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Prevention of pneumonia by selective decontamination of the digestive tract (SDD)

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Abstract. Prevention of respiratory tract infections is only possible when the pathogenesis is known. Three types of infection can be distinguished: primary endogenous infections, caused by pathogens carried in the throat at the commencement of mechanical ventilation, generally develop early and can only be prevented by intravenous antibiotics. Secondary endogeneous infections, caused by hospital-acquired pathogens, generally develop later and can be prevented by selective decontamination of the digestive tract (SDD). The GI-tract is decontaminated by oral nonabsorbable antibiotics and for oropharyngeal decontamination a sticky antibiotic ointment is used. To date 16 controlled SDD trials in intensive care have been fully published. In all except one study, the pneumonia rate decreased significantly from 40%–50% in controls to about 10% in SDD-treated patients. All studies showed a consistent reduction of ventilator days, ICU-stay and an improved outcome in SDD-treated patients. However, in only few studies did these differences reach statistical significance. Selection of resistant strains has not been observed during prolonged use of SDD. Sucralfate reduces the pneumonia rate compared to H_2-blockers or antacids by not interfering with the gastric barrier. However, gastric colonization is reduced rather than eliminated and sucralfate has almost no effect on oropharyngeal or tracheal colonization. Whether sucralfate is significantly better than a placebo remains to be established. SDD is superior to sucralfate in preventing both colonization and infection.

Key words: Intensive care – Pneumonia – Selective decontamination (SDD)

Bacterial pneumonia has the highest incidence of all nosocomial infections in the ICU and the pneumonia rate has not changed essentially in the past 10 years [1, 2]. The pneumonia rate is mainly determined by patient selection. In mechanically ventilated patients in a mixed medical-surgical ICU the overall pneumonia rate is approximately 20% [2, 3], whereas in patients requiring mechanical ventilation for more than 5 days, the infection rate is more than 40% [1, 2].

In recent years a large number of studies have shown that pneumonia in mechanically ventilated patients can by prevented effectively by selective decontamination of the digestive tract (SDD). However, the controversial issues concerning this method include the use of a systemic 'broad-spectrum' antibiotic prophylaxis and the fact that despite a dramatic reduction in infections, morbidity and mortaility did not decrease.

Another recent method to reduce ventilator-associated pneumonia is the use of stress-ulcer prophylaxis with sucralfate instead of H_2-blockers or antacids.

The purpose of this manuscript is to review the studies on this subject and to discuss some of the controversial issues about SDD and sucralfate.

To understand the similarities and the differences between the different studies, the pathogenesis of respiratory tract infections should be discussed first.

Pathogenesis

Respiratory tract infections can be divided according to their pathogenesis into endogenous and exogeneous infections (Fig. 1).

Exogenous infections are caused by potentially pathogenic micro-organisms (PPM) from outside the patient. An infection is by definition exogenous if the pathogen causing the infection is not carried by the patient in the oral or intestinal flora, e.g. a pneumonia caused by *Pseudomonas aeruginosa* from a contaminated humidifier. Exogenous infections used to be the major problem in the early days of intensive care, but nowadays are rare. Endogenous infections are caused by PPM carried by the patient in the throat or gastrointestinal tract. For prevention purposes, endogenous infections should be subdivided into primary and secondary endogenous infections.

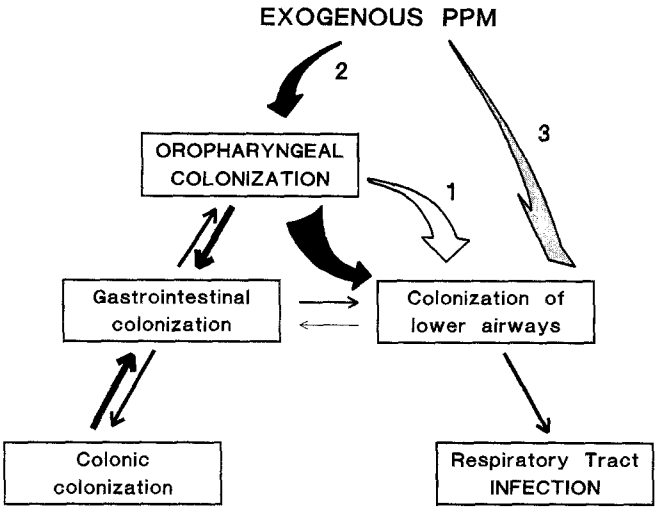

Fig. 1. Pathogenesis of respiratory tract infections. The oropharynx is the most important source of PPM causing respiratory tract infections. The flora of the stomach is mostly determined by PPM carried in the oropharynx. Reflux from gastric contents may amplify the problem. *1*, primary endogenous infection; *2*, secondary endogenous infection; *3*, exogenous infection

Primary endogenous infections are caused by PPM which are carried in the throat or GI-tract upon admission to the ICU, e.g. a pneumonia with *Staphylococcus aureus* in a patient mechanically ventilated for a head injury.

The pulmonary defense mechanisms of patients requiring mechanical ventilation are severely compromised by shock, acidosis, edema, hypoxia, corticosteroid therapy or lung damage, particularly in the first few days of ICU-stay. At the same time large numbers of PPM are introduced into the lower airways by aspiration or endotracheal intubation. Infection with these micro-organisms may develop very rapidly, often within 48 h after commencement of mechanical ventilation [2, 4]; these early infections are frequently erroneously diagnosed as ARDS [5, 6]. More than 40% of pneumonia episodes develop within the first four days [2, 4]. The type of PPM carried by the patient on admission to the ICU depends on many factors e.g. the underlying disease, prior antibiotic use, hospitalization and age (vide infra).

Secondary endogenous infections are caused by hospital-acquired PPM which have first multiplied inside the oral cavity or GI-tract, e.g. a patient admitted to the ICU with normal flora, is colonized in throat and stomach after a few days by *Ps. aeruginosa* acquired from other patients within the ICU. Later he develops pneumonia with *Ps. aeruginosa.*

Although secondary endogenous infections are caused by exogenous (hospital-acquired) micro-organisms, they should be distinguished from exogenous infections because in secondary endogenous infections the PPM first multiply inside the oral cavity and GI-tract before they can cause an infection, whereas in an exogenous infection this multiplication occurs outside the patient.

Normal flora and colonization defence

A multiple trauma patient admitted to the ICU shortly after the accident is likely to have a normal oropharyngeal and intestinal flora. The normal flora consists mainly of anaerobes and viridans streptococci, enterococci and coagulase-negative staphylococci. Approximately 30%–40% of healthy persons carry *S. aureus* in the throat and 30%–80% may carry *Streptococcus pneumoniae* or *Haemophilus influenzae* [7]. Gram-negative PPM are rarely present in the throat or only transiently. The stomach and small intestines generally have high counts of PPM. In the colon 10^5 aerobic Gram-negative bacilli per mg faeces are present, predominantly *Escherichia coli.* Other PPM are rare.

In healthy individuals exogenous PPM have almost no chance to colonize the oral cavity or GI-tract because the defense mechanisms against colonization are extremely powerful. A complex of factors including salivary flow, swallowing, mucus, secretory IgA, fibronectin, gastric acid, bile, persistalsis, and the anaerobic flora, kill and eliminate exogenous PPM.

In critically ill patients many of these defense mechanisms are failing: the salivary flow is decreased, swallowing and the motility of the gut is impaired by medication and instrumentation, the gastric barrier may be rendered ineffective by administration of antacids or H_2-blockers, the secretion of bile and IgA may be reduced and the anaerobic flora may be destroyed by inappropriate antibiotics [8]. This explains the rapid colonization by exogenous PPM from the environment of the patient. Even small numbers of PPM, which would normally be eliminated, are now able to colonize the patient.

Type of PPM causing endogenous infections

In a patient admitted to the ICU with 'normal flora', e.g. a multiple trauma patient, most primary endogenous (early) respiratory tract infections are caused by community-acquired PPM such as *S. aureus, S. pneumoniae* and *H. influenzae* [4]. However, in patients with severe underlying disease, prolonged hospitalization or antibiotic treatment prior to admission to the ICU, the flora may have completely changed. As a consequence the primary endogenous infections in these patients are predominantly caused by Gram-negative PPM e.g. *E. coli, Klebsiella, Enterobacter* and *Proteus* spp.

Secondary endogenous infections, being responsible for the majority of late infections, are almost invariably caused by ICU-acquired Gram-negative PPM and yeasts.

It is thus impossible to distinguish between primary and secondary endogenous and exogenous infections by the type of pathogen, with the exception of infections with community-acquired PPM, which are almost always pimary endogenous, e.g. a pneumonia caused by *Ps. aeruginosa* might be either primary endogenous, if the patient was already carrying the PPM upon admission, or secondary endogenous, if the patient has become colonized by *Ps. aeruginosa* during ICU-stay, or exogenous, if the patient does not carry *Ps. aeruginosa* in throat or GI-tract.

Infection prevention

Infections can generally be prevented by elimination of the source, interruption of transmission of the pathogens or decreasing the susceptibility of the host.

The distinction between exogenous, primary endogenous and secondary endogenous infections is useful to devise a coherent infection prevention strategy in the ICU.

Exogenous infections can be prevented by hygienic measures and strict implementation of the CDC-guidelines (Category I) [9]; i.e. interruption of transmission.

Primary endogenous infections can be prevented by prophylaxis with a suitable intravenous antibiotic; i.e. decreasing the susceptibility of the host. *Secondary endogenous* infections can be prevented by selective decontamination of the digestive tract (SDD); i.e. interruption of transmission and elimination of sources.

Systemic antibiotic prophylaxis

At the time the patient is admitted to the ICU, PPM from the oral or intestinal flora have already reached access to the distal respiratory tract and lung. The infection can be either incubating or established at the commencement of mechanical ventilation. Therefore the systemic antibiotic prophylaxis can also be considered as 'early therapy'. To be effective for early therapy or prophylaxis a systemic antibiotic should fulfil the following criteria: (i) an adequate spectrum; (ii) an excellent penetration in bronchial secretions; (iii) a broad therapeutic range; (iv) and it should not disturb the indigenous flora.

The spectrum should include both community- and hospital-acquired PPM. A prophylaxis study using small spectrum systemic antibotics (Penicillin G or cefoxitin) in mechanically ventilated patients proved to be unsuccessful. Both the overall pneumonia rate and the early pneumonia rate was not significantly reduced, although cefoxitin seemed to have some effect on early infections, but at the expense of more late infections [10]. However, it is generally accepted that a systemic antibiotic prophylaxis may alter the host flora allowing suprainfections with more resistant strains and therefore it should be combined with SDD.

Selective decontamination of the digestive tract (SDD)

Selective decontamination is defined as the selective elimination of aerobic Gram-negative PPM and yeasts from the oral and gastrointestinal flora, without affecting the indigenous (mostly anaerobic) flora [11].

Even more important than the elimination of the PPM that are already present, is the prevention of acquisition and secondary colonization with ICU-associated PPM.

SDD is achieved by the administration of a suspension of topical nonabsorbable antibiotics (Polymyxin E 100 mg, Tobramycin 80 mg and Amphotericin B 500 mg) (PTA) by nasogastric tube, four times a day. The oral cavity is decontaminated, with the same frequency, with a sticky ointment (OrabaseR) containing a mixture of the same antibiotics each at a concentration of 2% (w/w) [12].

Review of available trials

So far 16 controlled trials with this regimen have been fully published (Table 1) which are reviewed in detail elsewhere [13, 14]. Very heterogenous patient populations have been studied, including medical and surgical patients with many different diagnostic groups. However, most studies included only patients who required prolonged mechanical ventilation. In all studies except the one by Brun-Buisson et al. [15], the rate of respiratory tract infections decreased significantly from approximately 40% – 50% in controls, to 10% in SDD-treated patients (Table 2). Not only the number of infections decreased, but also the severity and the duration of the infections.

Although some of the reported respiratory tract infections in these studies might have been tracheitis or bronchitis rather than pneumonia, these infections were sufficiently serious to necessitate antibiotic treatment.

With conventional antibiotic strategies the distinction between colonization and infection and thereby the decision to commence antibiotic treatment, is exceedingly difficult. On the other hand, with SDD the absence of any bacterial respiratory tract infection can be easily diagnosed because colonization of the trachea is prevented.

The reduction in infection rate is also reflected by the fact that significantly less systemic antibiotic are used for the treatment of infections in the SDD-treated patients [3, 16].

The one study that failed to decrease infection [15] differed from the other studies in that a relatively low dose polymyxin E was used in combination with neomycin and nalidixic acid instead of high dose polymyxin E

Table 1. Published SDD-trials in intensive care

Trials (authors) [ref]	Design			Numbers		Incl. criteria (days)		
	RCT	PTA	Ctx	Ctrl	SDD	ICU	MV	Inf
Stoutenbeek [12]		+	+	59	63	≥5	≥3	–
Unertl [27]	+	–	–	20	19		≥4	–
Ledingham [3]		+	+	161	163	–	–	+
Kerver [28]	+	+	+	47	48	≥5	+	+
Konrad [29]		+	+	83	82		≥4	+
Brun Buisson [15]	+	–	–	50	36	>2	–	+
Ulrich [30]	+	–	–	52	48	>5	–	+
Thülig [18]	X[a]	+	+	101	99	≥5	≥3	+
Aerdts [31]	+	–	+	39	17		≥5	+
Godard [32]	X[a]	+	–	84	97	–	–	+
McClelland [33]		+	+	12	15		≥5	+
Sydow [34]		+	+	48	45	≥7	≥4	–
Flaherty [25]	+	–	–	56	51	–	≥1	–

RCT, randomized controlled trial; PTA, polymyxin E, tobramycin, amphotericin B; CTX, cefotaxime; C, control group; SDD, SDD treated group; ICU, ICU-stay in days; MV, duration of mechanical ventilation; Inf, infection present on admission; patient, patient selection; X[a], consecutive trial in 2 ICUs with cross-over of the treatment

Table 2. Pneumonia and mortality rates (9)

Author	Pneumonia rate Control – SDD (%)	Mortality Control – SDD (%)
Stoutenbeek [5]	59 – 8	8 – 3
Unertl [16]	70 – 21	30 – 26
Ledingham [3]	18 – 3	24 – 24
trauma		26 – 0
ICU stay ≥ 7 d		34 – 13
Kerver [28]	40 – 6[a]	32 – 29
infection-related		17 – 4
Konrad [29]	42 – 6	22 – 30
Brun-Buisson [15]	22 – 20	24 – 22
infection-related		10 – 9
Ulrich [30]	50 – 15	54 – 31
infection-related		15 – 0
Thülig [18]	46 – 10	46 – 34
infection-related		23 – 7
Aerdts [31]	69 – 6	15 – 12
Godard [32]	15 – 2	18 – 12
ICU-stay > 48 h		18 – 6
McClelland [33]	50 – 7	58 – 60
infection-related		50 – 27
Sydow [34]	75 – 7	14 – 0
infection-related		6 – 0
Flaherty [25]	9 – 2	2 – 0

[a] Number of infections (infection rate not reported); since one patient can have more than one infection, the infection rate may be lower

with tobramycin; secondly, patients did not receive oropharyngeal decontamination with Orabase but with povidone-iodine; and thirdly, patients did not receive a systemic antibiotic prophylaxis.

So far there is no evidence for selection of resistant Gram-negative PPM, using the same regimen for over 9 years in the same unit [17]. On the contrary, the prevalence of resistant Gram-negative PPM decreases during SDD-treatment due to the elimination of sources [15]. Although coagulase-negative staphylococci and enterococci are not eliminated by SDD because they belong to the indigenous flora, these micro-organisms do not cause more infections under SDD.

Morbidity and mortality

Since infections increase morbidity and mortality, prevention of infection should reduce morbidity and mortality. In many of the SDD-trials a consistent, albeit statistically not significant, difference of approximately 3 days in the duration of ICU-stay has been found in favour of the SDD-treated patients. However, because of the large standard deviation and the relatively small numbers of patients studied the difference did not reach statistical significance.

The mortality is consistently lower in SDD-treated patients in most studies (Table 3). However, none of the SDD-studies was designed to find a difference in mortality and therefore had not enough statistical power; e.g. in Thülig's cross-over study in 195 patients in two ICUs, although the overall mortality was reduced by 22% in the SDD-treated patients, this difference was not significant [18].

Table 3. Indications for SDD in intensive care

Mechanical ventilation with expected duration > 48 h
Preoperative in high risk operations or high risk patients
Large burns
Treatment of severe infections
Outbreaks of multiply resistant PPM
Prevention and treatment of MOF

A properly designed mortality study should include only primarily non-infected patients, with a curable underlying disease and a high risk of dying of acquired infections. A sample size calculation based on the assumption that SDD reduces the mortality of acquired infections from 20% to 10%, shows that the study should include 501 patients. Until such a study has been performed the issue whether SDD reduces infection-related mortality cannot be conclusively settled.

Alternatives to SDD

Recently stress-ulcer prophylaxis with sucralfate has received much attention as an alternative infection prevention regimen. H_2-blockers and antacids by promoting outgrowth of Gram-negative PPM in the stomach are a risk factor for pneumonia. The concentration of Gram-negative bacilli may increase up to 10^8 bacteria/ml at a gastric pH > 4 [19]. A high gastric pH is associated with a high pneumonia rate. However, only in about 30% of cases it can be demonstrated that PPM first colonize the stomach and then the respiratory tract [19]. The oropharynx appears to be far more important than the stomach as source of respiratory pathogens (Fig. 1).

A number of studies [20–22] have shown that sucralfate, which has no influence on the gastric pH, decreases pneumonia rate compared to H_2-blockers or antacids. No significant effect of sucralfate on morbidity or mortality has been found. However, in these studies sucralfate had no effect on the carriage of Gram-negative bacilli or *S. aureus* in the throat and in the majority of sucralfate-treated patients the trachea was still colonized by Gram-negative PPM or *S. aureus* [20, 22]. Therefore the diagnosis of infection relied heavily on the clinical criteria of infection. A three-armed blinded randomized controlled study of H_2-blockers/antacids versus placebo versus sucralfate with pneumonia rate as primary endpoint is required to answer the question whether sucralfate is superior to placebo.

It is unlikely that the gastric barrier is functioning effectively using sucralfate, because 75% of sucralfate-treated patients had gastric pH levels between 3.5 and 4.5 [22]. As a consequence relatively high gastric colonization rates in sucralfate treated patients are found (*C. albicans* 49%; Gram-negative bacilli 48.8%; *S. aureus* 24.5%) [22].

The conclusion that by decreasing gastric colonization the pneumonia rate would decrease, is in contrast with the finding that SDD, applied to the GI-tract only (without oropharyngeal decontamination), had no significant effect on the pneumonia rate, although the gastric

colonization was completely prevented [4]. On the other hand, oropharyngeal decontamination without gastrointestinal decontamination is shown to effectively prevent pneumonia [23, 24]. This confirms the crucial role of colonization of the oropharynx in the pathogenesis of pneumonia. Colonization of the stomach is only important because it may amplify the bacterial load to the lung.

Flaherty et al. [25] compared SDD with H_2-blockers or antacids versus sucralfate in postoperative cardiac surgical patients and showed that SDD was superior to sucralfate in preventing colonization of the oral cavity and/or stomach. SDD proved to be more effective than sucralfate in reducing both pneumonia and other infections.

Indications for SDD

The indications for SDD are summarized in Table 3. The indications are not solely determined by the colonization and infection risk of the individual patient, but also by the perceived benefit of preventing infections. Cost-effectiveness and epidemiological factors should also be taken into account.

Preoperative SDD in high risk patients or high-risk surgery, e.g. esophageal resections [26], seems to be particularly promising for the prevention of postoperative respiratory tract infections. Since SDD can be commenced prior to the trauma i.e. surgery, SDD takes effect within 48 h and the period of perioperative systemic antibiotic prophylaxis can be limited to 24 h even when prolonged postoperative mechanical ventilation is necessary.

Conclusions

Proven effects of SDD are:

- elimination of PPM carried by the patient upon admission
- prevention of acquisition and secondary carriage by hospital-acquired PPM
- reduction of the colonization and infection rate (not only the number of infectious episodes, but also the severity of infections and the duration of infections)
- reduction of systemic antibiotic use
- prevention of selection of multiply resistant *Enterobacteriaceae* and *Pseudomonadaceae*
- control of outbreaks with multiply resistant strains.

Yet unproven effects of SDD are:

- reduction of infection-related mortality
- increase of cost-effectiveness
- prevention and treatment of multiple organ failure

Large controlled studies specifically designed to examine these issues are necessary to solve these questions.

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