233

BACTERIAL TRANSLOCATION AND ENDOTOXIN ABSORPTION IN ORGAN DONORS.

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The mucosa of the GI-tract provides an effective barrier to the entry of intestinal bacteria and endotoxins. As shown in animal experiments this barrier function can be lost in critical illness and thus may lead to translocation of bacteria and endotoxins, resulting in bacteraemia, endogenous infections and endotoxaemia. Since hardly any information is present about these phenomena in humans without (preexistent) GI-tract disease, we did a prospective study in organ donors because they are at risk for bacterial translocation and endotoxin absorption.

Materials and methods: Twenty-one organ donors (mean age 26, range 3-58 years) entered the study. Before surgery a bloodsample was taken from the peripheral blood for culture, endotoxin level and endotoxin inactivating activity (EIA). After laparotomy a sample of abdominal fluid was taken for culture and endotoxin level. Subsequently mesenteric lymph nodes (MLN) were sampled at the proximal jejunum, the distal jejunum and the distal ileum for culture. Before starting organ perfusion a bloodsample was taken from the portal vein for culture, endotoxin level and EIA. After removal of the organs biopsies were taken of the lung, spleen and liver, for culture and from the proximal jejunum, the distal jejunum, the distal ileum and the caecum for light and electron microscopy and culture. Cultures were considered positive as more than 10^2 cfu/gram tissue or $>10^2$ cfu/ml fluid were isolated.

Results: Positive cultures were found in the MLN of 11 donors, in the lung of 7, in the liver of 2, in the spleen of 5 and in the peripheral blood of 1 donor. All cultures of portal blood and peritoneal fluid were negative. Three times only gram negative bacteria were isolated, 19 times only gram positives and 4 times both. All but five of the isolated strains were also isolated from the small bowel. Elevated plasma endotoxin levels (>5 pg/ml) in the peripheral blood were found in 4 donors, in the portal blood in 2 donors and in peritoneal fluid in 9/17 donors. The EIA (mean $\pm$ SD, μ g/ml) in both peripheral (2.25 $\pm$ 2.9) and portal blood (1.94 $\pm$ 2.6) were significantly ($p < 0.0001$) lower as in a reference group of healthy individuals (8 $\pm$ 1). No mucosal damage was found in the biopsies.

Conclusion: Bacterial translocation is a common feature in organ donors and is probably frequently accompanied with endotoxin absorption leading to endotoxaemia and/or decreased endotoxin inactivating capacity.

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Nosocomial pneumonia prophylaxis

235

UTILITY OF SELECTIVE DIGESTIVE DECONTAMINATION IN A GENERAL POPULATION OF MECHANICALLY VENTILATED PATIENTS. M. Ferrer, A. Torres, J. González, J. Puig de la Bellacasa, J.M. Gatell, M. Roca, M.T. Jiménez de Anta, R. Rodríguez-Roisin.

To assess the utility of selective digestive decontamination (SDD) in the prophylaxis of nosocomial respiratory tract infections in a general population of mechanically ventilated (MV) patients, we performed a prospective randomized double-blind clinical study using an association of Polymyxin E, Tobramycin and Amphotericin B topically in the oropharynx and through a nasogastric tube versus placebo. Eighty MV patients have been studied (56 males and 24 females), aged 61 ± 19 yrs (mean $\pm$ SD). Thirty-nine patients received antibiotic association and 41 received placebo. Patients received Cefotaxime (2 g/6 h) during 4 days to prevent the primary endogenous infection, except when another antibiotic treatment was necessary. The overall incidence of nosocomial pneumonia and purulent bronchitis was 24% and the mortality rate was 29%. There were not significant differences between both groups (SDD and placebo) regarding the incidence of pneumonia and purulent bronchitis (23% vs 24% respectively), the mortality rate (31% vs 27%), the duration of MV (13.5 vs 12.6 days) and the length of ICU hospitalization (15.3 vs 14.3 days). By contrast, the SDD group showed a significant lower rate of bronchial colonization by gram negative bacilli (31% vs 78%, $p < 0.00003$) and particularly by *P. aeruginosa* (23% vs 67%, $p < 0.0004$), and by *Candida* (21% vs 40%, $p < 0.059$). These differences were similar in pharyngeal and in gastric colonization. Although it was not statistically significant, colonization by methicillin-resistant *S. aureus* (MRSA) was higher in the SDD group (36% vs 30% in bronchial aspirates and 33% vs 18% in pharyngeal swabs). The most frequent microorganisms causing nosocomial pneumonia in both groups were *P. aeruginosa* and MRSA. Three cases of *P. aeruginosa* pneumonia in the SDD group were exogenous and three cases in the placebo group were endogenous. MRSA pneumonias in both groups were endogenous. Our results suggest that, although SDD is useful in the prevention of pharyngeal and bronchial colonization by gram negative bacilli, this treatment does not reduce the overall incidence of nosocomial respiratory tract infections and the mortality rate in a general population of MV patients. The different pathogenesis of gram negative pneumonia in both SDD and placebo group should be confirmed in further studies.

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234

THE CLINICAL VALIDITY OF TESTING ENDOTOXIN IN SEVERE SEPSIS/SHOCK IN ICU PATIENTS

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Early treatment, within 24 h maximally, can be desirable in persisting septic shock, associated with a high mortality. Quick and highly predicting procedures for identification of the type of infection still remain a big problem. Besides fully supportive and appropriate antibiotic therapy, today adjunctive immunotherapy with antibodies against endotoxin (HA-1A, Centoxin®) is available (Ziegler EJ et al., N Engl J Med 1991; 324: 429).

Objective: to evaluate the effectiveness of determination of endotoxin (LPS) to identify endotoxemia, as a predictor of gram-negative infection; a retrospective survey after ICU admission.

The LPS concentration in serum samples was determined using the Coatest® Endotoxin test by KabiVitrum, Sweden. The assay was modified for measuring in serum or plasma. Serum samples were diluted 10-fold with endotoxin-free water and heated at 75 - 80° Celsius for 5 minutes. After cooling to room temperature, 25 μ L of the pretreated solution is brought to 37° Celsius. After 4 minutes, 25 μ L LAL-solution is added to each tube and the solution is stirred. Incubation time is 30 minutes. Next, 50 μ L of the S2324 chromogen substrate / buffer (1 : 1) solution is added and stirred again. After another 5 minutes the reaction is terminated by adding 50 μ L 50% acetic acid. After adding 450 μ L water, the extinction was measured at 405 nm immediately.

Concentrations were determined by reading them from a standard curve. The sensitivity of the assay was about 25 pg/mL⁻¹, while the time needed for the assay was 3 h, maximally, with a capacity of 15 samples in duplo.

14 ICU patients with septic shock were included; the mortality was 43%, half of which was due to sepsis. Results: 71% showed endotoxemia (57 ± 30 pg/mL⁻¹, range 26 - 121 pg/mL⁻¹). Three patients received adjunctive immunotherapy with HA-1A, 100 mg, and they survived. One patient received a second dose, 3 days after the first.

In conclusion:

- LPS measurement in septic shock can be of diagnostic and therapeutic value and provides a quick tool (< 3 h) in comparison with conventional blood culture techniques, which take 24 - 48 h. These are, however, of obligate value for identification of the infection.

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236

PROPHYLAXIS OF PNEUMONIA IN MECHANICALLY VENTILATED PATIENTS BY CONTINUOUS SUBGLOTTIC ASPIRATION.

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In the pathogenesis of endogenous ventilator-associated nosocomial pneumonia (NP), the relationship between chronic aspiration through a tracheal cuff and the development of pneumonia is well established.

The aim of this study was to evaluate the efficiency of continuous suction of subglottic secretions (SS) accumulated above the cuff in the prevention of nosocomial pneumonia in mechanically ventilated patients.

Method. This prospective study was conducted on 123 patients under mechanical ventilation (MV) for more than 72 hours. They were randomized and divided into two groups: Group I (n= 60) underwent continuous aspiration of SS and Group II (n= 63) didn't receive aspiration. Both groups were intubated with a special tracheal tube (TT)(Hi-lo-evac. Mallinckrodt) which disposes of an additional lumen in order to suction the accumulated secretions above the cuff. During the period of study, pressure of the TT cuff was checked every 4 hours in both groups. In Group I, total amount of aspirated SS was measured every day and semiquantitative culture was performed each 5 days. Protected specimen brush (PSB) and bronchoalveolar lavage (BAL) were performed in patients who fulfilled the established standard criteria for NP.

Results. Both groups were similar in terms of demographic characteristics, severity of illness (APACHE II), mortality risk and risk factors for NP. Treatment with antimicrobial agents was significantly higher in Group I (91.7%) vs Group II (68.3%) ($p < 0.05$). NP developed in 26 (21.1%) of the 123 patients studied, 9 (15%) in Group I and 17 (27%) in Group II ($p = 0.159$). *P. aeruginosa* was the most frequent bacteria isolated in PSB and BAL. The mean ($\pm$ SD) number of days until development of NP was 11.4 ± 6.7 in Group I and 6.47 ± 3.45 in Group II ($p < 0.05$).

Discussion. These results indicate a tendency to reduce the risk of NP in patients with MV for more than 3 days when SS are continuously aspirated. However, further studies will be needed to confirm the validity of this method of prophylaxis.

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237

SELECTIVE DECONTAMINATION OF THE DIGESTIVE TRACT AND EARLY SYSTEMIC CEFOTAXIME IN PATIENTS WITH BLUNT TRAUMA: EFFECT ON INFECTION AND MORTALITY

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Selective decontamination of the digestive tract (SDD) with antimicrobial drugs has been shown to reduce the frequency of upper airway colonisation and respiratory tract infection. The aim of this study was to determine the effect of SDD on respiratory infection and mortality in patients admitted to an intensive care unit with blunt trauma who needed tracheal intubation for at least 2 days.

The patients were a predefined sub-group from a larger study of SDD in which patients treated with SDD between December 1988 and December 1989 are compared with controls from the preceding and following years. Patients were matched by diagnostic category, APACHE II score, age and sex. The SDD regimen was a polymyxin, gentamicin and amphotericin B paste applied to the buccal mucosa 6 hourly, the same antibiotics in suspension given nasogastrically 6 hourly and cefotaxime 1gm 6 hourly for the first 4 days.

The mean ($\pm$ SD) age, APACHE II score and injury severity scores in the pre-SDD (n=67), SDD (n=68) and post-SDD (n=51) groups were 33.6 ± 18.1 , 33.7 ± 17.1 and 35.8 ± 19.2 years; 11.6 ± 5.6 , 12.5 ± 6.6 and 12.3 ± 6.4 points; and 24.2 ± 12.1 , 28.4 ± 14.4 and 23.9 ± 12.3 points respectively. The frequency of nosocomial pneumonia was 55%, 35% and 59% in the successive groups (Chi-square 8.12, $p=0.017$). The frequency of positive cultures from wounds, urine, blood, intravascular catheters or sputum during the first 4 days was similar in the 3 groups. After 4 days the frequency of bacterial isolates from wounds, urine, blood and intravascular catheters remained similar but there was a significant difference in positive sputum cultures: 28%, 12% and 18% in successive groups (Chi-square 6.1, $p=0.048$). Variations in Gram-negative bacterial isolates caused this difference. Mortality was 16%, 3% and 10% in successive groups (Chi-square 7.0, $p=0.03$; odds ratio SDD vs controls 0.19, 95% confidence interval (0.04 - 0.92).

Patients with blunt trauma treated with SDD had a lower frequency of nosocomial pneumonia, positive sputum cultures after 4 days and death.

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239

OROPHARYNGEAL GENTAMICIN FOR LONG-TERM VENTILATED PATIENTS ON SUCRALFATE?

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Sucralfate has been demonstrated to reduce incidence of stress ulcer bleeding and nosocomial pneumonia in long-term ventilated patients. In a placebo-controlled trial we studied, whether gentamicin administered topically to the oropharynx (OPG) had additional clinical benefits in patients on mechanical ventilation for ≥ 5 days and stress ulcer prophylaxis with sucralfate (6 x 1g/day).

In the OPG group (n=33) 40 mg gentamicin and in the control group (n=34) 5% dextrose were administered to the oropharynx 4 times per day. During OPG pharyngeal colonization rate (21 vs 44%) and tracheal secretion colonization rate (12 vs 41%) were significantly lower than during placebo ($p<0.05$). Despite these differences nosocomial pneumonia rate (3 vs 12%) duration of intubation (9.5 ± 4.8 vs 7.9 ± 3.5 days) and mortality (27 vs 41%) were not significantly affected by OPG. Moreover, 13 of 15 bacteria (87%) that occurred during OPG were resistant to gentamicin.

Despite its reduction of bacterial colonization rates of pharyngeal and tracheal secretions OPG did not seem to offer additional clinical benefits in long-term mechanically ventilated patients on stress ulcer prophylaxis with sucralfate.

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238

THE EFFECT OF TOPICAL ANTIMICROBIAL PROPHYLAXIS ON COLONIZATION OF OROPHARYNX, STOMACH AND TRACHEA IN PATIENTS RECEIVING AND NOT-RECEIVING PROPHYLAXIS

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Topical antimicrobial prophylaxis (TAP) with non-absorbable antibiotics has been used to prevent nosocomial pneumonia in mechanically ventilated patients (pts). Since colonization is modulated by TAP, both colonization of pts not receiving TAP as well as cross-acquisition could be influenced. Colonization was studied in 2 identical general ICUs. Pts in group 1 (ICU I, n=24) received TAP while pts in group 2 (ICU I, n=41) and group 3 (ICU II, n=32) received no TAP. TAP consisted of: (a) 1 ml Tobramycin (T) (8mg/ml)/Colistin (C) (5mg/ml) in each nostril and 5 ml by nasogastric tube, (b) application in oropharynx of T/C/Amphotericin B (A) 2% in Orabase, (c) suspension of 0.5 ml A (100 mg/ml) in each nostril and 2.5 ml by nasogastric tube, (d) 1 g sucralfate, all 4 times daily. TAP included no systemic antibiotics. Oropharyngeal swabs (O), tracheal (Tr) and gastric aspirates (G) were cultured on admission and subsequently at least twice a week. The 3 groups were comparable for age, APACHE II-score and colonization on admission.

Table 1 shows the number of pts, >5 days in ICU, with persistent negative cultures (no) and acquired colonization in O, G and Tr with Enterobacteriaceae (Eb) and *Pseudomonas aeruginosa* (Ps); * $p<0.05$ as compared to group 3:

gr:	n:	Oroph.:			Gastric asp.:			Tracheal asp.:		
		no	Eb	Ps	no	Eb	Ps	no	Eb	Ps
1	22	4*	3*	1*	4	3*	1	6*	4	2
2	18	4*	2*	1*	3	5	0	3	4	2
3	23	0	10	7	1	9	2	1	9	7

Table 2 shows the percentages of pts colonized with *Enterococcus faecalis* (Ef) in O, G and Tr according to the duration of stay on the ICU; * $p<0.05$ as compared to group 3:

days:	Oroph.:			Gastric asp.:			Tracheal asp.:		
	2-6	7-13	≥ 14	2-6	7-13	≥ 14	2-6	7-13	≥ 14
gr.1	18	29	46	32	29	30	5	5	15
gr.2	6	13	43	6	20	43	3	0	0
gr.3	3	9	15	3*	5	15	0	5	0

Conclusion: TAP decreased colonization in oropharynx, stomach and trachea with Eb and Ps, but tended to increase colonization with Ef in oropharynx and stomach in treated and untreated pts in the same ICU, as compared to pts in another ICU.

240

NOSOCOMIAL PNEUMONIA: SELECTIVE DIGESTIVE DECONTAMINATION AND SUCRALFATE.

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To compare the effects of Selective Digestive Decontamination (SDD) and Sucralfate on patient's colonization, nosocomial pneumonia (NPn) and other infections, we conducted a prospective, randomised, multicentre (10 hospitals) study. Inclusion criteria were: Patients not infected (any location) at the time of inclusion, not receiving antibiotic therapy, and requiring mechanical ventilation >4 days. Those with ARDS, leukopenia or pregnant were excluded. Patients were assigned into 3 groups (Gr): Gr I or Control (C) received only antacids or H₂-blockers; Gr II (SDD) oral and gastric decontamination with polymyxin E tobramycin and amphotericin B, every 6 hours for the period of endotracheal intubation, and cefotaxime (CTX) 1 gr IV every 8 hours, 4 days; Gr III (S) received 1 gr every 6 hours by nasogastric tube for the period of intubation and CTX 4 days. Bacteriological surveillance cultures (oropharyngeal and rectal swabs, tracheal and gastric aspirated, urine) were done twice weekly. Infection were diagnosed according to CDC criteria, and recommended high sensitivity methods for NPn. Statistical analysis was performed by chi-square, Kruskal-Wallis and Mann-Whitney tests.

Results: 150 patients were studied, 21 were excluded because early extubation or death. All patients were comparable for age, sex and APACHE II scores. The incidence of NPn was 50% (21/42) in C, 17% (7/41) in SDD and 30.4% (18/46) in S, $p=0.005$, with no significant difference between C and S groups. Early NPn (1-5 days) appeared more frequently in C group, 61.9%, than in SDD 28.57% or S groups 16.6%, $p=0.01$. Infection rate was 59.5% in C group, 39% in SDD and 54.3% in S, $p=0.15$, but early infections were more frequent in C, 56%, 15% and 8% ($p=0.0002$). The mainly pathogens causing infections were Gram negative in C and S groups respect SDD, 58.8%, 69.2 and 31.6% ($p=0.025$). No difference in total mortality rates was observed between the 3 groups (28.5%, 22.5% and 21.7%) except when trauma patients were analysed separately, 36.3%, 0 and 16% ($p=0.006$).

Conclusions: SDD reduced the incidence of NPn in ventilated patients, but S did not. The overall infection rate was not significantly reduced in SDD and S groups, but infections appeared later than in control group. Gram negatives bacterias were less frequent in SDD group infections. Mortality rate decreased only in SDD trauma patients.

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