Longitudinal Data on Positive Tuberculin Skin Tests From Three US States

To the Editor:

Tuberculosis (TB) is a global health problem. In characterizing the epidemiology of TB in the United States, emphasis has mostly been placed on identifying the number of active cases, because of their threat to the public health. However, these active cases only represent a small subset of the total reservoir of TB infection, and steps toward effective eradication would also require a better assessment of the total reservoir of TB in the United States.

While US national reporting of active TB began in 1953, there are only four states that require reporting of a positive tuberculin skin test (TST). These are South Dakota (SD), Missouri (MO), Indiana (IN; Indianapolis excluded), and Arkansas (nursing homes and prisons). We investigated the annual positive TST rate in these states. The Department of Health TB control programs in all four states were contacted. Longitudinal data were available from three states: SD, MO, and IN. These were accumulated and analyzed for patterns and relationship to demographic characteristics. Positive TST rate increased in all three states: in SD from 715 to 795 cases (11% increase) from 1994 to 1997; in MO from 1,905 to 4,083 cases (120% increase) from 1991 to 1997; and in IN from 4,612 to 4,624 cases from 1996 to 1997. Denominator data were not available.

Active TB has declined in the United States due to increased public health effort, better diagnostic tools, directly observed therapy, and increased awareness of the association between HIV and TB. However, our limited data suggest that despite this declining trend of active TB, the number of positive TSTs is increasing or not changing. This may have two possible explanations. It could simply reflect improved reporting methods, or it may represent an increased population with latent, potentially drug-resistant TB. In order to better delineate the disease potential for TB, we favor a more complete prospective analysis of TST data in defined populations throughout the United States.

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Reference


Factors Contributing to Pneumothorax After Thoracentesis

To the Editor:

We read with interest the report by Colt et al (July 1999) on the factors contributing to pneumothorax following thoracentesis. The authors found that pneumothoraces occurred in 5.4% of cases and chest tube drainage was required in 0.78% of cases. The authors concluded that pneumothorax following thoracentesis is a rare event and not easily predictable if performed by experienced operators.

We wish to report the results of our prospective study. We performed 620 consecutive thoracenteses in a 4-year period. Based on the radiographic criteria, 397 effusions (64.03%) were small (visually assessed to be < 15% on chest radiograph). We identified 15 pneumothoraces (2.46%), and chest tube drainage was required in three instances (0.48%).

Hospitalization status, critical illness, effusion size or type, underlying illness, operator, needle type, amount of fluid withdrawn, patient characteristics, occurrence of dry tap, and type of thoracentesis were analyzed. The only predictor variable demonstrating statistical significance was noncollaborator patient (six patients with a diagnosis of dementia, two patients < 10 years old, two patients with Down’s syndrome, and a patient with cerebral paralysis).

One limitation of this study is that we perform postprocedure chest radiographs only on a clinical suspicion basis, and this could explain the low incidence of pneumothoraces. On the other hand, it is our practice not to use ultrasound examination unless we don’t recover pleural fluid at the first attempt (dry tap).

In summary, thoracentesis is a very safe procedure with few
To the Editor:

We thank Dr. Diaz and colleagues for their interest in our article (July 1999). Their findings further confirm that thoracentesis is a particularly safe procedure, although the lack of routine chest radiographs in their study may have caused them to miss asymptomatic pneumothoraces. From a clinical standpoint, we agree that postprocedure chest radiographs need only be performed in case of clinical suspicions of a complication. Their selective use of pleural ultrasonography is logical. Of course, it also raises issues of logistics and institutional practice patterns. Most primary care and medical subspecialty physicians do not have ready access to an ultrasound machine, forcing them to refer patients to the interventional radiologist. Although ultrasound examinations need not be performed for most thoracenteses, I remain a firm believer in the eventual democratization of pleural ultrasonography. Widespread use of ultrasound has already occurred in several medical and surgical specialties, and is likely to occur eventually, in pulmonary medicine as well. In addition, the incorporation of pleural ultrasonography into pulmonary training and practice, I believe, will eventually result in a better understanding of pleural-pulmonary relationships, increased levels of confidence for our trainees, and, as demonstrated by several investigators, fewer procedure-related complications.

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To the Editor:

We read with interest the recent article of Rosenthal et al (September 1999).1 where the use of regular twice daily salmeterol in steroid naive mild asthmatic patients was reported to show no loss of bronchoprotection against methacholine challenge between 4 weeks and 24 weeks. The authors concluded that regular treatment with salmeterol does not lead to clinical instability or vulnerability to unpredictable asthma attacks. We believe that this amounts to over-interpretation of the presented data for a number of reasons. According to the latest asthma management guidelines,2 the use of regular long-acting β2-agonists such as salmeterol is advocated only for add-on therapy at step 3 for patients with moderate persistent asthma whose symptoms are suboptimally controlled on a low-to-medium dose of inhaled corticosteroid. Hence the use of regular twice daily salmeterol as monotherapy in steroid naive asthmatic patients, as reported by Rosenthal et al, would seem to be inappropriate treatment and not consistent with accepted good clinical practice. The apparent failure to show any attenuation in bronchoprotection between 4 weeks and 24 weeks of treatment does not take into account the previous studies that have shown a rapid onset of tolerance for bronchoprotective effects with salmeterol, which occurs within the first 24 h of treatment, in either steroid-naïve or steroid-requiring patients.3,4,5 In other words, tolerance had already developed by the time of the first methacholine challenge at 4 weeks, and hence the apparent sustained bronchoprotection that was observed over the subsequent 20 weeks of evaluation.

The study of Rosenthal et al evaluated the effects of salmeterol on its own in the presence of increased airway tone due to methacholine. In this setting of increased bronchomotor tone, as might occur in an acute asthma attack, salmeterol behaves as a partial β2-adrenoceptor agonist and consequently might function as an antagonist in the presence of competitive receptor occupancy by albuterol, which exhibits a higher degree of intrinsic agonist activity.6,7 Indeed, this phenomenon has been demonstrated in vivo in asthmatic patients after single or repeated doses of salmeterol, in terms of antagonism of the protective effect of a high dose of albuterol (1600 µg) against methacholine-induced bronchoconstriction.8,9 In children with asthma receiving inhaled corticosteroid therapy, it has also been shown that concomitant treatment with regular salmeterol resulted in almost complete blunting of the bronchodilator response to repeated doses of inhaled terbutaline.10

Physicians should therefore be aware of the possibility for regular salmeterol to induce tolerance to its protection against bronchoconstrictor stimuli and of its potential for antagonism of rescue therapy with albuterol in the setting of increased airway tone. Moreover, one would predict that tolerance with salmeterol would be accentuated in 40% of asthmatic patients who exhibit the homozygous glycine-16 β2-adrenoceptor polymorphism, which predisposes to agonist induced down-regulation and desensitisation.11,12

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REFERENCES


Salmeterol and Tolerance

To the Editor:

We read with interest the recent article of Rosenthal et al (September 1999),1 where the use of regular twice daily salmeterol in steroid naive mild asthmatic patients was reported to show no loss of bronchoprotection against methacholine challenge between 4 weeks and 24 weeks. The authors concluded that...
8 Lipworth BJ, Aziz I. A high dose of albuterol does not overcome bronchoprotective subsensitivity in asthmatic patients receiving regular salmeterol or formoterol. J Allergy Clin Immunol 1999; 103:88–92

To the Editor:

In response to the issues raised by Drs. Lipworth and Jackson, we would point out that ours was a study of airways hyperresponsiveness as affected by long-term treatment with the long-acting β2-adrenoceptor agonist, salmeterol. It was not a treatment study of salmeterol as monotherapy, and despite the demonstrated efficacy and safety of same, there was no proposal made for its use in this way. The issue at hand is whether or not salmeterol treatment leads to clinical instability or vulnerability to asthma attacks. Clearly, a long-term salmeterol treatment study with concomitant corticosteroid added as per the guidelines would have made that assessment impossible. Moreover, our conclusion that long-term salmeterol treatment does not lead to clinical instability even in the absence of inhaled corticosteroids is certainly not compromised by the absence of corticosteroid treatment in the study cohort. Given the results of our study, we believe that the data supports the safety of regular therapy with salmeterol per se, and lends additional support for the regular use of salmeterol in combination with inhaled corticosteroids as per the guidelines.

Studies that demonstrate tolerance to the immediate bronchoprotective effect of salmeterol were referenced in our original article (September 1999). In these studies, a modest decrease in the initial maximal or near-maximal bronchoprotective effects of salmeterol was observed. In contrast to the bronchoprotective effect, the bronchodilator effect of salmeterol is fully preserved with chronic dosing, and the bronchodilator effect of albuterol is maintained in patients receiving salmeterol irrespective of their use of inhaled corticosteroids. This lack of tolerance is likely due to high β-receptor reserve and the partial agonist property of salmeterol, which results in lower levels of desensitization and internalization of the β2 receptors relative to β-agonists with higher intrinsic efficacy. Regarding the notion of salmeterol as a partial agonist in the presence of methacholine, although we did not study the response to albuterol after dosing with salmeterol, we not only reported that methacholine sensitivity was significantly less after salmeterol dosing than at baseline, but noted no difference in the spontaneous recovery from methacholine challenge after dosing. Importantly, a decrease in the magnitude of the initial bronchoprotective effect of salmeterol has only been demonstrated in experimental situations that utilize high levels of functional antagonism (e.g., methacholine challenge), and the clinical relevance of these studies is unclear.

We did not investigate the immediate bronchoprotective effects of salmeterol, but chose to investigate the protective effects at the end of the dosing period for salmeterol when the patient would be most vulnerable to a loss of protection or asthma control. With regular use for 24 weeks, the bronchoprotective effect was maintained 10 to 14 h after salmeterol dosing, with associated improvements in all measures of pulmonary function and symptom control. The bronchoprotective effect observed in our study is consistent with the long duration of protection observed after a single dose of salmeterol. More importantly, after washout of salmeterol (ie, 3 and 7 days posttreatment), the provocative dose of methacholine required to reduce FEV1 by 20% from baseline for patients previously receiving salmeterol remained slightly above baseline and placebo values, demonstrating that even if there was some rapidly occurring onset of tolerance to salmeterol, long-term therapy did not adversely affect airway hyperresponsiveness. Our findings are consistent with a recent study of similar design and duration that showed comparable effects of salmeterol and beclomethasone on airway responsiveness to methacholine in patients with persistent asthma.

The genotype of patients enrolled in our study was not determined. Therefore, the response of patients exhibiting the glycine-16 polymorphism could not be measured. However, we found no evidence of a significant subset of salmeterol-treated patients who exhibited reduced bronchoprotection, a posttreatment increase in airway hyperresponsiveness, or worsening of asthma control.

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REFERENCES


Use of Fluticasone in Asthma

To the Editor:

I read with interest the recent study of Baraniuk et al (September 1999), which reported significantly superior asthma control with fluticasone propionate, 440 g/d, or the combination of fluticasone propionate, 176 g/d, plus salmeterol, 84 g/d, vs monotherapy with triamcinolone acetonide 1,200 µg/d. There were, however, some potential flaws in the study design that made it difficult to draw valid conclusions from these data.

In terms of the active treatment moieties, fluticasone given as monotherapy or as cotherapy comprised taking a total of 4 puffs/d of fluticasone, in contrast to a total of 12 puffs/d of triamcinolone acetonide, with salmeterol being a total of 4 puffs/d. Although the study was double-blind and triple-dummy, there is no mention in the description of the study design as to whether the various active or placebo inhalers within each treatment arm were randomized according to the sequence in which they were taken, either in the morning or the evening. Thus, there was a likelihood for patients to begin their dosing sequence with the treatment that involved the least number of puffs (ie, either fluticasone propionate or salmeterol or their matching placebo), rather than the treatment that involved a greater number of puffs (ie, triamcinolone acetonide or its matching placebo). The likelihood of such a sequence bias was increased as a consequence of (1) the high total number of puffs of active treatment and placebo for each treatment arm (a total of 20 puffs/d); (2) the 12-week duration of the trial; and (3) the patients’ poor asthma control while already taking a high number of puffs of inhaled corticosteroid therapy prior to entering the study (6 to 16 puffs/d). This would result in patients being less inclined to comply with taking the higher number of puffs with triamcinolone acetonide as compared to salmeterol or fluticasone.

As well as potential problems with compliance, there was no mention made as to whether any formal checks were made on inhaler technique at each of the assessments over the 12-week treatment period. As pressurized metered-dose inhalers (pMDI) are notoriously difficult to use without reinforced instruction, one cannot exclude the possibility that suboptimal inhaler technique might be an explanation for the apparently poorer response to the treatment regimen that contained the highest number of puffs of active treatment (ie, triamcinolone acetonide). Again, looking at the inclusion criteria for required treatment with a high number of puffs of inhaled corticosteroid, one has to question whether poor inhaler technique was a cause for their suboptimal asthma control.

A further potential problem with the patient inclusion criteria was that there were no patients enrolled who were already receiving fluticasone propionate as their usual maintenance inhaled corticosteroid therapy. This would again tend to bias the results towards a better response to the treatment regimens containing fluticasone as opposed to those containing triamcinolone acetonide (which comprised 42% to 46% of the enrolled patients).

The likelihood of compliance and adequate inhaler technique being a confounding factor in the apparently suboptimal response to triamcinolone acetonide 1200 µg/d is supported by data from a previous dose-ranging study (triamcinolone acetonide 200 µg/d to 1600 µg/d) in similar type of patients, where a plateau in the dose-response curve for asthma control parameters occurred between 400 µg/d and 800 µg/d.

In terms of the safety profiles, no comment was made by the authors on the finding of hoarseness or dysphonia in 4% of patients receiving fluticasone 440 µg/d as compared to <1% in patients receiving triamcinolone acetonide 1,200 µg/d. Presumably, this reflects the effects of the integrated spacer attachment with the triamcinolone acetonide pMDI compared to the pMDI alone with fluticasone propionate. Alternatively, this finding could be interpreted as being due to better compliance with the fluticasone-containing regimes that involved taking a fewer number of puffs. However, the higher incidence of hoarseness with fluticasone may also have been related to its increased glucocorticoid potency, and, in this respect, there has been a recent case report of laryngeal aspergillosis in association with fluticasone propionate.

Aside from compliance issues, the findings of Baraniuk et al suggest superior overall asthma control with the addition of salmeterol to a lower dose of fluticasone propionate as compared to monotherapy with a higher dose of fluticasone propionate. This finding would be consistent with the long-acting bronchodilator properties of salmeterol when given alone during twice-daily treatment. However, this does not take into account what may be happening to the underlying asthmatic inflammatory process, which may not be adequately suppressed by lower doses of inhaled corticosteroid. Indeed, it has been shown that, in patients taking regular twice-daily salmeterol, apparently good control of symptoms and lung function occurs in the presence of increased airway inflammation, prior to an exacerbation during tapering of inhaled corticosteroid therapy. This emphasizes the importance of following accepted asthma management guidelines by optimally titrating the dose of inhaled corticosteroid before considering adding in regular long-acting β2-agonist therapy, as the latter may inadvertently mask uncontrolled airway inflammation.

Finally, I was also concerned that the final conclusion, “the largest improvements were evident with the lowest recommended dose of fluticasone propionate (176 µg/d combined with salmeterol),” might potentially send the wrong message to asthma...
caregivers, that patients with more severe asthma (range of percent predicted FEV₁ in present study was 40 to 85%) would benefit most from the lowest dose of inhaled corticosteroid therapy combined with long-acting ß₂-agonist therapy. The current guidelines clearly advocate the use of long-acting ß₂-agonist in combination with a higher dose of inhaled corticosteroid in this category of patients.7

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REFERENCES

To the Editor:
In response to Dr. Lipworth’s questions about compliance and possible “sequence bias,” patients in this study were not instructed to use the three study inhalers in any particular sequence. The labeling on the canisters did not suggest the order of administration. In addition, patients were taking up to 16 puffs/d of inhaled corticosteroid prior to entering the study. In this study, patients were using 20 puffs/d of study medication, and improvements in pulmonary function and symptom control were observed in all treatment groups. The mean self-reported compliance rate for each of the delivery devices for salmeterol, fluticasone propionate (FP), and triamcinolone acetonide (TAA) was approximately 97%.

Dr. Lipworth hypothesizes that suboptimal asthma control with TAA compared with FP and the combination regimen occurred as a result of poor inhaler technique. Patients were instructed in proper inhaler technique at screening and at randomization in this study. If inhaler technique was inadequate, suboptimal asthma control would have been observed equally across all treatment groups.

Patients were not entered into this study if they had previously used FP as their maintenance inhaled corticosteroid. FP aerosol had just become commercially available in the United States at the time the protocol for this study was developed. The inhaled corticosteroids used by patients prior to entering the study according to entry criteria reflected the use of these drugs at the time.

The lower incidence of hoarseness or dysphonia observed with TAA compared with FP is likely a result of the spacer built into the TAA metered-dose inhaler as suggested by Dr. Lipworth. It is well known that spacers can reduce the frequency of oropharyngeal side effects that are characteristic of the inhaled corticosteroids.1 Therefore, the difference in frequencies of these effects (4% vs <1%) is not clinically significant. The clinical relevance of the case report of laryngeal aspergillosis mentioned by Dr. Lipworth is also questionable because the low incidence of this condition makes a causal relationship difficult to establish (reported in the literature in only 12 patients over a period of 30 years).2

Dr. Lipworth mentions that salmeterol may mask symptoms of airway inflammation. The reference that he cites is based on a study that used a steroid-reduction model that tapered inhaled corticosteroid doses on a weekly basis rather than in intervals of a few weeks and completely withdrew patients from inhaled corticosteroids, a practice that is not in accordance with accepted management guidelines.1,3 As suggested by Dr. Lipworth, an exacerbation is a result of poorly controlled asthma and therefore reflects uncontrolled airway inflammation. If salmeterol were masking airway inflammation, one would expect to see higher rates of exacerbations with the use of salmeterol or the combination of salmeterol with FP. However, many studies, including this study, have shown that the opposite is true. In this study, only 13 patients experienced an exacerbation in the FP 88 microg bid/salmeterol combination group compared with 32 patients and 29 patients in the FP 220 microg bid and TAA 600 microg bid treatment groups, respectively. The rate of exacerbations with concomitant use of inhaled corticosteroids with long-acting ß₂-agonists has been shown to be similar to or lower than that observed with the use of inhaled corticosteroid alone.4–8 Furthermore, because of data available from clinical trials, treatment guidelines recommend adding salmeterol to an inhaled corticosteroid rather than increasing the dose of inhaled corticosteroid, since this regimen has been shown to be more effective in improving pulmonary function and asthma symptom control.1,4–8 These data suggest that salmeterol does not mask the underlying inflammatory process.

Finally, we agree with Dr. Lipworth that individualizing treatment regimens for the maintenance of asthma stability is important. Clinicians are advised to prescribe the lowest effective dose of inhaled corticosteroid for optimal asthma control and to minimize adverse effects.1

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Fatal Pulmonary Hemorrhage During High-Dose Valproate Monotherapy

To the Editor:

Valproic acid is a widely used antiepileptic drug. Liver toxicity is the major serious described side effect.1 Thrombocytopenia can also occur; however, few patients with this complication require drug discontinuation. Up to now, pulmonary hemorrhage has not yet been described. We report the case of a thrombocytopenia-related fatal pulmonary hemorrhage in a patient receiving valproate monotherapy.

A 30-year-old woman with mental retardation was admitted to our hospital with fever, cough, and dyspnea. She had received valproic acid since the age of 20 for generalized seizure disorder. Three weeks before admission, she presented an episode of viral rhinopharyngitis. On physical examination, she had bruising with cutaneous ecchymotic areas on her upper and lower extremities. Crackles were heard over both lungs. Her consciousness level was normal. Chest radiographs revealed lower lobe infiltrates. At admission, laboratory data revealed the following: hematocrit, 15%; hemoglobin, 4.9 g/dL; WBC count, 3000/µL, and platelet count, 15,000/µL. Arterial blood gas analysis while breathing oxygen via a face mask (3 L/min) revealed pH of 7.46; PaO₂, 59 mm Hg; and PaCO₂, 33 mm Hg. Initial serum valproate level was 124 µg/mL (therapeutic range, 50 to 100 µg/mL). Broad-spectrum antibiotics were administered, and transfusions of packed RBCs and platelets were given, rising her platelet count to 50,000/µL and hemoglobin to 8 g/dL. A bone marrow aspirate was performed, showing a myelodysplastic syndrome probably related to a toxic effect of valproate. On day 2, she developed hemoptysis. Bronchoscopy revealed blood throughout the airways consistent with alveolar hemorrhage on cytologic examination of the lavage fluid. Results of bloody lavage fluid, blood, and urine cultures were negative. On day 3, chest radiographs revealed evolving diffuse bilateral infiltrates and the patient developed a severe respiratory failure with cardiac arrest and died.

Bone marrow suppression and cardiorespiratory failure have been reported in fatal valproate overdoses;1,2 however, to our knowledge, this is the first case of fatal pulmonary hemorrhage during long-term valproate monotherapy. Despite the fact that hematologic complications of valproic acid are usually mild, our patient died of diffuse alveolar hemorrhage related to thrombocytoopenia. It has been suggested that viral infections may cause clinically significant episodes of thrombocytoopenia in patients taking valproate.4 Thus, the rhinopharyngitis noted 3 weeks before admission may have precipitated thrombocytoopenia in our patient. This observation suggests that fatal complication with bone marrow depression can appear several years after initiation of valproate therapy. In long-term therapy, serum valproate levels and platelet function monitoring are required in case of ecchymosis or viral infection and in patients about to have surgery.

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REFERENCES

Confident Diagnosis of Solitary Fibrous Tumor of the Pleura Using Cutting-Needle Biopsy

To the Editor:

In a recent issue (June 1999), Urschel et al3 presented a case of solitary fibrous tumor of the pleura. They stated that “ultimately, thoracotomy and tumor resection are usually required for diagnosis.” Until recently, such a statement was common and undisputed.2 However, we have published an article (November 1997)3 providing strong evidence that a confident preoperative diagnosis of fibrous tumor of the pleura can be made by histologic and immunohistochemical analysis of material obtained by transbronchial cutting-needle biopsy. The biopsy can be done safely within a few minutes under radioscopic guidance, even in an outpatient setting. The cost of this minimally invasive procedure is low. Making the definitive diagnosis allows for a proper planning of a curative thoracotomy. The resection of a solitary fibrous tumor of the pleura is usually simple because the lesion is attached to the pleura, well-circumscribed, and often pedunculated. Hence, good outcome can be contemplated after surgical cure, even in patients with bad pulmonary reserve or poor general status. This is often not the case when an alternative diagnosis is made with the cutting-needle biopsy, such as malignant mesothelioma or some cases of peripheral lung cancer. Thus, making the diagnosis of solitary fibrous tumor of the pleura by cutting-needle biopsy permits a proper and cost-effective allocation of medical resources.

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CHEST / 117 / 2 / FEBRUARY, 2000
The Mechanism of Hypoxemia in Liver Disease With Pulmonary Hypertension

To the Editor:

In a recent issue of CHEST (June 1999), Schott and coworkers1 reported that orthotopic liver transplantation (OLT) could be performed successfully, even though pulmonary hypertension (PH) is severe. They proposed that severe PH (mean pulmonary artery pressure > 40 mmHg) should not be automatically considered as a contraindication to OLT.

Concerning the arterial blood gas analyses, the authors stated that the important increase in the alveolar-arterial oxygen pressure difference (P[A-a]O2) before OLT was due to a ventilation/perfusion mismatch because an intracardiac or intrapulmonary shunt was excluded. They speculated that the increase in the P(A-a)O2 was in part the consequence of a very high blood flow in the pulmonary circulation due to the very high cardiac output. Because the contrast-enhanced echocardiographic study is a sensitive method to detect intrapulmonary right-to-left shunt, their speculation may be true in part. However, the other possibilities are also considered. Hypoxemia is often observed in patients with chronic liver diseases in the absence of intrinsic lung disease. Recent evidences suggested that nitric oxide (NO) is an important mediator of impaired oxygenation in patients with cirrhosis.2–4 NO is a vasodilating substance, which can abolish the local vasoconstrictive reflex to alveolar hypoxia, increasing the ventilation/perfusion mismatch, which is one of the mechanisms of oxygenation abnormalities in cirrhosis. Rolla and coworkers5 reported that the exhaled NO output is well correlated with P(A-a)O2 in patients with liver cirrhosis. Matsumoto et al6 also reported that increased NO levels in exhaled air in patients with decompensated liver cirrhosis. Furthermore, the increase in NO concentration after liver transplantation is reported to be correlated with the improvement in oxygenation.4 There is a possibility that the increased production of NO in the lung may be the other cause of vasodilation and intrapulmonary shunting responsible for hypoxemia in the patient. However, the mechanism of hypoxemia in liver disease may not be simple. Inhaled NO might worsen hypoxemia in cases where the ventilation/perfusion mismatching is the prominent mechanism, but may benefit patients with increased shunt flow in the better ventilated lung. Several investigators have reported that NO inhalation improved postoperative hypoxemia in patients following liver transplantation for hepatic dysfunction.2–4 Thus, the effects of NO inhalation before and after liver transplantation may have some clinical merit for the study of the pathophysiology of hypoxemia. In addition, delivering 100% oxygen by a nonrebreathing mask may have a diagnostic value of functional right-to-left shunting.7 Because the improvement of oxygenation in liver disease after live transplantation is considered to be complicated,8–11 the simple explanation may not solely be true. It may depend on the degree of intrapulmonary shunt, portal hypertension, increased cardiac output, and increased NO production in lungs.8–11 Although severe pulmonary hypertension should not automatically be considered as a contraindication to OLT, as stated by others, the other exclusion criteria may be necessary for the indication of OLT in liver diseases with pulmonary hypertension.

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To the Editor:

Teramoto et al have discussed the possible mechanisms of gas exchange impairment in patients with end-stage chronic liver disease. In our case report (June 1999), in fact, we did not discuss these mechanisms in detail. We rather focused on a more practical message: which patients should be scheduled for liver transplantation when they suffer from portopulmonary hypertension? In particular, the mechanism of pulmonary hypertension must be considered: a patient having severe pulmonary hypertension without signs of right ventricular failure and mild to moderate increase in pulmonary vascular resistance should not be systematically excluded from the liver transplantation list.
ever, as stated by Teramoto et al, the pulmonary hemodynamic measurements are not the sole criteria.

With regard to the mechanism of hypoxemia, we have stated in our report that it was the consequence of ventilation/perfusion mismatch. Since hyperventilation and intracardiac or intrapulmonary shunts were excluded, and since limitation in diffusion of oxygen cannot induce a marked resting hypoxemia, the ventilation/perfusion mismatch was the only possibility left. The question is, what explains such a ventilation/perfusion mismatch? Teramoto et al raise the interesting point that an increase in nitric oxide is responsible for a poor or absent hypoxic pressor response as a cause of hypoxemia. This was established in the hepatopulmonary syndrome, but to our knowledge never explored in portopulmonary hypertension. The increase in nitric oxide production in the lung is an interesting hypothesis; this increase could be due to (1) the stimulation of type II nitric oxide synthase (NOS) by proinflammatory cytokines or endotoxin, or (2) an increase activation of type III NOS. The latter could be due in our patient to the very high increase in cardiac output, since shear stress is a well-known stimulus of type III NOS. In fact, arterial blood gas abnormalities in our patient were similar to those usually observed in primary pulmonary hypertension. Perhaps it was the decrease of alveolar-arterial oxygen gradient observed after liver transplantation due to the disappearance of NOS II and NOS III stimuli. The fact that alveolar-arterial oxygen gradient was still elevated after that procedure could be secondary to irreversible small artery lesions.

Pulmonary hemodynamics and gas exchange in patients with chronic liver failure are an interesting area. Understanding their mechanisms in hepatopulmonary syndrome and portopulmonary hypertension could give clues on the hypoxic pulmonary vasoconstriction and the development of pulmonary vascular diseases.

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REFERENCES


Community-Acquired Chlamydia pneumoniae pneumonia

To the Editor:

We read with great interest the article by Ishida et al (December 1998) regarding their investigation of the etiology of community-acquired pneumonia (CAP) among the Japanese population. The first time and their finding that Chlamydia pneumoniae was identified in 3.4% of episodes by using the enzyme-linked immunosorbent assay (ELISA). Of these patients, two (18.1%) had dual infections. In several recent CAP studies, however, C pneumoniae has been found to account for up to 10% of CAP cases in Western countries. Furthermore, C pneumoniae has been reported to cause pneumonia frequently in association with other microorganisms, mainly Streptococcus pneumoniae. We would like to expand these observations with our findings, using the traditional diagnostic methods for detection of C pneumoniae.

We undertook a study to determine the etiology of CAP in Japan between April 1998 and July 1999. Traditional diagnostic methods, including paired serum samples for the microimmunofluorescence test to detect C pneumoniae, were used in combination with cell cultures for isolation and the use of culture plates for detection of C pneumoniae. Culture for C pneumoniae was performed in cycloheximide-treated HEP-2 cells.

Nine out of 112 patients (8.0%) received diagnoses of C pneumoniae by this method. Serologic criteria established the diagnosis in nine cases and isolated the bacteria in two. Culture-positive specimens were also found to be positive by serology. Of these patients, five had polymicrobial infections, which were associated with S pneumoniae in two cases, Legionella pneumo- phila in one, Haemophilus influenzae in one, and S pneumoniae and Staphylococcus aureus in one. One of these patients died. The mean length of hospitalization of these five patients with mixed C pneumoniae pneumonia was significantly longer than that of patients with C pneumoniae monoinfection or those with non-C pneumoniae pneumonia (45.2 days vs 16.9 days). It has been noted that mixed infection with C pneumoniae and other microorganisms often increases symptoms and even mortality. This was also observed in our study, especially in the patients infected with C pneumoniae and S pneumoniae.

We found C pneumoniae in 8.0% of the CAP cases using specific methods, and the clinical results were comparable with those of recent reports in Western countries. Therefore, we believe that, in addition to S pneumoniae, C pneumoniae is also an important pathogen among the Japanese population, and we believe that diagnostic tests must be readily available for early recognition of C pneumoniae infections.

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To the Editor:

We thank Dr. Miyashita and colleagues for their interest in our article (December 1998). In our study, screening for Chlamydia
pneumoniae was chiefly conducted using enzyme-linked immuno-
sorbent assay (ELISA). However, because it often takes several
weeks to recognize the significant elevation of antibody titer,
there may have been patients with conditions that could not be
diagnosed using ELISA while hospitalized and who were not
followed after discharge. It is therefore possible that the actual
incidence of C pneumoniae pneumonia was slightly higher among
all community-acquired pneumonia (CAP) cases. The incidence
of C pneumoniae pneumonia may also have differed because of
the year in which the survey was conducted.

We conducted a separate prospective multicenter study of the
etiology of CAP at three hospitals in Japan and diagnosed C
pneumoniae pneumonia in 7.9% of all cases. Statistics kept
independently by our hospital over the past 5 years show that C
pneumoniae pneumonia accounted for 33 (6.0%) of all 552 CAP
cases, and was the fourth leading causative organism after
Streptococcus pneumoniae, Haemophilus influenzae, and Myco-
plasma pneumoniae. Of the 33 C pneumoniae pneumonia pa-

tients, 10 had dual infections involving another pathogenic
organism. As also pointed out by Dr. Miyashita and colleagues, C
pneumoniae appears to be an important cause of CAP in Japan as
it is in Western countries. However, we often find difficulty in
diagnosing C pneumoniae pneumonia, so the widespread avail-
ability of a simple and rapid diagnostic method is needed.

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