were equal to the number of single bed rooms. Intensivists working in secondary, teaching and university hospitals cared during daytime for respectively 5.6±3, 6.5±3 and 6.5±3 patients, and during night-time for respectively 7.8±4, 11.5±5 and 14.1±12 patients. Nurses working in secondary, teaching and university hospitals cared during daytime for resp. 2.2±2, 3.2±5 and 3.4±5 patients and during night-time for respectively 2.6±3, 3.9±6 and 3.3±6 patients respectively.

We contacted 20 of the non-responding ICUs (10% of the non-responders) and 10% of these used SDD; this proportion was lower, albeit not statistically significantly different from the 15%

observed in the responders (P=0.67). The calculated absolute "non-respondent bias" was 2.2%.

Of the local treatment modalities studied, ICUs with an antibiotic stewardship program were 4 times more likely to use SDD than those without such a program (Table II). When analysing the specific items of antibiotic stewardship, having a written protocol for starting and stopping antibiotic drugs was significantly associated with the use of SDD, in univariate analysis and in the multivariate analysis (Table III). On the other hand, ICUs using subglottic suction and head elevation were 4-5 times more likely not to use SDD (Table II). In the multivariate analysis, these items remained independent determinants of SDD use, except for head elevation (Table II).

Of the department factors we assessed, surveying for Gram-negative pathogens producing carbapenemase was associated with a two times higher probability of SDD use in the univariate analysis (Table IV). Also larger ICUs were more likely to perform SDD: each operational bed increased the likelihood to use SDD by 4% (Table IV). Of these variables, only the size of the ICU (*i.e.*, number of operational beds) remained an independent predictor of the use of SDD in the multivariate analysis. Noteworthy, national resistance pattern of Escherichia coli was not associated with the use of SDD. Neither resistant Gram positive nor Gram negative pathogens causing most infections were related to the use of SDD (Table IV).

Of the items related to the opinion of the nominated lead of each ICU about SDD, agreeing that there is enough evidence that supports SDD, that SDD is cost-effective, being familiar with SDD, support from intensivist colleagues and the notion that there are only cluster randomised trials to support the use of SDD were all associated with the use of SDD (Table V). Of these, agreeing that SDD is cost effective was the strongest determinant of the use of SDD. In the multivariate analysis, only agreeing that SDD is cost effective remained an independent predictor of SDD use.

In Western Europe, prevalence of the use of SDD was the highest in Germany and the Neth-

Table II.—*Local treatment modalities and their relationship with selective digestive tract decontamination (SDD) in European countries.*

Variable	Univariate analysis OR (95% CI)	Multivariate analysis OR (95% CI)
Antibiotic stewardship	4.06** (1.19-13.80)	4.75** (1.30-17.4)
Subglottic suction	0.18** (0.04-0.77)	0.21** (0.05-0.95)
Head elevation	0.23** (0.06-0.90)	0.24* (0.06-1.05)
How many bed a intensivist care for (daytime)	1.10** (1.00-1.22)	1.11** (1.01-1.23)
Handwash	0.38* (0.09-1.61)	
Interruption sedation	1.35 (0.59-3.09)	
New type of tubes	0.53 (0.15-1.86)	
How many beds a nurse care for (daytime)	0.92 (0.80-1.08)	
Education	0.95 (0.40-2.23)	
Routine change of ventilator set	1.03 (0.47-2.28)	

OR: odds ratio with 95% CI: confidence interval. * P<0.20, **P<0.05.

Table III.—*The effect of the specific items of antibiotic stewardship and its association with the use of SDD.*

Variable	Univariate analysis OR (95% CI)	Multivariate analysis OR (95% CI)
Written protocol to start antibiotic drug	3.6** (1.5-8.3)	2.5** (1.0-6.1)
Written protocol to stop antibiotic drug	4.1** (1.8-9.2)	3.0** (1.3-7.2)
Intensivist with ID background	0.8 (0.4-1.8)	
No survey for resistant MO	0.6 (0.1-3.0)	
Survey for resistant MO on individual basis	1.2 (0.5-2.6)	
ICU based survey for resistance	1.0 (0.4-2.2)	

OR with 95% CI. ID: infectious disease; MO: micro-organism. * P<0.20, **P<0.05.

Table IV.—*Department factors of European Countries and its association with the use of SDD.*

Variable	Univariate OR (95% CI)	Multivariate OR (95% CI)
Total of operational beds	1.04** (1.01-1.07)	1.04** (1.01-1.07)
E. coli cephalosporin resistance	0.99 (0.91-1.07)	
Gram positive MO cause most infections	0.68 (0.27-1.69)	
ESBL most infections	0.68 (0.31-1.50)	
Carbapenemase MO cause most infections	0.36 (0.05-2.86)	
Acinetobacter cause most infections	0.26* (0.03-2,09)	
No survey for MDR MO	0.70 (0.22-2.16)	
Survey ESBL	1.75* (0.78-3.94)	
Survey carbapenemase	2.38** (1.05-5.26)	
Survey acinetobacter	2.02* (0.91-4.48)	

Univariate and mulitivariate analysis for the department factors, with the odds ratio (OR) and 95% confidence interval (CI). MO: micro-organism; ESBL: extended spectrum beta lactamase; MDR: multidrug resistance.* P<0.20, **P<0.05.

Table V.—*Doctor's opinion regarding SDD of European countries and its association with the use of SDD.*

Variable	Univariate			Multivariate
	Disagree OR (95% CI)	Partly agree/ Partly disagree	Agree OR (95% CI)	OR (95%CI)
There is enough evidence to support SDD	46% 1.90 (0.7-6.0)	36%	18% 8.1** (2.6-25.6)	
SDD is costs effective	51% 2.13 (0.7-6.9)	33%	16% 14** (4.0-49.2)	2.12** (1.3-3.6)
I am familiar with SDD	50% 1.2 (0.3-4.8)	18%	32% 4.0** (1.1-15.0)	
Infectious disease department supports use of SDD	42% 1.3 (0.4-4.4)	17%	41% 1.6 (0.5-5.3)	
The Pharmacy department supports the use of SDD	40% 0.6 (0.2-2.1)	18%	42% 1.8 (0.6-5.26)	
Intensivist colleague support the use of SDD	38% 0.9 (0.7-3.0)	25%	37% 2.9** (1.0-8.4)	1.64* (1.0-2.7)
Surgeons and internists support the use of SDD	38% 1.1 (0.4-3.1)	20%	42% 1.0 (0.3-2.8)	
Nurses support the use of SDD	38% 0.5* (0.2-1.3)	25%	37% 1.0 (0.4-2.6)	
There are only cluster randomized trials to support the use of SDD	41% 1.8 (0.7-4.6)	45%	13% 6.5** (2.2-19.4)	
There is only evidence for the use of SDD in a low resistance environment	40% 1.6 (0.7-3.9)	43%	17% 1.6 (0.5-4.8)	

Opinion of the nominated lead of the ICUs: OR with 95% CI are displayed predicting the use of selective decontamination of the digestive tract (OR>1 predicts use of SDD). "Disagree" and "Agree" statements are compared to "partly agree/partly disagree".* P<0.20, **P<0.05.

erlands. In a post-hoc analysis containing only these two countries, "routinely surveying for Acinetobacter" was significantly associated with not using SDD (OR 0.23, CI: 0.6-0.84). All other factors in these two countries resembled to all Western European countries.

Discussion

The results of this survey showed that only 17% of the responding ICUs registered in the ERIC database use SDD. Most of these ICUs were located in The Netherlands and Germany. Furthermore, use of antibiotic stewardship and total number of beds was associated with the use of SDD in ICU. In contrast, resistance to antibiotics was not related to the use of SDD.

Analyses on the determinants of SDD use were only performed on ICUs in countries participating in the "Antimicrobial resistance surveillance program" by the European Centre for Disease Prevention and Control (ECDC). As the

fear for development of antibiotic resistance is a widely stated argument for not using SDD,[10-13] resistance was a main subject of this survey. Consequently, we only analysed data from countries participating in this European survey issued by the ECDC. National resistance patterns of *Escherichia coli* for cefotaxime was used in this survey to reflect the national resistance pattern. We focused on *E. coli* as the ECDC observed that the resistance of *E. coli* is continuing unimpeded and it is the most frequent Gram-negative rod isolated from blood cultures. The *E. coli* resistance for cefotaxime was chosen as cefotaxime is the most frequently used systemic drug in the classical SDD strategy.

There are few interventions in intensive care medicine that have been shown to improve survival, but SDD constitutes one of these. In spite of this, the use of SDD is limited in European ICUs. One of the main reasons could be the fear of antibiotic resistance;[10-13] however, this fear was never substantiated. Some studies report an increase of Meticillin-resistant *Staphylococcus aureus* supporting this fear.[15-18] We did not put a direct question in the survey regarding resistance in order not to be suggestive. Instead, we asked "the micro-organisms which cause the most infections", whether "the ICU actively survey for resistant micro-organisms", and more importantly, the national incidence of Gram negative resistance. Our results strongly suggest that resistance is not a main determinant of the use of SDD. This finding is in accordance with the current literature. Increased resistance of Gram-positive microorganisms was not demonstrated in several SDD studies.[1, 2, 4, 6, 8, 9] Most studies report no change [1, 7, 15, 18] or a decrease of resistance pattern [8, 9] for Gram negative microorganisms. Even in a large meta-analysis, there was no relationship between the use of SDD and the development of antimicrobial resistance.[19] The decreased resistance pattern of Gram negative microorganisms persisted after 2 years [17] and 5-year use of SDD.[20, 21] Moreover, SDD is successively used to combat outbreaks of multi-resistant Gram-negative micro-organisms.[22-24] This finding is in accordance with the current evidence that Gram-negative resistance was not a factor in determining whether SDD is used or not in ICUs registered in the ERIC database.

The use of antibiotic stewardship was a strong independent determinant of SDD use in our study. Antibiotic stewardship was first defined by the Infectious Diseases Society of America.[25] The European commission has modified the operational issues after a survey performed.[26] In spite of this, operationalization of the definition of antibiotic stewardship varies greatly between continents, countries and studies and is for sure not adapted to the intensive care setting. In this survey, factors that would indicate the use of antibiotic stewardship were shortlisted by the ESICM SDD Trialists Group. Complying with all these factors identified the ICUs with an antibiotic stewardship program, characterised by a protocolized antimicrobial use with resistance auditing. Interestingly, only the antibiotic stewardship items "written protocol to start and stop antibiotic drugs" was significantly related with the use of SDD. This could mean that centres using SDD have more focus on prudent antimicrobial use. This might be one of the reasons why so many studies show a decreased resistance while using SDD, contrary to the expectations. In addition, intestinal eradication of Gram-negative bacilli could also explain a lower incidence of resistant microorganisms while using SDD.

The total number of beds also predicted the use of SDD in ICUs. One possible reason for this could be that in most studies (including the original study) the indication to start SDD was an expected duration of mechanical ventilation longer than 48 hours, or expected ICU stay longer than 72 hours. Smaller ICUs tend to have a shorter length of stay,[27] probably due to postoperative patients who are discharged the next morning.

Agreeing that there is "enough evidence for the use of SDD", that "SDD is cost effective", "familiarity with SDD" and the fact that "there are only cluster randomised trials for SDD", was strongly related to the use of SDD. Cluster randomized trials are sometimes criticized as baseline characteristics may differ (in contrast to individually randomized studies) leading to post-hoc baseline imbalances corrections. On the other hand, SDD is thought to be effective only as an

unit-wide intervention,[28] which may make cluster randomization imperative. In our survey, not accepting the accuracy of cluster-randomized trials was not associated with the lack of use of SDD.

Factors that hindered the use of SDD in the univariate analysis were handwashing and subglottic suctioning as prevention measure for VAP, lack of support of nurses and Acinetobacter causing the most infections. In the multivariate analysis, significant factors hindering the use of SDD were the application of subglottic suction and the use of head elevation to prevent VAP. Subglottic suction, head elevation, handwashing are key factors in preventing ventilator associated pneumonia formulated by the Infectious Diseases Society of America.[29, 30] That these factors hindered the use of SDD could be explained by the thought that VAP is already prevented, not needing to add SDD. The above mentioned key factors received in 2008 moderate evidence grading for preventing VAP. These guidelines were revised in 2014 and head elevation, handwashing and subglottic suction still were graded as moderate evidence to prevent VAP, however the use of selective oral or digestive decontamination was graded high evidence for preventing VAP.[29]

Our follow-up interview showed that the use of SDD was equally distributed between responders and non-responders indicating that non-response did not introduce relevant bias. There is no consensus about what can be considered an adequate response rate.[14] Definitions of an adequate response rate differ considerably, from 50% to 80%.[14] In a large retrospective study it was observed that physicians response rate to mailed questionnaire varied between 50% and 60% in the period 1985-1995, and remained constant.[31] In critical care setting, median response rate to surveys is 63%, and when the survey is sent only to physicians, the median response rate is 60%.[32] Our response rate of 57% seems comparable to those of others. In addition our non-responder analysis showed that non-response did not confer relevant bias.

In conclusion, in spite of the available data on survival benefit, SDD is used in a minority of the European ICUs. Larger ICUs and ICUs with a prudent antibiotic policy were more likely to use SDD. On the other hand, antibiotic resistance was not associated with using SDD.

Key messages

— Selective digestive decontamination (SDD) is used in a minority of the European ICUs registered in the ERIC database. Larger ICUs and ICUs with a prudent antibiotic policy were more likely to use SDD. Antibiotic resistance was not a determinant in not-using SDD.

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