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COMBINING INHALED NITRIC OXIDE (NO) AND IV NITRIC OXIDE SYNTHASE (NOS) INHIBITION IN AN OVINE LAVAGE MODEL OF ARDS

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NO is synthesized by endothelial cells from L-arginine and increases cyclic GMP in vascular smooth muscle cells causing vasodilation. Inhibition of endogenous NOS increases vascular tone and enhances hypoxic pulmonary vasoconstriction (HPV). Inhaled NO produces selective pulmonary vasodilation of ventilated lung regions. We hypothesized that combining selective pulmonary vasodilation by NO inhalation, with HPV enhancement by infusing the NOS inhibitor N^G-nitro-L-arginine methyl ester (LNA) might reduce $\dot{V}_A/\dot{Q}$ mismatch and improve gas exchange and pulmonary hemodynamics in a lavage model of ARDS.

Six anesthetized and mechanically ventilated (FiO_2 0.90) lambs (25-35 kg) underwent bilateral lung lavage with Tween 80 in saline at 37°C. Pulmonary artery pressure (PA) and cardiac output (CO) were measured and intrapulmonary shunt ($\dot{Q}s/\dot{Q}t$) was calculated at baseline (BL), lung lavage (LL), 60 ppm NO inhalation (NO), 30mg/kg iv LNA (LNA) and again 60 ppm NO inhalation (LNA+NO). With each treatment 3 levels of CO, low (L), medium (M) and high (H) were obtained by using an A-V fistula and IVC balloon. Mean±SE. A paired t test and linear regression were used, * $p< 0.01$ H vs L CO, # $p<0.05$ vs preceding column.

		BL	LL	NO	LNA	LNA+NO
CO	L	1.7±0.2	2.0±0.2#	2.1±0.1	1.6±0.1#	1.8±0.2
(l/min)	M	3.2±0.5*	3.9±0.3*	3.6±0.1*	2.6±0.3*#	2.7±0.2*
	H	6.2±0.8*	5.9±0.5*	5.3±0.4*	3.8±0.3*#	4.2±0.4*
PA	L	13±0.3	15±0.9#	14±0.6	28±3.2#	19±1.9#
(mmHg)	M	17±0.6*	19±0.7*	16±0.8*#	29±2.1#	22±0.9#
	H	21±0.7*	22±1.1*	20±1.0*	34±1.8*#	26±1.8*#
$\dot{Q}s/\dot{Q}t$	L	7.9±1	34.6±5#	20.7±1#	31.2±4#	16.3±2#
(%)	M	10±2	50.4±4#	32.0±2*#	35.2±3	25.9±2*#
	H	14.5±2*	51.1±2#	42.3±3*#	45.7±6	36.5±4*#

The relationship between PA and $\dot{Q}s/\dot{Q}t$ was linear at all levels of CO (mean $r=0.92$). Inhaled NO either alone or combined with iv LNA improved $\dot{V}_A/\dot{Q}$ matching and decreased $\dot{Q}s/\dot{Q}t$ in this ovine experimental ARDS model. We conclude that inhaled NO combined with iv LNA may provide a useful therapy to reduce $\dot{Q}s/\dot{Q}t$ during ARDS. Supported by USPHS grant HL42397.

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PRODUCTION OF NO2 DURING NITRIC OXIDE (NO) INHALATION

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The risk of production of toxic metabolites following NO oxidation have been underlined. We studied the kinetics of NO_2 emergence in two different models: 1) simultaneously mixing air/NO or O_2/NO in a close box; 2) insufflating a mixture of air/NO or of O_2/NO in a Douglas bag. A suction catheter was placed in the close box or in the Douglas bag and analysis of the NO/NO_2 concentrations was perfomed using an electrochemical method (Polytron Dräger^R).

14 litres of air or O_2 and 2 litres of NO (225 ppm/l) were mixed in the close box. NO/NO_2 concentrations (ppm) were measured after ten minutes. NO_2 is over 2.2 ppm in presence of air and 3.2 ppm in presence of O_2.

6 litres/minute of air or O_2 and 2 litres/minute of NO (225 ppm/l) were insufflated in the Douglas bag during 4 minutes. NO/NO_2 concentrations (ppm) were measured after ten minutes. NO_2 reaches 2.2 ppm in presence of air and 11.6 ppm in presence of O_2.

These data confirm that NO_2 production is fast and is particularly important in presence of a high O_2 concentration. Consequently, it appears mandatory to measure NO/NO_2 concentrations during NO inhalation.

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PULMONARY INFILTRATES IN LIVER TRANSPLANT PATIENTS . DIAGNOSTIC VALUE OF PROTECTED SPECIMEN BRUSHING AND BRONCHOALVEOLAR LAVAGE.

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Liver Transplantation (LT) is often followed by a variety of respiratory complications that may cause significant morbidity and mortality.

We performed 51 fiberoptic bronchoscopic examinations on 41 liver transplant patients with pulmonary infiltrates. Protected specimen brushing (PSB) and bronchoalveolar lavage (BAL) via fiberoptic bronchoscopy were performed in each case. Samples were cultured in aerobic, anaerobic, mycobacterial, and legionella media. Cytologic examination of BAL fluid was also performed. In 39 of 51 (76,5%) cases pneumonia was considered the final diagnosis of the pulmonary infiltrates. By means of PSB and BAL examination a microbiologic identification was obtained in 25 of these 39 (64%) cases. The predominant pathogens isolated were Pseudomona aeruginosa (7 cases), Cytomegalovirus (7 cases) and Pneumocystis carinii (5 cases). The overall diagnostic yield of PSB + BAL was 58,8% (30 cases). The overall mortality was 26,8% (11 cases).

Our results indicate that combined PSB and BAL are valid tools for diagnosing pulmonary infiltrates in LT patients, resulting in a beneficial effect in clinical course.

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IS PROTECTED SPECIMEN BRUSH A REPRODUCIBLE METHOD TO DIAGNOSE ICU ACQUIRED PNEUMONIA (IAP)? JF TIMSIT, S FRANCOUAL, B MISSET, FW GOLDSTEIN, E BAVIERA, J CARLET. Hôpital Saint Joseph, Paris, FRANCE.

Protected specimen brush is considered as the gold standard for the diagnosis of ventilator associated pneumonia but intraindividual variability had not been previously studied.

PURPOSE: To compare the results of 2 protected specimen brushes (PSB) performed in the same subsegment on patients with suspected IAP.

STUDY DESIGN: Between October 1991 and April 1992, each mechanically ventilated patients with suspected IAP underwent bronchoscopy with 2 successive PSB in the lung segment identified radiographically. Results of the 2 PSB cultures were compared considering 10^3 cfu/ml cut off, bacterial index, log10 of each microorganisms found. Four definite diagnoses were established: **definite pneumonia** (DP):if patients fulfilled positive pleural culture or rapid cavitation of the lung infiltrate or histopathologic evidence of pneumonia at autopsy performed within 8 days after diagnostic procedure **Probable pneumonia** (PRP):complete resolution after adapted antimicrobial therapy without other treated septic site **Excluded pneumonia** (EP): Full recovery without antibiotic therapy or no sign of pneumonia on postmortem examination and **Uncertain status** (US).

POPULATION: 42 episodes in 21 patients were studied. 60% patients received prior antibiotherapy always innefective on microorganisms found. 32 microorganisms were isolated from 24 pairs of PSB. Definite diagnosis was DP in 7, PRP in 8, EP in 17, and US in 10 cases.

RESULTS: Considering the 10^3 cut off, PSB1 and 2 gave discordant results in 24% microorganisms recovered and in 19% of episodes of suspected IAP. For 6 isolated microorganisms the 2 PSB specimen culture varied of a factor greater than 10^2. Discordance was independent from definite diagnosis. Considering log10 of each microorganism concentration the correlation between the 2 PSB was very significant ($p\leq10^{-5}$) but not very strong: $r=0.63$ signify that the knowledge of the first PSB culture explain only 40% of the variance of the second PSB.

There were no statistical effects of the order of samples between the two specimens for bacterial index and microorganism concentrations.

CONCLUSION: These findings argue for a poor reproducibility of PSB in suspected IAP and challenge the 10^3 cfu/ml threshold routinely used. Results of PSB must be interpreted with caution considering the intraindividual variability for diagnosis of IAP.

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HOW FAR IS THE PROTECTED SPECIMEN BRUSH (PSB) UNCONTAMINATED ? CYTOLOGIC EVALUATION OF PAIRED TRACHEAL ASPIRATES (TA) AND PSB SPECIMENS.

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The PSB technique is at present one of the most reliable means to determine the presence of pneumonia and identify the causative organism especially in intubated patients (IP). PSB with quantitative cultures (QC) is considered to be devoid of contamination with oropharyngeal flora (OPF) when compared to TA without QC. We prospectively assessed TA and PSB specimens for the presence of squamous epithelial cells (SEC), bronchial cells (BC) and alveolar macrophages (AM) in 52 IP and 56 non intubated patients (NIP) undergoing diagnostic bronchoscopy. Topical anesthesia of subglottic airways as well as suction prior to PSB collection were proscribed.

		SEC	BC	AM
NIP	PSB	12 (21 %)	56 (100 %)	24 (43 %)
n = 56	TA	40 (71 %)	38 (68 %)	24 (43 %)
		p = 0.001	p = 0.001	NS
IP	PSB	13 (25 %)	49 (94 %)	17 (33 %)
n = 52	TA	34 (65 %)	26 (50 %)	19 (37 %)
		p = 0.001	p = 0.001	NS

In NIP the presence of SEC in the PSB correlated with the presence of OPF in the culture of the PSB

These data demonstrate that even PSB specimens collected in distal airways are potentially contaminated though in a lesser degree than TA. This may be explained by aspiration around the endotracheal cuff in IP and by aspiration during bronchoscopy performed in the up-right position in NIP which have been both previously demonstrated.

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PROSPECTIVE EVALUATION OF THE CLINICAL SIGNIFICANCE OF A QUANTITATIVE CULTURE OF A PROTECTED BRUSH SPECIMEN (PBS) YIELDING ORGANISMS IN CONCENTRATIONS $\geq 10^2$ BUT $<10^3$ CFU/ml.

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In patients with a clinical suspicion of pneumonia, quantitative cultures of a PBS yielding $\geq 10^3$ CFU/ml of at least one microorganism have been considered useful in differentiating between airway colonization and lung infection, especially in mechanically ventilated patients. The amount of secretions collected by PBS is small and there is some uncertainty on its exact quantity. Thus, using a lower limit of 10^2 CFU/ml as a cutoff for diagnosing pneumonia might improve the sensitivity of the technique but could also alter its specificity. Nevertheless, the clinical significance of such a result, in the absence of active antimicrobial treatment, is unknown. 36 consecutive results of cultures of PBS yielding organisms in concentration $\geq 10^2$ but $<10^3$ CFU/ml in 32 patients (30 mechanically ventilated) were prospectively studied. No patient received any agent active on the isolated organism. In 6 cases, the diagnosis of pneumonia was ruled out by recovery without treatment, or negative postmortem lung cultures. A second PBS was cultured in 31 episodes (2.7±1.8 days after the first one). In 12 instances (Group 1) the cultures yielded $\geq 10^3$ CFU/ml of the same organism as in the first PBS (S. pneumoniae: 1; S. aureus: 1; H. Influenzae: 1; E. coli: 1; P. aeruginosa: 4; A. baumannii: 4) and the patients were therefore treated with appropriate antibiotics. In 18 cases, the second PBS yielded $<10^2$ CFU/ml and no antibiotic treatment was given for this episode. The organisms recovered from the initial PBS in the 24 cases (Group 2) in whom pneumonia was ruled out by recovery without treatment or a negative culture of a second PBS or of postmortem lung sample were as follows: S. aureus: 9; E. cloacae: 1; P. aeruginosa: 9; X. maltophilia: 2; A. baumannii: 2; C. albicans: 1. Comparison between Group 1 and Group 2 revealed no difference for age (60.4 ± 15.8 vs 59.9 ± 18.3 years) and Simplified Acute Physiology Score (11.2 ± 4.4 vs 12 ± 4.3). By contrast (when excluding from analysis patients who had 2 episodes), Group 1 patients had longer duration of mechanical ventilation (17 ± 9.4 vs 8.9 ± 8.4 days, p <0.04), and a greater fatality rate (6/8 vs 4/20, p <0.03). Treating all patients with a culture of PBS yielding organisms in concentration $\geq 10^2$ but $<10^3$ CFU/ml would lead to overtreatment in most cases. Nevertheless, the unpredictibility of the result of a second PBS makes its performance mandatory in case of persistence of clinical suspicion of pneumonia, in order to identify patients that should be treated (namely, those with a second culture yielding $\geq 10^3$ CFU/ml).

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DIAGNOSIS OF PNEUMONIA IN MECHANICALLY VENTILATED PATIENTS : REPEATABILITY OF THE PROTECTED SPECIMEN BRUSH (PSB) WITH QUANTITATIVE CULTURES.

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The repeatability (ie, the variation in repeated measurements of the same quantity) of the protected specimen brush (PSB) with quantitative cultures was assessed in 22 consecutive mechanically ventilated (MV) patients with suspected nosocomial pneumonia. Five PSB samples were collected in the same lung area during the same bronchoscopic procedure and processed for bacteriologic identification and quantitative culture. A laboratory control was also performed in order to assess the in vitro repeatability of the quantitative culture technique. The 5 PSB allways recovered the same microorganisms indicating a 100 % qualitative repeatability for the PSB. Conversely the quantitative repeatability was quite lower since the range of the quantitative results (QR) was > $\log_{10}$, which is the minimal precision affordable with quantitative cultures, in 59 % of the patients. With respect to the 10^3 cfu/ml recommended diagnostic threshold, this variability affected the conclusion about the diagnosis of pneumonia in 4 patients (18.2 %) since in these 4 pts the QR were spread on both sides of diagnostic threshold. The order of passage of the brushes did not influence the QR. The variability of the QR was not explained by problems with the quantitative culture technique which proved excellent repeatability in the laboratory. These data indicate that cautious interpretation of PSB quantitative cultures may be advisable in critically ill patients with suspected pneumonia, especially if one refers to the recommended diagnostic threshold and if a decision to treat or to abstain from treating is to be made.

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SHOULD BLOOD CULTURE BE PERFORMED AFTER A PROTECTED SPECIMEN BRUSH (PSB)? A PROSPECTIVE STUDY.

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The performance of PSB is very useful in differentiating between airway colonization and lung infection, especially in mechanically ventilated patients. Nevertheless, this may cause trauma to the tracheobronchial tree, potentially favoring the occurence of bacteremia, particularly in patients with pneumonia. To assess this risk, aero- and anaerobic blood cultures were prospectively obtained immediately following the performance of a PSB under fiberoptic bronchoscopy in 123 consecutive cases in 68 patients. PSB was performed in case of suspicion of infectious pneumonia (presence of alveolar opacities on chest X-ray, mucopurulent sputum). Blood cultures were negative in 110 cases (89%) and positive in 13 cases only (11%) (p<0.001).

	Positive PSB	Negative PSB
Positive blood culture	1	12
Negative blood culture	17	93

Among the 18 positive cultures of the specimens from PSB ($\geq 10^3$ CFU/ml) accounting for a total of 24 microorganisms (3 *S. aureus*, 1 *S. agalactiae*, 6 enterobacteriaceae, 1 *M. catarrhalis*, 13 gram-negative non-fermenting bacteria), only one was associated with a post-PSB positive blood culture (*E. faecalis*). This germ was different from those recovered from PSB specimen culture (*E. coli* + *A. baumannii*). The 12 other positive blood cultures were obtained from patients with negative culture of PSB specimen. Bacteria recovered from those blood cultures were considered non-pathogenic, according to usual criteria in 9 patients (1 *Sarcina*, 9 coagulase-negative staphylococci). In 2 cases the blood cultures grew with a *S. aureus*. These 2 patients had staphylococcal septicemia, with positive blood cultures both before and after PSB. In 1 case the blood culture yielded *E. faecalis* in the absence of any identifiable infection site.
The risk of bacteremia after PSB is very low even in case of pneumonia. Thus, it does not seem useful to systematically perform a blood culture after PSB.

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