ABSTRACTS

UTILITY OF TRANSBRONCHIAL BIOPSY IN PATIENTS WITH ACUTE RESPIRATORY FAILURE*

A POSTMORTEM STUDY

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Study objective: To determine the diagnostic yield of histologic specimens obtained by postmortem transbronchial biopsy (TBB) in patients with acute respiratory failure requiring mechanical ventilation.
Design: Standard postmortem histologic examination of lung tissue specimens.
Setting: An urban university-affiliated hospital.
Patients or participants: Thirty patients with diffuse pulmonary infiltrates and acute respiratory failure, who underwent postmortem examination.
Interventions: Following removal of the lungs from the thorax. TBBs were obtained from the lower lobe of each deflated lung and comparison was made to a 1-cm^3 tissue block obtained from the ipsilateral lower lobe.
Measurements and results: Standard postmortem histologic examination provided a specific diagnosis in 85% of the 60 lungs examined, and histologic evidence of acute pneumonia was present in 30% of the lungs. The overall yield of TBB was 48% for establishing a specific histologic diagnosis and 15% for the diagnosis of actue pneumonia. Using standard postmortem histologic examination as the gold standard, the sensitivity and specificity of TBB for making a specific diagnosis were 57% and 100% respectively, with corresponding positive and negative predictive values of 100% and 29%. For the histologic diagnosis of acute pneumonia, the sensitivity of TBB was 50%, the specificity was 100%, and the positive and negative predictive values were 100% and 82%, respectively. The kappa statistic for the agreement between the two diagnostic methods was 0.28 for establishing a specific diagnosis and 0.58 for the diagnosis of acute pneumonia. Obtaining 12 TBBs rather than six TBBs did not increase the diagnostic yield for TBB.
Conclusions: These findings suggest poor overall agreement between standard postmortem histologic examination and TBB specimens. Although not performed in a clinical setting, this postmortem investigation suggests that TBB may be of limited value in mechanically ventilated patients with acute respiratory failure because of its low sensitivity.

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THE USE OF CONTINUOUS IV SEDATION IS ASSOCIATED WITH PROLONGATION OF MECHANICAL VENTILATION*

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Study objective: To determine whether the use of continuous IV sedation is associated with prolongation of the duration of mechanical ventilation.
Design: Prospective observational cohort study

Setting: The medical ICU of Barnes-Jewish Hospital, a university-affiliated urban teaching hospital.
Patients: Two hundred forty-two consecutive ICU patients requiring mechanical ventilation.
Interventions: Patient surveillance and data collection.
Measurement and results: The primary outcome measure was the duration of mechanical ventilation. Secondary outcome measures included ICU and hospital lengths of stay, hospital mortality, and acquired organ system derangements. A total of 93 (38.4%) mechanically ventilated patients received continuous IV sedation while 149 (61.6%) patients received either bolus administration of IV sedation (n=64) or no IV sedation (n=85) following intubation. The duration of mechanical ventilation was significantly longer for patients receiving continuous IV sedation compared with patients not receiving continuous IV sedation (185±190 h vs 55.6±75.6 h; p<0.001). Similarly, the lengths of intensive care (13.5±33.7 days vs 4.8±4.1 days; p<0.001) and hospitalization (21.0±25.1 days vs 12.8±14.1 days; p<0.001) were statistically longer among patients receiving continuous IV sedation. Multiple linear regression analysis, adjusting for age, gender, severity of illness, mortality, indication for mechanical ventilation, use of chemical paralysis, presence of a tracheostomy, and the number of acquired organ system derangements, found the adjusted duration of mechanical ventilation to be significantly longer for patients receiving continuous IV sedation compared with patients who did not receive continuous IV sedation (148 h [95% confidence interval: 121, 175 h] vs 78.7 h [95% confidence interval: 68.9, 88.6 h] p<0.001).
Conclusion: We conclude from these preliminary observational data that the use of continuous IV sedation may be associated with the prolongation of mechanical ventilation. This study suggests that strategies targeted at reducing the use of continuous IV sedation could shorten the duration of mechanical ventilation for some patients. Prospective randomized clinical trials, using well-designed sedation guidelines and protocols, are required to determine whether patient-specific outcomes (eg, duration of mechanical ventilation, patient comfort) can be improved compared with conventional sedation practices.
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PULMONARY METASTASES OF ENDOCRINE ORIGIN* THE ROLE OF SURGERY

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Purpose: To determine the clinical course and outcome of patients undergoing pulmonary resection for metastatic endocrine tumors.
Methods: Retrospective review of 47 patients with known endocrine tumors and pulmonary metastases who were evaluated for surgical resection between 1975 and 1996.
Results: Tumors evaluated included the following: carcinoid (16), thyroid (12), pancreatic adenocarcinoma (10), adrenocortical carcinoma (6), pheochromocytoma (2), and parathyroid (1). Thirty-three patients were asymptomatic, hormone secretion was noted in five patients. Twenty-five patients, who had isolated lung metastases, good control of the primary tumor, and no medical contraindication had surgical resection. The number of pulmonary nodules was not a limiting factor as long as all disease could be resected with adequate residual pulmonary function. CT was successful in directing resection in all patients. Twenty-six operations were performed in 25 patients and 22 patients were treated medically. Wedge resection was performed for lesions <2 cm (15), and lobectomy for larger or multiple nodules (10). Four patients had bilateral nodules resected. There was no operative mortality and no major complications. Actuarial 5-year survival was 61% for surgically

treated patients. Independent predictors of poor survival included positive mediastinal lymph nodes at time of surgery (p=0.004) and shorter disease-free interval (p=0.01). at a median of 6.7±1.2 years, six patients have developed radiographic appearance of a recurrence. A single patient with recurrent Hurthle cell cancer has had a successful reresection. The remaining patients have received chemotherapy. No patient with pancreatic carcinoma or adrenocortical carcinoma was a candidate for resection. All medically treated patients died within 6 months.

Conclusion: Patients with endocrine tumors and pulmonary metastases are usually asymptomatic, their conditions are diagnosed accurately with CT, and they can achieve long-term survival comparable to other tumors (sarcoma) after pulmonary metastasectomy.

Clinical implications: Patients with carcinoid, thyroid, pheochromocytoma, and parathyroid tumors with pulmonary metastases should undergo surgical resection if there is the following: (I) no evidence of extrathoracic disease; (2) good control of the primary tumor; (3) no medical contraindications for surgery; and (4) pulmonary function that can tolerate resection of all documented disease. The role of adjuvant chemotherapy in patients with positive lymph nodes needs further study.

(CHEST 1998; 114:526-534)

LONG-TERM WITHIN-SUBJECT VARIABILITY OF INSPIRATORY NEURAL DRIVE RESPONSE TO HYPOXIA*

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Study objective: We analyze the within-subject variation of mouth occlusion pressure ($P_{0.1}$) response to progressive isocapnic hypoxic stimulation over long time periods in normal subjects.

Patients and interventions: We studied 21 healthy subjects (14 male and 7 female; aged 40±12 yrs) (means±SD). Lung volumes, basal $P_{0.1}$, and $P_{0.1}$ response to hypoxia were measured on two separate occasions 2 months apart, under similar ambient and clinical conditions.

Results: There was no significant change in clinical condition, FVC, FEV_1, arterial oxygenation saturation, end-tidal and mixed venous Pco_2 levels, or $P_{0.1}$ between the two visits. The mean $P_{0.1}$ responses to hypoxia in the two explorations were 0.032±0.022 and 0.034±0.022 kPa/%, respectively. There was a moderate intrasubject variability of $P_{0.1}$ response to hypoxia, with a coefficient of reproducibility of 0.01 kPa/%. Power calculations to establish the optimal sample size required for hypoxic stimulation are presented.

Conclusion: Long term within-subject variability of P0.1 response to hypoxia is moderate. This intrinsic variability needs to be emphasized when interpreting the effects of experimental interventions on hypoxic sensitivity.

(CHEST 1998; 114:521-525)

THE VALIDITY OF RADIOGRAPHIC ESTIMATION OF TOTAL LUNG CAPACITY IN PATIENTS WITH RESPIRATORY DISEASE*

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Study objective: To evaluate the validity of a state-of-the-art computerized planimetry technique for estimation of total lung capacity (TLC) from chest radiographs, when applied to patients with clinical lung disease receiving routine chest radiographs.
Design: Retrospective clinical survey.
Setting: An occupational medicine diagnostic clinic.
Patients: A convenience sample of 40 subjects with asbestos-related lung disease, 5 patients with nonasbestos-related restrictive defects, 15 subjects with occupational asthma, and 10 subjects with irritant tracheobronchitis.
Results: Estimation of TLC using state-of-the-art computerized algorithms demonstrated limited agreement with conventional measures of TLC when applied to patients with occupational lung disease receiving routine chest radiographs. The most pronounced difference occurred in patients with asbestos-related lung disease and restrictive defects, where the radiographic method of measurement significantly overestimated helium dilution TLC by 986 mL ($r=0.73$, $p<0.001$) and 1, 135 mL ($r=0.82$, $p<0.05$), respectively. Good inspiratory effort was associated with significantly increased radiographic TLC relative to helium dilution TLC; however, radiograhic features did not fully account for the observed differences between radiogrpahic and helium dilution techniques.
Conclusions: Our findings suggest that this planimetric technique should not be used as a substitute for conventional measures of TLC in clinic populations receiving routine radiographs. The large diagnostic group specific mean differences observed between radiographic and conventional measures of TLC also suggest that this method is of limited utility in clinical evaluation of occupational lung disease.
(CHEST 1998; 114:513-520)

COLCHINCINE, D-PENICILLAMINE, AND PREDNISONE IN THE TREATMENT OF IDIOPATHIC PULMONARY FIBROSIS*

A CONTROLLED CLINICAL TRIAL

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Study objective: We compared the long-term efficacy of the combination of colchicine and/or D-penicillamine with prednisone, in comparison to prednisone alone in patients with idiopathic pulmonary fibrosis (IPF).
Design: Nonrandomized prospective study in patients with IPF confirmed by biopsy specimen.
Setting: National Institute of Respiratory Diseases, Mexico.
Patients: Fifty-six IPF patients were icluded in this

study. Patients received either colchicine / prednisone (n=19), D-penicillamine / prednisone (n=11), D-penicillamine / colchicine / prednisone (n=11), or prednisone alone (n=15). Prednisone therapy was started at 1.0 mg/kg/d for 1 month followed by a biweekly taper to a maintenance dose of 15 mg/d. colchicine was administered at a daily dose of 1.0 mg, and D-penicillamine was given at a daily dose of 600 mg.

Measurements and results: Response to therapy was assessed by changes in lung function test results as measured by total and vital lung capacities, arterial blood gas analysis at rest breathing room air, and survival. No significant differences either in lung mechanics or in arterial gases were found in any group relative to the baseline measurement. Thirteen of the 56 patients died during the first 2 years, and 29 were dead at 5 years follow-up. Comparison of survival curves by Cox regression model showed no statistically significant difference among the four groups. Known side effects attributable to prednisone were more common and severe than those attributable to the other drugs.

Conclusions: Our results suggest that neither colchicine nor D-penicillamine modified the progressive course of prednisone-treated IPF, and that the search for new drugs is imperative.

(CHEST 1998; 114:507-512)

PULMONARY WEGENER'S GRANULOMATOSIS*

CORRELATION BETWEEN HIGH-RESOLUTION CT FINDINGS AND CLINICAL SCORING OF DISEASE ACTIVITY

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Study objective: To evaluate the usefulness of high-resolution CT (HRCT) for monitoring pulmonary disease activity in Wegener's granulomatosis (WG).

Design: Prospective study of CT and clinical data.

Setting: Main referral hospital for rheumatic disease and department of diagnostic radiology of collaborating university hospital.

Patients: Seventy-three patients with WG underwent 98 staging examinations using HRCT. The status of pulmonary disease activity at the time of examination was scored according to clinical, bronchoscopic, BAL, and radiographic findings as follows: activity (n=25, group 1), past activity (n=45, group 2) and lack of any pulmonary disease (n=28, group 3). HRCT findings were correlated with the clinical scoring of pulmonary disease activity.

Results: Of 98 staging examinations 78 (79.6%) revealed abnormal CT scans showing the following main abnormalities: (a) nodules or masses (group 1: 16 [60.4%], group 2: 9 [20%]); (b) parenchymal bands (group 1: 12 [48%], group 2: 27 [60%], group 3: 6 [21.5%]); (c) septal thickening (group 1: 8 [32%], group 2: 6 [13.3%]); (d) parenchymal opacification (group 1: 7 [28%], group 2: 4 [8.9%]); and (e) pleural irregularity (group 1: 14 [56%], group 2: 22 [49%], group 3: 9 [32%]). Nodules/masses and areas of parenchymal opacification were significantly associated with florid disease activity of the lungs. Parenchymal bands and septal thickening were observed in both groups with pulmonary involvement, but statistical analysis revealed no significant difference. Pleural irregularities were nonspecific.

Conclusion: HRCT may be a useful adjunct to clinical scoring of pulmonary disease activity in patients with WG and suspected lung involvement.

(CHEST 1998: 114:500-506)

BRONCHIAL RESPONSIVENESS AND ANGIOTENSIN-CONVERTING ENZYME GENE POLYMORPHISM IN SARCOIDOSIS PATIENTS*

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Background: Angiotensin-converting enzyme (ACE) inactivates bradykinin and tachykinins, which are potent bronchoconstrictors and mediators of inflammatory reactions. It has recently been shown that an insertion (I)/deletion (D) polymorphism in the ACE gene accounts for variation in serum ACE level. We investigated bronchial responsiveness in patients with sarcoidosis to determine whether it might be associated with ACE gene polymorphism.

Subjects: Bronchial responsiveness was assessed in 21 patients with sarcoidosis, 21 patients with asthma, and 18 healthy control subjects. ACE polymorphism was also examined in the 21 patients with sarcoidosis.

Methods: Bronchial responsiveness was measured by recording respiratory resistance with continuous inhalation of methacholine from 49 to 25,000 μg/mL in concentration. The ACE genotype was determined using the polymerase chain reaction.

Results: We found a significant increase in bronchial responsiveness in sarcoidosis patients as compared with healthy control subjects ($p<0.01$). In the sarcoidosis group, patients with the II genotype demonstrated significantly more coughing ($p<0.05$) and a greater bronchial responsiveness ($p<0.05$) than did those with DI or DD genotypes.

Conclusion: Patients with sarcoidosis have increased bronchial responsiveness to some extent, the degree apparently depending on the ACE genotype.

(CHEST 1998; 114:495-499)

RESPIRATORY NITRIC OXIDE LEVELS IN EXPERIMENTAL HUMAN INFLUENZA*

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Background: Exhaled oral nitric oxide (NO), a reported marker of inflammation in the respiratory tract, can be elevated by "upper respiratory tract infections." However, the responsible viruses and the time course of this rise in NO are not clear.

Objective: To determine the expired nasal and oral NO levels during experimentally induced influenza A infection in 14 healthy volunteers without a history of asthma, rhinitis, or sinusitis.

Methods: After being housed in individual rooms, susceptible volunteers were inoculated with 10^6 50% tissue culture infective dose of influenza A/Texas/36/91/(HINI) virus on a single occasion by intranasal drops. Volunters remained in the isolation unit for 8 days and returned for follow-up 21 days after inoculation. Symptom scores and nasal washing for viral culture were obtained daily. NO samples from the mouth and nose were obtained on days 0 through 4, 8, and 21 by having the patient perform a slow vital capacity maneuver through a plastic tube into a Mylar balloon.

Results: All patients had influenza virus cultured from nasal washings (12 of 14 on day 1, 14 of 14 by day 5). Patient symptom scores peaked on day 3

(mean±SE; 15.4±3.2) and returned to baseline by day 8. Preinfection exhaled nasal NO (right, 28.4±3.7 parts per billion [ppb]; left, 27.7±4.6 ppb) was significantly higher than oral NO (5.8 ppb; $p<0.001$). Exhaled oral NO was significantly elevated on day 8 postinoculation (12.9±0.8 ppb; $p<0.01$ Bonferroni) and returned to baseline at follow-up. Nasal NO levels showed a slight decrease on days 2 to 4 but returned to baseline by day 8.

Conclusion: Experimental influenza virus infection can increase oral but not nasal exhaled NO levels. The timing of exhaled NO changes suggests that NO does not contribute to illness manifestations directly.

(CHEST 1998; 114:452-456)

PULMONARY INFILTRATES IN NEUTROPENIC PATIENTS WITH ACUTE LEUKEMIA DURING CHEMOTHERAPY*

OUT COME AND PROGNOSTIC FACTORS

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Study objectives: To determine predictors of mortality from pulmonary infiltrates in neutropenic patients with acute leukemia during chemotherapy, and the significance of those factors related to the underlying malignancy and its therapy as well as of those related to the severity of the illness associated with pulmonary infiltrates.

Design: A historical cohort study.

Setting: A university teaching hospital and tertiary referral center.

Patients and methods: Overall, 53 patients with neutropenia during chemotherapy and with first episodes of pulmonary infiltrates during a 4-year period were studied. Prognostic analysis included 38 variables. Multivariate analyses were perofrmed by logistic regression.

Results: The survival rate from pneumonia was 57% (30/53). The following eight parameters were significantly associated with death in univariate analysis: comorbidity present; development of "late" pulmonary infiltrates (≥14 days after hospital admission); heart rate ≥100 beats/min; a ratio heart rate/systolic blood pressure (HR/SBP) ≥1.2; urea nitrogen >7 mmol/L; radiographic score ≥3; neutropenia $<1.0 \times 10^9$/L at the treatment end point; and failed complete remission. In a multivariate model including only parameters available at diagnosis of pulmonary infiltrates, the presence of a ratio HR/SBP ≥1.2 and of a radiographic score ≥3 remained independently associated with death. In a second model also including the evolutionary parameter neutropenia $\leq 1.0 \times 10^9$/L at the treatement end point, both parameters remained significant together with neutropenia $<1.0 \times 10^9$/L at the treatment end point. The presence of a ratio HR/SBP ≥1.2 was a strong marker of early death.

Conclusion: Both therapy-and malignancy-associated neutropenia as well as the severity of illness associated with pulmonary infiltrates are independent prognostic factors. Patients with a ratio HR/SBP ≥ 1.2 at diagnosis of pulmonary infiltrates suffer from potentially reversible acute illness, are at risk for early death and, therefore, may be appropriate candidates for treatment in an ICU.

(CHEST 1998; 114:444-451)

BLASTOMYCOSIS IN NORTHEAST TENNESSEE*

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Study objectives: To study the epidemiologic and clinical features of blastomycosis in northeast Tennessee.
Design: Retrospective review of blastomycosis cases in the region from 1980 through 1995.
Setting: Hospitals located in the Tri-Cities region of northeast Tennessee.
Patients: Seventy-two patients with confirmed blastomycosis infection.
Interventions: None.
Results: During the 1980 to 1995 study period, we documented 72 cases of blastomycosis. The mean age was 52 years (range, 13 to 86 years), most were male (69.4%), and nine were immunocompromised. A possible environmental exposure was noted for 28 patients. Pulmonary involvement represented the most common site of infection (61 cases), but multiorgan involvement was common (17 cases). Most patients with pulmonary blastomycosis (66%) presented with a chronic illness, and radiologic findings usually revealed local consolidation or a mass-like lesion. Nine patients developed ARDS with an associated mortality rate of 89%, compared with a 10% mortality for non-ARDS pulmonary cases. Antifungal treatment regimens varied widely, with amphotericin B often used for sicker patients. An epidemiologic evaluation revealed that the mean yearly incidence rate for blastomycosis quadrupled between 1980 and 1987 (0.31 cases/ 100,000 population) and 1988 to 1995 (1.23 cases/100,000 population) (p=0.00001). Most new blastomycosis cases in the 1988 to 1995 period occurred in three counties in the region where significant new construction projects have been underway.
Conclusion: Blastomycosis is endemic in northeast Tennessee and the number of cases is increasing, coinciding with major new construction in the region. Clinicians in the area must be alert to this condition.

(CHEST 1998; 114:436-443)

SEQUENTIAL EVALUATION OF SERUM ADENOSINE DEAMINASE IN PATIENTS TREATED FOR TUBERCULOSIS*

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Study objective: To delineate the course of serum adenosine deaminase (s-ADA) in patients with tuberculosis who are receiving effective therapy.
Setting: A medical ward and an outpatient clinic in a general hospital.
Patients: Twenty-five immunocompetent patients with pleural or pulmonary tuberculosis.
Interventions: All patients received standard chemotherapeutic regimens with isoniazid, rifampin, and pyrazinamide.
Measurements and results: Six measurements of several variables, including s-ADA, were carried out at different periods of time during the 6 months of follow-up. There were no significant differences in s-ADA values between sexes and there was no significant correlation with age or with the other variables analyzed. There was a significant decline in the s-ADA values during the first 2 months in the patients as a whole (p=0.04), followed by a stabilization of the s-ADA activity. This decline was due to a

marked decrease in the s-ADA in the 13 patients (52%) who had initial high levels of the enzyme (p=0.03), whereas there were no changes in those patients with normal initial levels (p=0.27). Patients with increased s-ADA activity at the time of the first measurement reported symptoms for a longer period than patients with normal s-ADA (median, 15 vs 10 days; p=0.02).

Conclusions: s-ADA levels in patients with tuberculosis decrease during the initial months of effective treatment. Perhaps this decrease might reflect the normalization of the altered lymphocyte turnover induced by tuberculosis. The measurement of s-ADA could be of some help to evaluate the response to therapy, particularly in those patients with increased values of the enzyme.

(CHEST 1998; 114:432-435)

CORTICOSTEROIDS IN LIFE-THREATENING VARICELLA PNEUMONIA*

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Background: Varicella pneumonia that results in respiratory failure or progresses to the institution of mechanical ventilation carries a significant morbidity and mortality despite intensive respiratory support and antiviral therapy. There has been no reported study of the role of corticosteroids in life-threatening varicella pneumonia.

Design and methods: This was an uncontrolled retrospective and prospective study of all adult patients with a diagnosis of varicella pneumonia who were admitted to the ICUs of the Johannesburg group of academic hospitals in South Africa between 1980 and 1996. Patient demographics, clinical and laboratory features, necessity for mechanical ventilation, and complications were reviewed. The outcome and therapy of varicella pneumonia was evaluated with particular reference to the use of corticosteroids. Patients with comorbid disease and those already taking immunosuppressive agents were excluded. Key endpoints included length of ICU and hospital stay and mortality.

Measurement and results: Fifteen adult patients were evaluated, six of whom received corticosteroids in addition to antiviral and supportive therapy. These six patients demonstrated a clinically significant therapeutic response. They had significantly shorter hospital (median difference, 10 days; p<0.006) and ICU (median difference, 8 days; p=0.008) stays and there was no mortality, despite the fact that they were admitted to the ICU with significantly lower median ratios between PaO_2 and fraction of inspired oxygen than those patients (n=9) who did not receive corticosteriod therapy (86.5 vs 129.5; p=0.045).

Conclusion: When used in addition to appropriate supportive care and early institution of antiviral therapy, corticosteroids appear to be of value in the treatment of previously well patients with life-threatening varicella pneumonia. The observations presented in this study are important and should form the basis for a randomized controlled trial, as no other relevant studies or guidelines are available.

(CHEST 1998; 114:426-431)