Ariflo™ — A Brief Report On A New Second-Generation Phosphodiesterase 4 Inhibitor

Yu-Wung Yeh, Jiunn-Song Jiang, Shang-Jyh Kao

Even though the search for new medications continues, at the end of the day, we still rely on time-honored drugs such as β -agonist, anti-cholinergics, steroids, and theophylline for the treatment of asthma and chronic obstructive pulmonary diseases. Phosphodiesterases play a very important role in terms of biological functions in the human body. They affect the concentration of cyclic AMP and cyclic GMP. Theophylline, in fact, is a non-specific phosphodiesterase inhibitor. As different isozymes of phosphodiesterases have different distribution properties in various tissues, by targeting different isozymes, one can theoretically develop drugs with different properties acting on different target organs. Since the 1970's, there has been intensive research on the potential use of phosphodiesterase inhibitors, and in particular, the phosphodiesterase 4 (PDE4) inhibitors, in treating asthma and chronic obstructive pulmonary diseases. PDE4 inhibitors can inhibit neutrophil functions, decrease TNFα production, impair mast cell degranulation, and decrease T cell proliferation. However, the known PDE inhibitors have not been proved to be clinically useful due to their side effect profiles. SmithKline Beecham Pharmaceuticals is planning to launch a new second-generation PDE4 inhibitor Ariflo™. In phase II trials, Ariflo™ could effectively improve exercise dyspnea scores, increase FEV1, and improve small airway closures. Compared to the first-generation phosphodiesterase 4 inhibitors, Ariflo™ has markedly improved side effect profiles. ***(Thorac Med 2000; 15: 157-164)***

Key Words: Ariflo™, phosphodiesterase, asthma, chronic obstructive pulmonary disease (COPD)

Introduction

Chronic obstructive pulmonary disease (COPD), including asthma, is an old disease desperately in need of new medicine. In addition to traditional bronchodilators and anti-inflammatory medications such as β -agonist, ipratropium bromide, steroids, and theophylline, scientists have been working on developing new drugs based on what is known about the pathogenesis of COPD. SmithKline Beecham Pharmaceuticals is launching a new phosphodiesterase 4 (PDE4) inhibitor, Ariflo™, which may bring new hope to asthma and COPD patients. On January 9th, 2000, the Eighth Wu Ho-Su Memorial Symposium was held at Shin Kong Wu Ho-Su Memorial Hospital in Taipei,

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Taiwan. In the symposium, a lecture was given by Dr. Anthony S. Rebuck, the vice president and director of the clinical research and development division, Asia Pacific Region, SmithKline Beecham Pharmaceuticals, on the new second-generation PDE4 inhibitor Ariflo™ and its application in the treatment of COPD. With the upcoming launching of the newest PDE4 inhibitor in mind, we will briefly summarize what is known about the biological significance of the PDE inhibitors, with a focus on PDE4 inhibitors, and give a synopsis of Dr. Rebuck's lecture in the following text. We will introduce this new medication to the Taiwanese public by reviewing the rationale behind the development of PDE4 inhibitors in the treatment of asthma and COPD.

Historical Background

Phosphodiesterases have been the focus of intense research since the 1970's. It has now been recognized that the phosphodiesterases are actually a family of enzymes with a diverse distribution in various tissues and different pharmacokinetics and biological actions. Their main known activity is the termination of the actions of cyclic AMP and cyclic GMP, which act as second messengers for many biological reactions. One of the time-honored drugs used in the treatment of asthma is theophylline, a nonselective inhibitor of all PDE isozymes in vitro. Although it is not clear how much of theophylline's therapeutic effect is related to its PDE inhibitory activity, it is generally accepted that much of its side effect is a result of non-selective PDE inhibition [1-2]. Following the discovery that the concentrations of different PDEs varied among different tissues, there came the proposal that by selectively targeting different PDEs, one could thereby develop drugs with some degree of tissue specificity [3-4].

The Phosphodiesterase Family

There are seven families of PDE isozymes; each family is comprised of products from one to four different genes. Each gene, in turn, may produce multiple splice variants, resulting in a large number of enzymes, each with its own distinct characteristics [5-7]. PDEs inactivate cAMP and cGMP by hydrolytically cleaving the 3'-phosphoester bond to form inactive 5'-nucleotide monophosphate products. Cyclic AMP is involved in many aspects of the pathophysiology of asthma. It is known to suppress the activity of immune and inflammatory cells in general [8-11]. It is also believed to play a role in mediating the bronchodilating effect caused by β -adrenoceptor agonists via protein kinase A (PKA). Several studies indicate that cyclic AMP exerts an overall inhibitory effect on airway smooth muscle proliferation through a complex mechanism [12-14]. Changes in the cAMP concentration in vascular endothelial cells are linked to the degree of inflammatory cell and plasma protein infiltration of the airway [15].

Immune and Inflammatory Cells

PDE4 and PDE3 are the major phosphodiesterases in immunocompetent cells in the human body. They are the major enzymes responsible for metabolizing cyclic AMP. Human lung mast cells contain both PDE3 and PDE4 [16]. Upon antigen challenge, mast cells will release histamine and cysteinyl leukotrienes, an action that can be inhibited by PDE4 inhibitors [16-18]. PDE3 inhibitors, on the other hand, potentiate the effect of the PDE4 inhibitors [18]. PDE4 suppresses a wide range of eosinophil actions in the animal model. However, there are very few studies available with human eosinophils. The most important activity of the PDE inhibitors in macrophages and monocytes is their ability to inhibit lipopolysaccharide-induced TNF-α production [19]. Both PDE3 and PDE4 are important in this regard. PDE4 is the predominant cyclic AMP metabolizing enzyme in human neutrophils [20]. Synergistically with adenyl cyclase activators, PDE4 inhibitors

suppress most of the human neutrophil functions [20-21]. Cyclic AMP and PDE4 inhibitors can suppress T cell proliferation, but the mechanism is complex and not completely understood. Part of it stems from the suppression of the production of cytokines such as IL-2, IL-5, IFN-γ, and granulocyte-macrophage colony-stimulating factor [22-23].

Airway Smooth Muscle and Nerves

It is believed that PDE3 and PDE4 co-regulate cyclic AMP content in human airway smooth muscle. Inhibition of either isozyme partially reverses the spontaneous tone of the isolated human bronchi [24]. The role which cyclase activators play in the synergistic relaxation of the human airway smooth muscle is not clear. Inhibitory NANC nerves, mediated by nitric oxide, are the primary relaxant innervation to the airway. PDE4 inhibitors potentiate this effect through as yet unclear mechanisms.

Studies With Phosphodiesterase Inhibitors

PDE4 inhibitors prevent antigen-induced bronchoconstriction mainly through an anti-inflammatory mechanism rather than through direct bronchodilation. They can reduce antigen-driven eosinophil infiltration by inhibiting mast cell degranulation and thus mediator release as well as producing a generalized inhibitory effect on inflammatory cell trafficking [25]. In addition to reducing eosinophil infiltration, they can suppress eosinophil activity [26] and reduce airway hyperreactivity [27] and pulmonary microvascular leakage [28].

There is a potential synergistic interaction between PDE inhibitors and adenyl cyclase activators in terms of their anti-inflammatory properties. Many actions of the PDE inhibitors can be potentiated by adenyl cyclase activators [8]. More importantly, they act on several points in the anti-inflammatory process. Therefore, the therapeutic actions of PDE inhibitors in vivo cannot be predicted in a straightforward fashion.

PDE4 inhibitors can act synergistically with PDE3 inhibitors to produce a bronchodilatory effect. However, experiments in which PDE3 and PDE4 inhibitors were co-administered produced profound cardiovascular side effects in addition to bronchodilation [29].

An increased cyclic AMP level can up-regulate PDE activity through increased expression [30]. However, an increased level of PDE4 will reduce intracellular cyclic AMP content, thus resulting in self-regulation. The use of β-adrenoceptor agonists can up-regulate PDE4 activity in cells, and this may be implicated in the observed deterioration of asthma control with regular use of β-agonists [31-32].

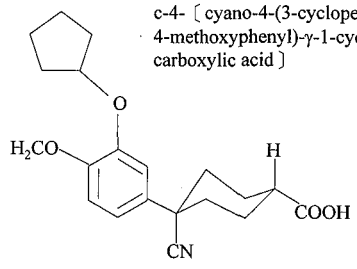
Several isozyme-selective PDE inhibitors have been tested in humans. For one reason or another, none of them have proven to be superior to the existing anti-asthma drugs. The PDE3 inhibitors enoximone and cilostazol, although providing satisfactory pulmonary effects, are limited by their side effects of increasing heart rate and decreasing blood pressure [33]. The PDE5 inhibitor zaprinast showed equivocal pulmonary effects. Studies with two dual PDE3/4 inhibitors, benafentrine and zardaverine, have also shown mixed results [34-35]. In addition, PDE4 inhibitory activity potentiates the cardiovascular side effects of PDE3 inhibitors, further limiting the clinical applications of these agents. CDP840, a PDE4 inhibitor, ablated the late asthmatic response, but not the early asthmatic response to allergens [36]. The first generation PDE4 inhibitors are also limited in clinical application due to the side effects of nausea, vomiting, and increased gastric acid secretion.

Second-Generation PDE4 Inhibitors

The present efforts in developing second-generation PDE4 inhibitors focus on the co-existence of two conformers of PDE4, one of them binding the first-generation PDE4 inhibitor prototype rolipram with a high affinity (HPDE4),

Figure 1

Ariflo: SB 207499



Courtesy of SmithKline Beecham Pharmaceuticals

Fig. 1

Figure 2

SB 207499 (Ariflo™) COPD Phase 2

- Study 038 (US)
  - Dose-ranging Safety/Efficacy n=224
  - 2.5, 5 mg bid v placebo
  - 4 weeks double-blind
- Study 032 (Europe)
  - Dose-ranging Safety/Efficacy n=400
  - 5, 10, 15 mg bid v placebo
  - 6 weeks double-blind

Courtesy of SmithKline Beecham Pharmaceuticals

Fig. 2

the other with a lower affinity (LPDE4). Certain therapeutic effects of PDE4 inhibitors seem to be related to the inhibition of LPDE4 while the side effects appear to be related to the inhibition of HPDE4. The second-generation PDE4 inhibitors aim to have a higher affinity for LPDE4 and a lower affinity for HPDE4 in order to improve their therapeutic profile. The new second-generation PDE4 inhibitor Ariflo™, by SmithKline Beecham, claims to have achieved this goal. Phase II trials with Ariflo™ showed increased FEV1, an improved exercise dyspnea score, and improved small airway closures. The true test of this claim is yet to be performed as we await the conclusion of the phase III trials.

The following text is a synopsis of Dr. Anthony S. Rebuck's lecture at the Shin Kong Wu Ho-Su Memorial Hospital in January 2000, transcribed courtesy of SmithKline Beecham Pharmaceuticals.

Lecture Synopsis

COPD is a disease with a very high prevalence not only in Taiwan, but also in the US, Europe, and the UK. It is the fifth most common cause of death in North America despite a decrease in the smoking population. This is presumably due to worsening air pollution and the increased longevity of the general population. High costs of care are involved in COPD, both direct and indirect. It has a higher rate of hospitalization, longer length of stay, and a higher mortality rate compared to asthma.

The cellular pathophysiology of COPD is not as clear-cut as asthma. However, we do know that the polymorphonuclear leukocyte is the key player. Therefore, any drug aiming to control COPD must have action against the neutrophil.

Ariflo™ (Figure 1), by Smith Kline Beecham, is a second-generation PDE4 inhibitor that is both potent and selective. The first generation PDE4 inhibitors such as rolipram have significant liabilities. They have a broad spectrum of activity in the inflammatory disease model and, therefore, have significant side effects such as nausea, vomiting, and increased gastric acid secretion.

Ariflo™ has an improved HPDE4/LPDE4 ratio; it has ten times the selectivity for PDE4 and virtually none for PDE2 and PDE3. It also has excellent drug metabolism and pharmacokinetic characteristics. It inhibits IL-8-induced chemotaxis, LTB4-induced neutropenia in rabbits, and LPS-induced neutrophil infiltration and pulmonary edema in guinea pigs. In terms of neutrophil function, Ariflo™ impairs degranulation, inhibits IL-8-induced neutrophil infiltration and goblet cell degranulation, and impairs zymogen-induced IL-8 release. Finally, it impairs TNF(production by human monocytes. There are other added actions of Ariflo™ on

Figure 3

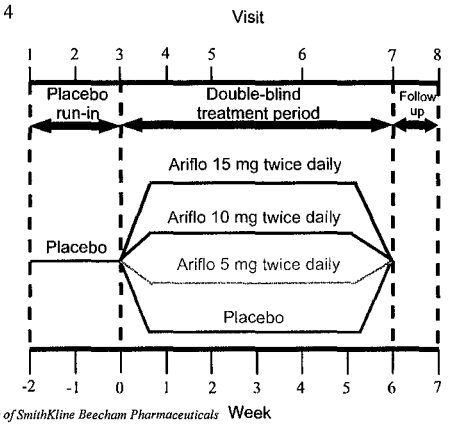
Ariflo 032: Key Demography

Ave Age	62.8	Range 31-80
FEV1	1.43 L	Range 0.57-2.54
FEV1% Pred	46.8%	Range 28.71-70.15
FEV1/FVC	53.7%	Range 30.23-74.4
B2 Reversibility	5.4%	
Pack Years	39.72	Range 10-160

Courtesy of SmithKline Beecham Pharmaceuticals

Fig. 3

Figure 4



Courtesy of SmithKline Beecham Pharmaceuticals

Fig. 4

respiratory smooth muscles. It inhibits non-adrenergic, non-cholinergic-induced contractions and potentiates relaxation. It also abolishes the antigen-produced enhancement of the citric acid cough model.

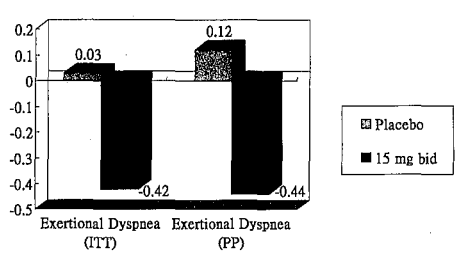
The above are the pre-clinical data on Ariflo™. In the clinical aspect, phase II trials have been conducted in both the US and in Europe (Figure 2). The European trials concentrated on dose finding. Four hundred patients were enrolled to receive Ariflo at the doses of 5, 10, and 15 mg bid vs. placebo in a double-blind study for 6 weeks. The US study focused on dose ranging, safety, and efficacy. The trial was conducted at the doses of 2.5 and 5 mg bid vs. placebo for 4 weeks. The following discussion refers to our pivotal European study, the data from which were presented to the FDA and the European authority.

The study was a double-blind trial; patients were randomized to 5, 10, and 15 mg of Ariflo™ bid (Figure 3). The patient population was COPD patients with an average age of 62.8 years, FEV1 46.8% predicted, FEV1/FVC ratio 53.7%, and β-2 agonist reversibility was 5.4% on average (Figure 4). The result was statistically significant. FEV1 was the primary efficacy end point. In addition, the 5% β-2 reversibility was achieved in the Ariflo population after the first week of treatment at trough level, and was sustained after 6 weeks. We saw the same pattern for vital capacity. If VC increases, then either the TLC must increase or the RV must decrease. As COPD patients already have hyperinflated lungs, TLC is unlikely to go up in this population. Therefore, the RV must have decreased in the study population. This means that the small airway closures must have improved. Correspondingly, the exercise dyspnea score also improved (Figure 5). Patients also reported decreased bronchodilator use (Figure 6). The side effects of Ariflo™, mainly nausea and headache, were reported no greater than 10% above the placebo population. Therefore, it has a good drug safety profile.

Phase III trials of Ariflo, which are multi-center studies conducted worldwide, are almost finished. We hope to see promising results from these trials.

Figure 5

Ariflo 032: Dyspnea



Courtesy of SmithKline Beecham Pharmaceuticals

Fig. 5

Figure 6

Ariflo 032: Bronchodilator Use

	N=	%	p=
Placebo	21/103	20%	-
5mg bid	28/105	27%	0.33
10mg bid	26/98	27%	0.32
15mg bid	40/104	38%	0.006

Courtesy of SmithKline Beecham Pharmaceuticals

Fig. 6

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Ariflo™：新第二代 Phosphodiesterase 4 阻斷劑之簡介

葉育雯　江俊松　高尚志

治療氣喘以及慢性阻塞性肺病的藥物日新月異，但最常用的仍不外乎乙型交感神經興奮劑、抗乙醯膽鹼、類固醇、以及茶鹼類藥物，phosphodiesterases 在人體的生理機能中佔了一極重要之地位，可調節 cyclic AMP 以及 cyclic GMP 之作用。如今常用之茶鹼類藥物即為不具特異性之 phosphodiesterase 阻斷劑，由於不同種類的 phosphodiesterase 在人體各個器官中分佈不同，理論上可依此選擇性地研發不同效用的藥品。自 1970 年代起，便有許多研究報告探討具特異性之 phosphodiesterase 阻斷劑在治療氣喘及慢性阻塞性肺病上潛在性之運用。其中又以 phosphodiesterase 4 (PDE4) 阻斷劑在肺部疾病的作用最為有效；它可抑制嗜中性白血球(neutrophil)的作用、減低腫瘤壞死因子(TNF-α 的合成、抑止肥胖細胞 mast cell)顆粒之釋放、以及減低 T 細胞的增生。但是，目前已研發出的 phosphodiesterase 阻斷劑由於副作用過大，在臨床上之運用並不廣泛。史克美占藥廠(SmithKline Beecham Pharmaceuticals)即將推出一新的第二代 phosphodiesterase 4 阻斷劑 Ariflo™。在第二階段實驗中，Ariflo™ 可有效地改善運動產生之呼吸困難，增進第一秒最大呼氣量(FEV1)，以及減低小支氣管的關閉(small airway closures)，比較第一代的 phosphodiesterase 4 阻斷劑，其副作用遠較第一代之 phosphodiesterase 4 阻斷劑為少。此藥之臨床運用功效曾在去年歐洲呼吸年會引起熱烈討論，與會專家感認其將為慢性阻塞性患者增添一治療的新利器，在第三階段實驗結果揭曉之前，為文介紹，以饗讀者。*(胸腔醫學 2000; 15: 157-164)*

關鍵詞：Ariflo™，phosphodiesterase，慢性阻塞性肺病，氣喘

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Hypersensitivity Pneumonitis with Recurrence—A Case Presentation and Review of the Literature

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A 76-year-old farmer suffered from fever, general malaise, and headache after he had trimmed the bushes near his farm. A chest radiograph revealed diffuse reticulonodular lesions, and thoracic high resolution computed tomography (HRCT) demonstrated patches of ground-glass opacity and reticulonodular centrilobular opacities. Based on the exposure history and HRCT findings, hypersensitivity pneumonitis was highly suspected. The symptoms subsided dramatically and the pulmonary infiltrates subsided gradually after corticosteroid prescription. Recurrence of hypersensitivity pneumonitis was noted two months after he had returned to his normal living and working environment. ***(Thorac Med 2000; 15: 165-171)***

Key words: hypersensitivity pneumonitis, extrinsic allergic alveolitis.

Introduction

Hypersensitivity pneumonitis (HP) is an allergic lung disease caused by an inhaled agent, particularly an organic antigen. Numerous inciting agents have been described, including agricultural dusts, bio-aerosols, and certain reactive chemical materials. The radiographic and pathologic abnormalities can be classified into acute, subacute, and chronic stages. Early recognition and removal from exposure can avert the ongoing pulmonary inflammation which can lead to irreversible pulmonary fibrosis.

Case Presentation

A 76-year-old man, a farmer, with a 2-week history of fever, headache, general malaise and dyspnea, was referred to our hospital. He had bilateral tardy ulnar palsy, and C-spine radiculopathy was suspected. His past surgical history included transposition surgery 5 years ago due to tardy ulnar palsy of the right side and an operation for a herniation of an intervertebral disc. He smoked socially. He felt a general malaise, fever and chill with severe headache after he had trimmed some bushes near his farm about 2 weeks previous. The bushes he had trimmed were contaminated with a moldy outgrowth. During the trimming process, his working environment was quite dusty and the air he breathed became unpleasant. He had done this trimming periodically every year, and never felt

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uncomfortable before. Since he felt uncomfortable this time he went home for a rest. The feeling of discomfort feeling wosened, and fever, chill, headache and general malaise developed.

He visited local medical clinics several times in the following two weeks, but the symptoms persisted despite medication. Then, he was brought to Changhua Christian Hospital for further evaluation. At Changhua Christian Hospital, laboratory data and the chest radiograph yielded negative results. Under the impression of a fever of unknown origin, he was observed at the emergency department. On the 4th hospital day, dyspnea and wheezing were noted, and the follow-up chest radiograph showed bilateral pulmonary infiltration (Fig.1). Under the impression of acute pulmonary edema, diuretics were prescribed. The symptoms showed no improvement despite medical treatment. The patient was transferred to our hospital 2 days later.

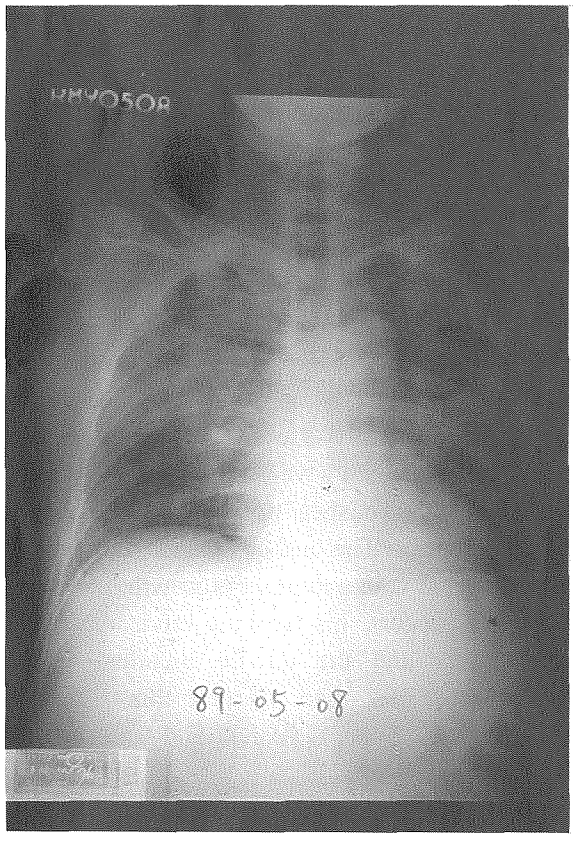

Fig 1. The chest radiograph showed bilateral pulmonary infiltration simulating acute pulmonary edema, but still reticulonodular lesions could be found.

At our emergency room, his body temperature was 38.9 °C; blood pressure, 154/86 mmHg; pulse rate, 90/min; and respiratory rate, 20/min. On physical examination, bilateral inspiratory crackles with mild wheezing were heard. Neither anemia (Hb 14.1 g/dL) nor leukocytosis (WBC 6180/cumm with normal differential counts: N/L/M/E 74/20/4/1) was found. Blood biochemical tests revealed elevated lactate dehydrogenase (1322 I.U./L), uric acid (8.8 mg/dl), total bilirubin (1.74 mg/dl), direct bilirubin (0.59 mg/dl), alkaline phosphatase (485 U/L), and a decrease of albumin (3.3 g/dl). The results of the arterial blood gas analysis while the patient breathed-in room air were as follows: pH, 7.538; pO_2, 46.5 mmHg; and pCO_2, 25.0 mmHg. The chest radiograph showed diffuse reticulonodular lesions in both lungs. A thoracic high resolution CT revealed several ground-glass patches with several reticulonodular centrilobular opacities and mild fibrotic changes, enlarged lymph nodes in the pre-tracheal, aorta-pulmonary window and subcarinal regions, and a minimal amount of bilateral pleural effusion (Fig.2).

Miliary tuberculosis, atypical pneumonia such as legionellar pneumonia, hypersensitivity pneumonitis in subacute form, and drug-induced lung disease were suspected. After admission, the 1hr-erythrocyte sedimentation rate (ESR) was 71 mm; the 2hr-ESR, 101 mm; and C-reactive protein (CRP), 160.1 mg/L. Sputum was sent for acid-fast stain, Gram's stain, mycobacterial culture, bacterial culture, fungal culture, and legionella culture; the results were all non-revealing. Blood cultures were performed for three sets and no microorganism was cultured out. Serum and urine were sent for legionella antibody and antigen detection, and negative findings were later reported. Blood levels of imunoglobulin E (IgE), IgG, and IgA were within normal limits. The mast allergy test was negative. The pulmonary function test showed a restrictive

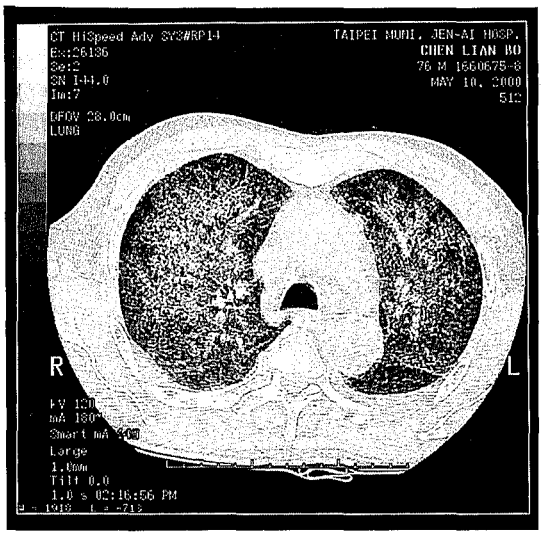

Fig 2. Ground-glass patches with several reticulonodular centrilobular opacities were disclosed in thoracic high resolution CT.

ventilatory defect with FVC 1.93 L (65.2% pred.), FEV1 1.8 L (98.9% pred.), FEV1/FVC 93.3%, and TLC 4.02 L (82% pred.). The patient had no previous drug history, the sputum acid-fast stain showed negative findings, a normal blood leukocyte count (WBC 6180/cumm with normal differential counts: N/L/M/E 74/20/4/1) was found, and high ESR and CRP were noted. Bacterial infection and drug-induced lung diseases were excluded initially due to normal leukocyte and differential blood counts and the absence of a drug history; although the acid-fast stain of the sputum showed negative findings, miliary TB still was included in the diagnostic list. Because of persistent hypoxemia, supplemental oxygen therapy with up to 6 liters/minute was given to keep SpO_2 around 90%. Hyperthermia with relative bradycardia was noted. Since subacute hypersensitivity pneumonitis and miliary tuberculosis could not be ruled out, solumedrol (methyl-prednisolone) 40 mg intravenous drip every six hours, and anti-TB medications [Rifater 5# (rifampicin 600 mg + isoniazid 400 mg + pyrazinamide 1250 mg) and EMB 2# (ethambutol 800 mg)], were given on the 2nd hospital day. The symptoms subsided dramatically after corticosteroid treatment and the anti-TB medications were discontinued on the 4th hospital day. The levels of ESR and CRP declined. The patient was discharged with oral prednisolone 20 mg Bid after one-week hospitalization, and was followed at an outpatient clinic. Ten days after discharge, the 1hr-ESR was 22 mm; the 2hr-ESR, 49 mm; CRP, 15.7 mg/L; and IgG, 1412 mg/dL. The pulmonary function test showed normal ventilatory functioning with FVC 2.44 L (81.9% pred.), FEV1 2.42 L (130.1% pred.), FEV1/FVC 99.2%, and TLC 4.91 L (99.4% pred.). Nearly complete resolution of the pulmonary lesions was found in the chest radiograph. Oral prednisolone was discontinued and the total period of steroid treatment was 2 weeks.

Three and half months later, the patient was admitted again, due to recurrence of hypersensitivity pneumonitis. The patient reported a fever, chills, headache, and malaise for 2 days. Diffuse fine crackles were heard on auscultation; body temperature was 39.7 °C; pulse rate, 84/min; respiratory rate, 24/min; and blood pressure, 166/84 mmHg. The results of arterial blood gas analysis in room air were as follows: pH 7.467; pO_2 61.5 mmHg; and pCO_2 28.5 mmHg. Slight anemia (Hb 12.8 g/dL) and a normal white blood cell count of 9830/cumm with a differential count of N/L/M/E 75/14/8/2 were found. Blood biochemistries revealed elevated creatinine (1.8 mg/dl) and uric acid (12 mg/dl). The 1hr-ESR was 96 mm; the 2hr-ESR, 112 mm; and CRP 55.9 mg/L. The levels of IgE, IgG, and IgA were within normal limits. The mast allergy test was negative. The pulmonary function test showed restrictive ventilatory impairment with FVC 1.12 L (37.2% pred.), FEV1 1.12 L (60.2% pred.), FEV1/FVC 100%, and TLC 4.49 L (90.9% pred.). The chest radiograph showed diffuse reticulonodular lesions (Fig.3). The thoracic HRCT revealed diffusely thickened intralobular septa with a reticular pattern, and fine reticulonodules involving bilateral lungs, which spared the right middle lobe and subpleural regions; mixed chronic and subacute hypersensitivity pneumonitis was considered. The clinical features were quite similar to those noted of thee last visit. Under the impression of hypersen-sitivity pneumonitis with recurrence, intravenous

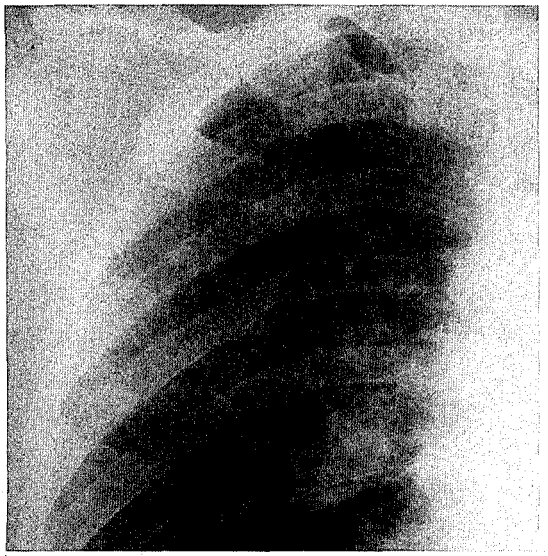

Fig 3 Close-up view of the chest radiograph in the episode of recurrence, the diffuse reticulonodular lesions were similar to the pictures disclosed in the first hospitalization (Figure 1).

solumedrol (methyl-prednisolone) 40 mg intravenous drip every six hours was prescribed. Again, the symptoms subsided dramatically after corticosteroid treatment. After hospitalization for 2 weeks, the patient was discharged with oral prednisolone 20 mg Bid and followed up at our outpatient clinic. The patient was suggested to move away from his home and farm to avoid continuous exposure to the etiologic antigen in order to prevent the development of a chronic form hypersensitivity pneumonitis.

Discussion

Hypersensitivity pneumonitis, or extrinsic allergic alveolitis, belongs to a group of immunologically-mediated pulmonary diseases caused by a variety of antigens. Over 300 etiologic antigens causing hypersensitivity pneumonitis have been reported. [1] Those antigens can be divided as organic (high molecular weight complete antigens) and inorganic (low molecular weight haptens). [2] The majority of etiologic antigens are derived from occupational exposure, such as in farming, breeding birds, mushroom packing, sugar cane harvesting or bathtub finishing. Most of the antigens do not proliferate (e.g., avian glycoprotein in bird droppings) or do not proliferate in physiologic temperature (e.g., Saccharopolyspora rectivirgula in farming dusts). [3] The most frequent allergens are thermophilic actinomycetes, which are found in warm humid environments (such as soil, hay, or forced heating and cooling systems). The prevalence of the disease varies by region, climate, and farming practices, and ranges from about 2 to 9% of exposed individuals. [1] Many different disease names have been reported, such as farmer's lung, bird fancier's disease, malt worker's disease, bathtub finisher's lung, bagassosis, sequoiosis, suberosis, mushroom worker's lung, late respiratory systemic syndrome, isocyanate disease, ventilation pneumonitis, Sax lung, or Japanese summer house hypersensitivity pneumonitis. Farmer's lung, which is the best-known hypersensitivity pneumonitis syndrome, results from the inhalation of fungal organisms (thermophilic actinomycetes) that grow in moist hay. Pathologic examination of the affected lung reveals antigen-mediated granulomatous inflammation of the lung parenchyma, alveolar walls, and terminal airways.

There are three stages related to hypersensitivity pneumonitis: the acute, subacute, and chronic. In the classic acute form, the affected person usually presents with fever, a general malaise, cough, and dyspnea 4 to 6 hours after heavy antigen exposure. The flu-like symptoms are often confused with the common cold, and bacterial and viral pneumonitis; patients usually are identified with delay. Symptoms abate after a few hours to a few days if exposure is avoided. The chronic form is characterized by productive cough, dyspnea, fatigue, and weight loss, due to prolonged exposure to the antigen. The very severe chronic form can progress to irreversible pulmonary fibrosis. Subacute disease is characterized by the gradual development of cough, dyspnea, fatigue, anorexia, and weight

loss. [4] The subacute form is an intermediate stage; it can lead to fibrosis if antigen exposure is not eliminated or it can resolve completely if proper treatment is prescribed. This condition should be suspected if flu-like symptoms occur after exposure to microbial spores, animal proteins, or certain chemicals. Prolonged illness may be associated with considerable weight loss, but symptoms usually tend to improve within 48 hours after removal from the causative agent.

On physical examination, lung auscultation may reveal diffuse dry crackles. The chest radiograph in acute or subacute forms may show a ground glass pattern or reticulonodular shadows; in the chronic form, diffuse reticulonodular infiltrates and fibrosis are characteristic. [4] Findings of hypersensitivity pneumonitis on thoracic HRCT depend on the stage of the disease. The acute form is rarely recognized, but shows bilateral air-space lesions and ill-defined small (1-3 mm diameter) nodules. The thoracic HRCT is performed much more commonly in the subacute stage, weeks to months following the first exposure to the antigen. Characteristic appearances of the subacute stage of hypersensitivity pneumonitis on HRCT are ill-defined centrilobular nodules, less than 5 mm in diameter, and patchy areas of ground-glass opacity. In the subacute stage, small nodules and areas of ground-glass opacity represent potentially treatable or reversible lesions. These findings often undergo dramatic improvement when patients with subacute disease are removed from exposure and treated with corticosteroid. The chronic stage of HP is characterized by the presence of fibrosis, which may develop months or years after the initial exposure. In patients with the chronic form, HRCT can show irregular reticular opacities representing fibrosis, traction bronchiectasis, or frank honeycombing, mimicking idiopathic pulmonary fibrosis. The findings of pulmonary fibrosis often show a middle lung zone predominance or an even distribution throughout the upper, middle, and lower lung zones. Relative sparing of the lung bases, seen in a majority of the chronic cases, can sometimes differentiate it from IPF, in which the fibrosis usually predominates in the lung bases. [5]

Pulmonary function tests in hypersensitivity pneumonitis often show a restrictive defect with a loss of lung volume. Airflow limitation can also be seen. By and large, there is often a mixed pattern of ventilatory impairment. [6] The lung biopsy in the acute form reveals interstitial infiltrates of plasma cells, lymphocytes, and neutrophils; granulomas with central necrosis and multinucleated giant cells formed by fused macrophages are often present. In the chronic form, the lung biopsy shows interstitial fibrosis destroying the lung architecture. [7] There is no single pathognomonic test for hypersensitivity pneumonitis. Specific precipitating antibodies (precipitins) to the causal agents in the serum are helpful in making the diagnosis. However, these antibodies are only a marker to exposure, not to disease. Negative results in the context of strong clinical evidence may suggest the disease and cannot exclude the diagnosis. [2, 3, 8]

No single mechanism can explain all of the pathologic features of hypersensitivity pneumonitis. In most experimental models, after antigen challenge, there is an increase in neutrophils in the alveoli and small airways, followed by an influx of mononuclear cells and granulomas formation. A variety of pro-inflammatory cytokines are released, and play an extensively important pathogenic role in the production of experimental granulomas, including interleukin-1 (IL-1), IL-2, IL-3, IL-12, interferon-□, granulocyte-macrophage colony-stimulating factor (GM-CSF), and CSF-1. The Gell and Coombs Type III and Type IV hypersensitivity reactions are probably not the best paradigm for explaining the immunological mechanisms that result in hypersensitivity pneumonitis. There is a lymphocytosis and generally CD8+ cells exceed the number of CD4+ cells in the BALF (bronchoalveolar lavage fluid). The patients appear to have some defect in the suppressor

function of CD8+ cells, suggesting an active modulation of granulomas formation. Individuals with more CD4+ cells are prone to develop fibrosis. Lymphocytes in BALF and bronchial biopsies have an increase in activation markers, such as Ia and CD25, on the cell surface. Macrophage activation has also been described. Increases in IL-8 and monocyte chemo-attractant protein-1 (MCP-1), a soluble form of intercellular adhesion molecules (sICAM), have been reported to occur in BALF. Activated macrophages and CD8+ cells incapable of suppressing these molecules are probably the immunogenetic mechanism driving the inflammation of hypersensitivity pneumonitis. [2,7]

In treating the acute and subacute phases, corticosteroids beginning with 1 mg/Kg prednisolone or its equivalent are often used to hasten recovery. [2] With avoidance from exposure and the administration of corticosteroids tapered over a several-week period, many individuals regain normal lung function if fibrosis has not already occurred. Avoidance of the etiologic antigen is the most important treatment. Masks, dust filters, respirators, and attention to the heating and air conditioning systems are all important. The patient may need to change occupations or move away from the living environment to eliminate the exposure completely. It is important to recognize the diagnosis as early as possible since fibrotic change can occur and is irreversible. There is no evidence that long-term steroid usage protects against lung damage from chronic exposure. [2, 11]

Conclusion

Hypersensitivity pneumonitis is an important occupational lung disease, which is caused by a variety of antigens. Early recognition with exposure avoidance can prevent irreversible processes. The disease is a *sequelae* of antigen exposure and no single diagnostic test, not even a lung biopsy, is pathognomonic for hypersensitivity pneumonitis. The diagnosis of hypersensitivity pneumonitis should be relatively straightforward, based on a consistent exposure history, physical examination, pulmonary function tests, chest radiograph, HRCT of the chest, temporal relationship to an antigen known to cause hypersensitivity pneumonitis, and precipitins to the causal antigens in the serum.

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過敏性肺炎—病例報告與文獻回顧

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過敏性肺炎，或稱外因性過敏性肺泡炎，是一種免疫反應性肺疾病。許多抗原可引起過敏性肺炎，包括微生物(黴菌、原蟲、細菌等)、動物性蛋白、昆蟲蛋白及某些低分子量無機化學物。臨床及病理上過敏性肺炎可分為三期：急性期、亞急性期及慢性期。急性期常表現發燒、咳嗽、全身不適等類似感冒的症狀。長期暴露在過敏抗原下(慢性期)，可導致體重減輕與肺纖維化。適度的治療與避免暴露過敏原方可根治肺部發炎。 持續性過敏原暴露可能導致瀰漫性不可逆的肺纖維化。

過敏性肺炎的診斷並無特殊的檢查方法。血清中存在對過敏原具特異性抗體(precipitins)對診斷雖有幫助，但陰性反應並不能排除診斷。急性及亞急性期胸部影像檢查可呈現毛玻璃樣型態或細微顆粒影像；慢性期可見瀰漫性網狀結節樣肺浸潤及肺纖維。肺功能檢查通常呈現侷限型通氣障礙及肺瀰散量低下。肺部巨噬細胞被活化及抑制型淋巴球(CD8+ lymphocyte) 無法抑制活化型巨噬細胞，可能是導致過敏性肺炎發炎反應的免疫機轉。

在急性及亞急性期，類固醇的使用可加速肺損傷的復原。避免致病抗原的繼續暴露，是預防慢性不可逆肺纖維化的唯一也是最重要的準則。*(胸腔醫學 2000; 15: 165-171)*

關鍵詞：過敏性肺炎，外因性過敏性肺泡炎

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DOTS－結核防治之最佳策略

江振源

DOTS 是世界衛生組織推薦的結核防治策略。DOTS-- Directly Observed Treatment, Short Course，不只是短程直接監督治療，不只是看著病人服藥，DOTS 是一個包括五大要項的配套策略：(1)結核防治之政治承諾，(2)痰塗片檢驗、因症就診之被動式病人發現法，(3)標準化之短程治療，且至少前兩個月之直接監督療法，(4)充足之藥物供應，(5)標準化之登記與通報系統。DOTS 源自於不當的治療比不治療更糟的觀念變革，以及國際抗癆暨肺病聯盟之國家結核防治典範計劃(Model National Tuberculosis Programme)之經驗累積。世界衛生組織於 1993 年史無前例地宣佈單一疾病--結核病之全球危機。至 1998 年底，採行 DOTS 的國家已增加到 119 個，DOTS 的涵蓋面已達全球 43%的人口。台灣每年約有一萬三千五百個新病人發病，結核疫情每十萬人口 61.3，而且原發性抗藥率逐步攀升，我們需要 DOTS 策略。*(胸腔醫學 2000; 15: 172-177)*

關鍵詞：DOTS，直接監督療法，結核病

前　言

DOTS 策略是世界衛生組織(World Health Organization)於二十世紀的最後十年，有鑑於全球結核防治之混亂與失焦，所提出之結核防治策略。DOTS 是結核防治策略的商標(brand name)，DOTS-- Directly Observed Treatment, Short Course，直接從字面上解釋其涵意，易生誤解。DOTS 不只是短程直接監督治療，不只是看著病人服藥，DOTS 是一個包括五大要項的配套策略[1]：

(1)結核防治之政治承諾(Government commitment to sustained TB control)，

(2)痰塗片檢驗、因症就診之被動式病人發現法(Case detection by sputum smear microscopy among symptomatic patients self-reporting to health services)，

(3)標準化之短程治療，且至少前兩個月之直接監督療法(standardized short-course chemotherapy for at least all confirmed sputum smear positive cases, with directly observed treatment (DOT) for at least the initial two months)，

(4)充足之藥物供應(A regular, uninterrupted supply of all essential anti-TB drugs)，

(5)標準化之登記與通報系統以進行結核防治計劃之評估(A standardized recording and reporting system that allows assessment of treatment results for each patient and of the TB control programme overall)。

DOTS 五大要項以政治承諾爲首。世界衛生組織 Director-General Dr. Gro Harlem Brundtland 說，結核防治工作之挑戰，政治性遠高於技術性[2]。結核防治工作之成功與否，其關鍵在於政治承諾。唯有承諾結核防治在施政上之優先性及緊迫性，結核防治之技術要件才能逐一落實。DOTS 之誕生，源自於不當的治療比不治療更糟的觀念變革，以及國際抗癆暨肺病聯盟(International Union Against Tuberculosis and Lung Disease, IUATLD)之國家結核防治典範計劃(Model National Tuberculosis Programme)之經驗累積。

不當的治療比不治療更糟

1978 年，Grzybowski 和 Enarson 發表論文論述結核防治的一個重要觀念變革：不當的治療比不治療更糟，不當的治療將使結核疫情更爲惡化[8]。

肺結核病人如果不治療，追蹤五年，約有 50%死亡、30%靠自身的免疫力痰陰轉、20%依然維持痰陽性之傳

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染狀態。1960 年代的一些開發中國家，接受化學治療的一些結核病人，追蹤兩年，死亡率下降至 13%，但痰陰轉率僅 62%，仍有 25%維持痰陽性之傳染狀態。不當的治療不只不能減少傳染源，治療之卻未將之治好，不只延長傳染的時間，並且導至抗藥性的產生。相對於此，在良好的結核防治下，如新加坡和加拿大，痰陰轉率達 85%以上，維持痰陽性之傳染病人則少於 5%，如此才符合減少傳染源之結核防治原則。

Karel Styblo 和 IUATLD Model Programme

從 1970 年代末期，IUATLD 之結核工作重點是爲開發中國家發展出一套國家結核防治典範計劃[9]。在瑞士、荷蘭、挪威、沙烏地阿拉伯等各國政府和非政府組織的支援下，在IUATLD的 Director of Scientific Activities, Karel Styblo 的領導下，此計劃首先試辦於坦桑尼亞(Tanzania)，其後推展於馬拉威(Malawi)、莫三比克(Mozambique)、和尼加拉瓜(Nicaragua)等九個結核疫情嚴重的開發中國家[1,6,9]。Styblo 利用既存的衛生機構，以涵蓋十萬至十五萬人口爲單位，設立防治站以進行結核病之診斷、治療、登記、與通報之作業。Styblo 以系統化的管理模式，取代混亂的個案發現和治療。

治療方式分爲長程治療和短程治療。長程治療之處方爲較便宜的 2 個月 isoniazid (INH)、thiacetazone (TH)、streptomycin(SM)繼之以 10 個月 INH、TH 的 12 個月治療；短程治療之處方爲較昂貴的 2 個月 INH、rifampin (RIF)、ethambutol (EMB)、pyrazinamide (PZA)繼之以 4 個月 INH、EMB、RIF 的 6 個月治療。執行結果長程治療之完治率不及 60%，而短程治療之完治率則提高到 80%以上，因而確立短程治療之優越性。

1991 年，接任 IUATLD Director of Scientific Activities 的 Donald A Enarson 發表專文，總結 IUATLD Model Programme 之經驗與原則如下[6,9]。

國家結核防治計劃成功的基本條件爲：(1)政府的政治承諾，(2)診斷與治療之物品與藥品的充足供應，(3)確保品質之顯微鏡檢服務網的建立(A network of microscopy centers with quality control)，(4)完整的個案登記與通報。具備以上條件，個案發現與治療成效將明顯改善，但是，唯有施行短程治療才能使完治率提高到足以對結核疫情產生衝擊效應。而要確保短程治療之成效，還有賴於：(1)治療初期之監督治療，(2)結核防治人員之適當的訓練與輔導，(3)短程治療之逐步推展(step-wise introduction of short-course chemotherapy)。在愛滋疫情擴張全球的時代，IUATLD 的 Model Program 爲失控的結核防治工作指出新的方向。

從漠視到醒悟

1990 年世界銀行(World Bank)估計低收入國家約有九百三十萬人死於各式各樣的傳染病：其中約一百二十萬人死於 malaria 和 schistosomiasis、leishmaniasis、Chagas disease 等熱帶疾病(tropical cluster)；二百九十萬人死於腹瀉之腸胃疾病，一百萬人死於麻疹，四百萬人死於急性呼吸道感染。而死於結核病者即高達二百萬人，居單一死因之冠[10]。但是國際組織包括世界衛生組織卻漠視結核防治幾近 20 年。1980 年代，在美國及西歐等已開發國家，結核疫情穩定下降，人們以爲根除結核爲期不遠，於是結核防治之經費刪減人員裁撤；而結核疫情嚴重的開發中國家，結核防治則未被列爲重點工作，人們以爲廣泛的施打卡介苗和使用一些廉價的藥物即可控制結核。1980 年代中期，世界衛生組織的結核防治成員僅僅剩下一位祕書和一位統計員[11]。1985 年起，美國結核疫情在愛滋病的衝擊下持續向上攀升[12]，間接促成了結核防治之醒悟。

世界結核疫情

世界衛生組織 TB Program 首席 Arata Kochi 於 1991 年發表世界衛生組織估計之全球結核疫情[13]：

(1) 全球已有三分之一人口感染結核桿菌。工業化國家和開發中國家感染結核之人口比例相近，但是，工業化國家 80%的感染者年齡大於 50 歲，而開發中國家 75%的感染者年齡小於 50 歲。

(2) 每年約有二百九十萬人死於結核病，結核是世上單一病原引起之最大死因。

(3) 每年新發病之結核病人高達八百萬人，95%在開發中國家。結核發生率以非洲最高(每十萬人口 272 人)。因爲人口眾多的關係，西太平洋區(WHO's Western Pacific Region)之結核病人數最多，東南亞區(South-East Asian Region)次之。

當時，世界各國有內建監測系統(built-in monitoring system)以掌握病人完成治療、死亡、和失落等情形之國家不到 15 個。許多開發中國家接受抗結核藥物治療之病人完成治療之比例不及一半。

從漠視到結核防治總動員

全球結核防治工作於九十年代開始大張旗鼓。世界衛生組織史無前例地於 1993 年宣佈單一疾病--結核病之全球危機(Global emergency)[14]，以策動全球結核防治

之總動員。世界衛生組織設定 70%個案發現率及 85%完成治療率爲公元 2000 年之工作目標。技術面則倚重 IUATLD Model Programme 之經驗，以擬定結核防治策略，並以 DOTS 之名將之品牌化。世界銀行於 1993 出版之世界發展報告(World Development Report)中評估各項衛生及醫療照護之議題， DOTS 是最具成本效益之項目之一[3]。世界銀行據之貸款給一些結核疫情嚴重之國家，推動 DOTS 結核防治策略。DOTS 策略是可行的，如中國大陸在 DOTS 下，1991 至 1994 年之 55,213 個新結核病人，其完治率高達 91.8%，57,629 個複治病人(relapse and retreatment cases) 之完治率也高達 84.4%[15]。世界衛生組織著手建立全球結核疫情之監視系統，並且對全球之結核菌之抗藥情形展開調查[16]。

DOTS 策略五大要項

細究 DOTS 策略之五大要項，其重點內容如下：

(1)結核防治之政治承諾：結核防治之政治承諾意謂著將結核防治提列爲施政計劃之重點項目之一。政治承諾具體反應在預算上，預算的編列及其比重可以反應施政的優先次序。政治承諾亦體現在適當的結核防治架構的建立[1,9]。

(2)痰塗片檢驗之被動式病人發現法：診斷與治療之評估必須立基於細菌學之檢查，並且必須建立鏡檢之品管系統(Diagnosis and follow-up of treatment must be based on bacteriological examination, with a system of quality control)。因症就診、懷疑罹患肺結核之病人應該驗三套痰[3]，以最直接而快速的方法診斷出結核病最重要的傳染源，痰塗片陽性者。痰塗片檢查是辨識傳染性結核病人之最佳工具[5]。迄今還沒有那一項新興之科技產物比痰塗片檢查更能區辨傳染性。因此要打斷傳染鏈，首要在於辨識最重要的傳染源，痰塗片陽性者。

(3)標準化之短程治療，及至少前兩個月之直接監督療法：採行標準化的病人分類及標準化的治療，方能確保治療之一致性與連續性(Table 1)。直接監督療法是治療過程中相當重要的一環，直接監督療法確保規則的治療，提高完治率，更重要的是保護 rifampin，避免抗藥性的產生[6]。直接監督療法降低續發性抗藥率(acquired resistance)，減少復發率，也導至原發性抗藥率(primary resistance)的下降[7]。

(4)充足之藥物供應：結核病之治療必須是免費的，必須確保每一個病人接受治療的權利。唯有建立完整的結核防治架構，同時編列充裕的經費，確保診斷與治療之物品與藥品的充足供應，才能確保每一個結核病人接受完整治療的權利。

(5)標準化之登記與通報系統：爲確保結核防治計劃之正確運作，必須依照國際共同確認之定義，訂定一標準化之登記與通報系統，以進行結核防治計劃之整體評估。計劃初期的新鮮與熱情會隨著時間而逐漸淡化，唯有規則定期的內在與外在的評估作爲反饋機制，針

Table 1* 各類結核病人之治療處方

治療之分類	結核病人	治療處方†	
		Initial phase	Continuation phase
第一類	痰塗片陽性之新肺結核病人，痰塗片陰性之新肺結核病人併肺部廣泛病灶者，嚴重型#之新肺外結核病人	2 EHRZ (SHRZ)	6HE
		2 EHRZ (SHRZ)	4HR
		2 EHRZ (SHRZ)	$4H_3R_3$
第二類	復發(relapse)、治療失敗、失落複治(treatment after interruption)之痰塗片陽性肺結核病人	2 SHRZE/1 HRZE	$5H_3R_3E_3$
		2 SHRZE/1 HRZE	5HRE
第三類	痰塗片陰性之新肺結核病人，非嚴重型§之新肺外結核病人	2 HRZ	6HE
		2 HRZ	4HR
		2 HRZ	$4H_3R_3$
第四類	經過監督複治(retreatment)依然痰塗片陽性之慢性開放病人	轉診專責機構接受二線藥治療	

*轉譯自 World Health Organization. Treatment Of Tuberculosis: Guidelines For National Programmes. Second Edition 1997. WHO/TB/97.220. Geneva, WHO, 1998.

†E=ethambutol, H=isoniazid, R=rifampin, Z=pyrazinamide, S=streptomycin, 2EHRZ=2個月每日一次EHRZ, $4H_3R_3$=4個月每週三次HR。

#嚴重型之肺外結核：meningitis, miliary, pericarditis, peritonitis, bilateral or extensive pleural effusion, spinal, intestinal, genito-urinary.

§非嚴重型之肺外結核: lymph node, pleural effusion (unilateral), bone (excluding spine), peripheral joint, skin.

對表現差異的地區要求解釋與說明，並且訂定修正計劃迅速做出反應，方能確保結核防治計劃之品質[9]。

推展 DOTS 之三個階段

推展 DOTS，第一步是討論與決定要不要採行 DOTS 策略。世界衛生組織之 Director General 於 1997 年宣佈 DOTS 是結核防治之重大突破(health breakthrough of the decade)，DOTS 是最有效的結核防治策略已怠無疑義。延宕愈久愈晚行動，就愈將成為結核防治之後進國家。

一旦決定採行 DOTS 策略，接下來是如何推展 DOTS，以及如何維護 DOTS 之品質。DOTS 策略之推展可分為三個階段[1]：(1)初始期(A pilot project phase)：必需妥善利用既存的醫療結構，首要工作是設置一些示範與訓練地區(demonstration and training districts)；(2)拓展期(An expansion phase)：以訓練、監督、和輔導為主，以示範與訓練地區作為其它地區人員之訓練場所，並且逐步拓展至其它區域；(3)維持期(A maintenance phase)：以新進人員之培訓和在職人員之複訓為重點，以因應人員之流動與汰換，並維持 DOTS 之執行品質。

世界衛生組織將全球分為六種國家[17]，第 0 類及第 1 類國家已愈來愈少：

第 0 類：未將結核防治情形通報給世界衛生組織之國家。

第 1 類：未採行 DOTS 策略、而結核通報個案率(notification rate)超過每十萬人口 10 人以上之國家。

第 2 類：採行 DOTS 策略，DOTS 之涵蓋率少於 10%人口之國家(Pilot phase)。

第 3 類：採行 DOTS 策略，DOTS 之涵蓋率為 10%-90%人口之國家(expansion phase)。

第 4 類：採行 DOTS 策略，DOTS 之涵蓋率超過 90%人口之國家(routine implementation)。

第 5 類：未採行 DOTS 策略、而結核通報個案率低於每十萬人口 10 人之國家(low incidence)。

至 1998 年底，採行 DOTS 的國家已增加到 119 個，DOTS 的涵蓋率已達全球 43%的人口[17]。Kochi 認為現在全球結核防治的歷史處境，和 1980 年代之全面性預防接種計劃(Expanded Programme on Immunization)十分相似：(1)一開始小型國家和中等國家很快就達成目標、許多大型國家卻進展緩慢、(2)策略已被廣為接受、(3)全球之注意力已經提昇。

結　語

全球現存約有一千六百萬個結核病人(point prevalence)，每年約有八百萬個新結核病人發病、包括三百五十萬(44%)個痰塗片陽性病人，約有兩百萬人死於結核病[18]。進入 21 世紀，我們打算怎麼面對結核病？台灣每年仍有約一萬三千五百個新病人發病，結核疫情每十萬人口 61.3[19]，而且原發性抗抗藥率逐步攀升[20]。我們有根除結核的理想嗎？結核防治是一個唐吉科德式的夢嗎[21]？鬆散的結核防治會使下降的疫情翻轉向上，而且是以抗藥性結核捲土重來。我們必需勇敢啟動新一輪的規劃與行動，將眼光投向遠方，而在靜定下來思考結核防治的時候，DOTS 是不可迴避的選擇。

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DOTS—The Most Effective Strategy For Tuberculosis Control

Chen-Yuan Chiang

DOTS (Directly Observed Treatment, Short-course) is the brand name of the WHO-endorsed tuberculosis control strategy. DOTS strategy has five components: (1) government commitment to sustained TB control, (2) case detection by sputum smear microscopy among symptomatic patients self-reporting to health services, (3) standardized short-course chemotherapy with directly observed treatment (DOT) for at least the initial two months, (4) a regular, uninterrupted supply of all essential anti-TB drugs, (5) a standardized recording and reporting system. The DOTS strategy was modeled after the program developed by Dr. Karel Styblo of the International Union Against Tuberculosis and Lung Disease. The issue of tuberculosis control has been ignored for more than 20 years by World Health Organization (WHO) when considering health priorities in low-income countries. The announcement by the WHO in 1993 that tuberculosis has become a global emergency was unprecedented. By the end of 1998, 119 countries had adopted the DOTS strategy for TB control; 43% of the global population had access to DOTS. There were 13,496 newly diagnosed TB cases with the incidence rate of 61.3 per 100,000 population in 1999 in Taiwan, and the antituberculosis drug resistance rate is increasing. We should implement DOTS strategy for tuberculosis control in Taiwan. ***(Thorac Med 2000; 15: 172-177)***

Key Words: DOTS, Directly Observed Treatment, tuberculosis

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呼吸衰竭病患使用壓力輔助控制通氣與容積輔助控制通氣的比較

李俊德

正壓呼吸器在臨床應用上甚為廣泛，現行使用的呼吸器常可提供多種不同的通氣模式，給予重症病患適當的呼吸照護。壓力輔助控制通氣是一種由病患或時間來驅動，經壓力限制及時間週期的運作，以完成通氣支持的呼吸型態，而傳統的容積輔助控制通氣則差別在以預設的潮氣容積及氣流速率來決定病患的吸吐比例。為了檢測壓力輔助控制通氣在呼吸衰竭但意識清晰的病患是否優於容積輔助控制通氣，我們進行此研究。20 位在加護病房中使用呼吸器的病患，若血流動態穩定且有驅動通氣能力者，即予壓力輔助控制通氣及容積輔助控制通氣各 45 分鐘，並分別記錄比較病患在使用這兩種通氣模式時的狀況變化。結果顯示，當病患使用壓力輔助控制通氣時，其血流動力變化、動脈血液氣體分析值及肺部機械功能的數據並未優於容積輔助控制通氣模式，反而在病患的主觀舒適上，容積輔助控制通氣較壓力輔助控制通氣模式為佳。

結論：臨床醫師在處理呼吸衰竭病患時，仍以容積輔助控制通氣模式為首要選擇。*(胸腔醫學 2000; 15: 178-182)*

關鍵詞：壓力輔助控制通氣，容積輔助控制通氣

前　言

正壓呼吸器的發展，約始於二次大戰時，先以壓力設定型態爲主，但因機械動力及最大氣流量的限制，造成許多使用上的不便。俟容積設定型態的呼吸器推出後，便大量取代了原先的壓力型呼吸器，也開創了呼吸治療的另一番天地。但自呼吸器的高容積或高壓力可能造成肺部的二度傷害引起重視之後，壓力設定型態的通氣模式又再度回到重症照護，且因經過改良，以往缺點不再，所以受到不少臨床醫師肯定。

新的壓力輔助控制通氣是一種由病患或時間來驅動，經壓力限制及時間週期的運作，而完成通氣支持的呼吸型態，由於吸氣流量方式固定爲漸降傾斜式，所以在吸氣初期可見到氣道壓力快速上升爲其特徵[1]。傳統的容積輔助控制通氣則差別在以預設的潮氣容積及氣流速率來決定病患的吸吐比例，且有多種吸氣流量方式可供選擇。在重症病患使用鎮靜劑及肌肉鬆弛劑以達到無自發呼吸的狀態下，壓力控制通氣及容積控制通氣是最常用的通氣型態，而兩者間的優劣比較至今尚無定論[2,3]。至於意識清晰但需使用呼吸器的病患，除了希望避免因使用機器而可能造成的併發症外，儘可能地顧及病患感受而適度調整呼吸設定也很重要。爲了檢測壓力輔助控制通氣在呼吸衰竭但意識清晰的病患是否優於容積輔助控制通氣，我們進行此研究。

材料及方法

本研究屬前瞻性、比較性，凡加護病房內病患插著人工氣道，使用侵犯性的正壓呼吸器且符合下列條件者，即列爲研究對象：(1)血流動態穩定，(2)意識清晰有自行帶動呼吸器能力，(3)沒有使用鎮定劑或肌肉鬆弛劑，(4)研究期間無明顯感染發燒現象。

所有被研究的病患都使用同一型呼吸器(7200ae, Puritan Bennett, USA)，並確定病患都有置放動脈導管以監測血壓並供抽取動脈血作氣體分析，連續心電圖監測心跳次數及心律不整，脈動測氧器可連續監測動脈血氧飽和度。將氣道流量導管連接上人工氣道近端及肺監視器(Bicore CP-100 pulmonary monitor)後，啓動監視器並

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作校定。

在生命跡象穩定狀況下，將每一病患依亂數次序分別先後使用壓力輔助控制通氣及容積輔助控制通氣法。壓力輔助控制通氣的設定如下：吸氣壓力足以保持潮氣容積約 10 毫升/公斤體重，呼吸次數每分鐘 10 次，吸吐氣比例值約 1/2；容積輔助控制通氣的設定如下：潮氣容積與呼吸次數同壓力控制通氣法，選用漸降頃斜式流量型態並調整流量速率使得吸吐氣比例值也接近 1/2。第一種通氣法之後，呼吸器設定回到原基準點，穩定後再進行第二種通氣法。測試期間氧氣濃度及吐氣末正壓值均不改變，各穩定通氣 45 分鐘後分別記錄病患的心跳次數、收縮血壓、舒張血壓、呼吸次數、潮氣容積、每分鐘通氣量、氣流速率、最高氣道壓力、平均氣道壓力、呼吸器呼吸功及吸氣時間與呼吸氣時間比值，同時從動脈導管抽取 0.5 毫升血液並立即打入分析儀(Premier, Mallinckrodt, USA)做血液氣體分析以得到動脈血氧氣分壓、動脈血二氧化碳分壓及酸鹼值。測試結束前一一詢問病患使用兩種通氣法時何者較舒適，因病患無法盡情表達，所以使用最簡單的詢問法:第一種舒適第二種不舒適;第一種不舒適第二種舒適;第一種舒適第二種也舒適;第一種不舒適第二種也不舒適，由病患點頭或搖頭表示之。若研究進行中病患無法適應而不願繼續，則隨時終止研究。

表一　病患基本資料

年齡	性別	氧氣濃度	診斷
61	女	0.30	慢性阻塞性肺疾病
69	男	0.30	急性胰臟炎
73	男	0.25	慢性阻塞性肺疾病
47	女	0.35	風濕性心臟病術後
76	男	0.35	肺炎
71	男	0.30	上腸胃道出血術後
80	女	0.30	急性腎衰竭
73	男	0.35	泌尿敗血症
57	男	0.30	肝硬化合併食道靜脈出血
76	男	0.30	泌尿敗血症
78	男	0.35	主動脈裂開
57	女	0.40	鬱血性心臟衰竭
73	男	0.30	心因性休克
79	男	0.45	肛邊膿瘍合併敗血症
77	男	0.30	上腸胃道出血術後
66	男	0.40	尿毒症
86	男	0.35	敗血症
43	男	0.35	空腸破裂術後
56	女	0.35	敗血症合併腎衰竭
78	女	0.40	擴張性心肌病變

統　計

所有被研究者的各項係數最後以平均值± 標準偏差來表示。壓力輔助控制通氣法及容積輔助控制通氣法二組間的係數差異以 Student's t-test 來檢視，何者較舒適則以卡方檢定比較，均以 $p<0.05$ 視爲有統計學上意義。

結　果

合於條件且完成研究的病患共計 20 位，其中男性佔 14 位，女性 6 位，平均年齡 68.8± 11.6 歲(43~86 歲)，使用氧氣濃度平均 0.34± 0.05(0.25~0.45)。(表一)

在血流動力變化上，使用壓力輔助控制通氣及容積輔助控制通氣時，病患的心跳次數及血壓並無明顯變化。動脈血液氣體分析也顯示，使用二種不同的通氣型態時，氧合狀況(PaO_2/FIO_2)、二氧化碳分壓及酸鹼值的差異沒有統計學上意義。(表二)

在呼吸及肺生理變化上，只有吸氣時間與吸吐氣時間比值在容積輔助控制通氣時較小，以及呼吸器呼吸功在容積輔助控制通氣時較大外，其餘如病患的呼吸次數、潮氣容積、每分鐘通氣量、氣流速率、最高氣道壓力及平均氣道壓力在二組間均無差別。(表三)

當問及病患二種通氣法何者較舒適時，14 位認爲兩種沒有差別，2 位表示容積輔助控制通氣較舒適，4 位則覺得都不舒服。(表四)

表二　病患的血流動力變化及動脈血液氣體分析結果

	壓力輔助控制通氣	容積輔助控制通氣	p-值
心跳次數 (beats/min)	93± 21	92± 19	NS
收縮血壓 (mmHg)	154± 30	150± 33	NS
舒張血壓 (mmHg)	68± 14	66± 14	NS
氧合指數 PaO_2/FIO_2(mmHg)	314.5± 78.2	318.6± 79.3	NS
動脈血二氧化碳分壓(mmHg)	29.5± 8.4	28.8± 8.4	NS
動脈酸鹼值	7.43± 0.05	7.43± 0.06	NS

NS:無統計學差異

表三 病患的呼吸及肺生理變化

	壓力輔助控制通氣	容積輔助控制通氣	p-值
呼吸次數 (breaths/min)	16± 5	16± 5	NS
潮氣容積 (L/breath)	0.73± 0.19	0.69± 0.08	NS
每分鐘通氣量 (L/min)	11.8± 3.2	10.9± 3.9	NS
氣流速率 (L/sec)	0.64± 0.21	0.65± 0.20	NS
最高氣道壓力 (cmH_2O)	26.9± 6.6	23.9± 7.2	NS
平均氣道壓力 (cmH_2O)	11.6± 2.7	10.9± 3.4	NS
呼吸器呼吸功 (L/joule)	1.70± 0.36	1.85± 0.42	$p<0.01$
吸氣時間/呼吸氣時間	0.42± 0.14	0.37± 0.13	$p<0.05$

NS:無統計學差異

表四 病患使用壓力輔助控制通氣與容積輔助控制通氣的舒適比較(以卡方檢定二組間差異結果$p < 0.05$)

舒適 \ 模式	壓力輔助控制通氣	容積輔助控制通氣	合計
是	14	16	30
否	6	4	10
合計	20	20	40

討論與結論

壓力型或容積型通氣模式一直是正壓呼吸器發展史上的兩大主流，如何選擇適當的輔助方式來幫助呼吸衰竭的病患，是呼吸治療從業人員最基本的課題。

就方便性及經濟面而言，容積輔助控制通氣模式是現今市場上每一部呼吸器的基本裝備，而壓力輔助控制通氣模式常被列爲"功能"配備。就本院而言，配有壓力輔助控制通氣模式的呼吸器數量僅佔所有呼吸器約四分之一，若堅持非使用壓力輔助控制通氣模式不可，便常造成使用調度上的困擾。

以臨床效果而論，許多研究均顯示容積通氣模式與壓力通氣模式對血流動態的影響都不大[4]，但在氧合及氣道高壓上有少數報告認爲壓力通氣模式較佳[3,5]，但進一步的研究則指出，其間的差異可能由於吸氣流量方式不同導致[6-8]。在本研究中，容積輔助控制通氣使用與壓力輔助控制通氣相類似的漸降傾斜式流量波形，即無二者間在氧合及氣道高壓上的差異，似也印證了此理論。

本研究結果顯示，若設定適當，壓力輔助控制通氣模式在血流動力變化、動脈血液氣體分析值及肺生理變化上並未明顯優於容積輔助控制通氣模式，反而當被詢及使用時的舒適度比較時，病患覺得容積輔助控制通氣模式略優於壓力輔助控制通氣模式，這可能與接受容積輔助控制通氣時，吸氣時間與吸吐氣時間比值較小使得病患容易在短時間內得到氣體，且呼吸器呼吸功較大，所以病患較不費力有關[9,10]。病患使用呼吸器時，客觀的舒適度可用血壓、心跳及呼吸次數等變化予以判斷，而主觀的舒適度尚未有人做過類似研究，我們也是第一次嚐試，但因病例數不多，有待日後更大型的研究證實及討論。

我們的結論是：臨床醫師在處理呼吸衰竭病患時，仍可以容積輔助控制通氣模式爲首要選擇。

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Comparison of Pressure Assist-Control Ventilation and Volume Assist-Control Ventilation in Patients with Respiratory Failure

Jiunn-Der Lee

Positive pressure ventilation has gained wide application in clinical medicine and currently available ventilators provide many different ventilatory modes for use in the critical care settings. Pressure assist-control ventilation (PACV) is a patient- or time-triggered, pressure-limited, time-cycled mode of ventilatory support, characterized by a rapid increase of airway pressure with a decelerating inspiratory flow pattern. To ascertain whether PACV offers any advantage in comparison with volume assist-control ventilation (VACV) in clearly conscious patients with respiratory failure, we study 20 patients with ventilatory support in intensive care unit. Patients are awake and hemodynamically stable without use of sedative or muscle relaxant. Each patient is ventilated with PACV and VACV, in random sequence, for 45 min. respectively. The results show that no evidence of the benefit with PACV in comparison with VACV on hemodynamic effect, blood gas exchange and lung mechanics. Patients feel more comfortable when using VACV than PACV.

We conclude that VACV is still a mode of first choice in the management of patients with respiratory failure. ***(Thorac Med 2000; 15: 178-182)***

Key Words: Pressure assist-control ventilation (PACV), Volume assist-control ventilation (VACV)

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Clinical and Radiological Manifestations of Pulmonary Sequestration

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Pulmonary sequestration is a rare congenital pulmonary disorder defined as an area of dysplastic and non-functioning pulmonary tissue with an anomalous systemic blood supply. In the past 11 years, we have identified 5 cases of pulmonary sequestration in National Cheng Kung University Hospital. Two patients had extralobar sequestration (ELS) and three patients had intralobar sequestration (ILS). All the ILSs were in the left lower lobes. The two patients with ELS were a neonate and a 13-year-old. The neonate presented with congenital pleural effusion which required repeated chest tapping, and the 13-year-old boy presented with right hemothorax with chest pain. Among the patients with ILS, 2 suffered from chronic cough and the third one presented with hemoptysis. A preoperative diagnosis of pulmonary sequestration was made in three patients after the computerized tomography scan of the chest, and the final diagnosis of these five patients was confirmed by operation and pathological findings. The prognosis after operation was good in all patients. ***(Thorac Med 2000; 15: 183-188)***

Key words: pulmonary sequestration, hemoptysis, hydrothorax, hemothorax, Spiral computed tomography

Introduction

Pulmonary sequestration is an extremely rare congenital anomaly characterized by a non-functioning abnormal lung parenchyma that has no connection with the tracheobronchial airway, and receives its blood supply from a systemic artery [1]. Sequestrations are found in two forms: (1) intralobar sequestration (ILS), in which abnormal lung tissue is found within the normal lung, and (2) extralobar sequestration (ELS), in which the sequestered portion of the lung completely separates from the normal lung and has its own pleural investment. The diagnosis is usually not made until the operation. In this report, we review the clinical manifestations and radiological images of 5 patients with pulmonary sequestration seen over a period of 11 years at National Cheng Kung University Hospital, and emphasize the clinical manifestations and the preoperative diagnosis by spiral computerized tomography (CT) scan.

Patients and Method

We reviewed the medical records of patients at our Medical Center who were diagnosed as pulmonary sequestration, from December 1988 to December 1999. Data obtained included: age, sex,

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clinical symptoms and signs, location of the pulmonary sequestration, and findings of the radiological examinations. All the diagnoses of pulmonary sequestration were confirmed by operation and pathological findings.

Results

During the past 11 years, five patients with pulmonary sequestration were confirmed by surgical operation and pathological diagnosis. Two of them had ELS and three had ILS. The two patients (patients 1 and 2) with ELS were younger (aged 0 and 13 years) than the three patients (patients 3, 4, and 5) with ILS (their ages ranged from 26 to 38 years old) (Table 1).

Regarding the clinical manifestations, patient 1 (ELS) was noted to have had massive left side pleural effusion since the gestational age of 28 weeks. He had received chest tapping 4 times before birth. Due to severe respiratory distress just after delivery, chest tapping was performed immediately, yielding effusion which was transudate in nature. Patient 2 (ELS) experienced right chest pain. The chest radiograph revealed right-side pleural effusion, and tapping disclosed hemothorax. There was no trauma history, malignant tumor, coagulation defect or other cause of hemothorax which could be found. Patients 3 and 5 (ILS) presented recurrent pulmonary infections requiring antimicrobial therapy. Patient 4 presented with recurrent hemoptysis for several months before operation.

Two patients (patients 1 and 2) underwent chest sonography; both revealed pleural effusion and intrathoracic mass, but an anomalous artery could be demonstrated in patent 1 only. The baby also received a MRI examination, but the result was disappointing due to motion artifact even

Table 1. Clinical data and radiologic results in 5 patients with pulmonary sequestrations

Patient	1	2	3	4	5
Age	1 day	13 y/o	26 y/o	36 y/o	38 y/o
Sex	Male	Male	Female	Male	Female
Type	ELS	ELS	ILS	ILS	ILS
Location	LLL	RLL	LLL	LLL	LLL
Symptoms	Respiratory distress	Right chest pain	Chronic cough	Hemoptysis	Chronic cough
Feeding artery	Thoracic aorta	R't intercostal artery	Thoracic aorta	Thoracic aorta	2 arteries from thoracic aorta
CXR	L't pleural effusion	R't pleural effusion	LLL opacity	Retrocardiac opacity	Retrocardiac opacity
CT	Sequestration	RLL mass & pleural effusion	Sequestration	R/O pulmonary varix	Sequestration*
Sonography	LLL mass, artery from aorta	R't intrathoracic mass	-	-	-
MRI	LLL mass	-	-	-	-

*: Patient 5 received CT scanning for 2 times. The first time (conventional) CT only disclosed LLL mass. The second time spiral CT angiograph showed 2 feeding arteries and the one draining vein.

- : not done

though the CT scan and sonography both disclosed an abnormal systemic feeding artery. All 5 patients received CT scans, and 3 of them were diagnosed with pulmonary sequestration preoperatively. The conventional chest CT only disclosed a left lower lobe lung mass in patient 5, but the spiral CT angiography (Fig.1-3) could demonstrate both aberrant feeding arteries (two arteries from the thoracic aorta) and one drainage vein (the hemiazygos vein). All three patients with ILS and the one patient with ELS had a systemic artery supply to the sequestration from the thoracic aorta. In the other patient with ELS, the anomalous artery arose from the intercostal artery. All three ILSs were located in the left lower lobe, one ELS was located in the right lower lobe, and the other ELS was in the left lower lobe. All five patients survived after operation.

Discussion

Pulmonary sequestration was first described by Pryce in 1946 to indicate a disconnected bronchopulmonary mass or cyst with an anomalous systemic arterial supply [2]. Since this original description, investigators have recognized many variants of sequestration not strictly meeting the original definition. In 1974, Sade [3] used the phrase "spectrum of pulmonary sequestration" to describe this rather diverse group of pulmonary abnormalities: normal vessels supplying abnormal lung at one end and abnormal vessels supplying normal lung at the other end.

Based on its relationship to the normal lung parenchyma, sequestration can be divided into intralobar or extralobar types. Intralobar sequestration is the most common form of classic pulmonary sequestration, accounting for 75 percent of the cases. The large majority of cases (98%) occur in the lower lobes, usually on the left side. All the ILS in this study involved the left lower lobe. The arterial supply for intralobar pulmonary sequestration usually arises from the descending thoracic aorta (73%), other sources are the upper abdominal aorta, celiac or splenic arteries, etc. In 95% of the cases, the venous drainage is to the left atrium via the pulmonary veins; others are to the systemic circulation via the azygos vein, the hemiazygos vein, etc. [4]. Most patients with ILS have clinical manifestations of cough, sputum production, and recurrent pneumonia. Two of the three patients with ILS in this study presented chronic cough. Another adult with ILS presented with the unusual symptom of recurrent hemoptysis. Fatal massive hemoptysis secondary to intralobar sequestration has also been reported before [5].

A majority of ELS cases develop symptoms in the first 6 months of life, often presenting in the first day after birth with dyspnea, cyanosis, and feeding difficulty. More than 80% of ELSs receive their arterial supply from the thoracic or abdominal aorta; and the arterial supply of the other 15% is from smaller arteries (such as the splenic, gastric, subclavian, or intercostal arteries). Like ILS, most cases of ELS occur on the left side [4]. Our patient 1 (ELS) had received chest tapping 4 times before birth and an immediate chest tube drainage after birth due to transudative left pleural effusion. The use of antenatal therapy (thoracocentesis or shunt placement) has been associated with a good prognosis in antenatally-diagnosed pleural effusion [6]. However, an ELS with a unilateral transudative pleural effusion is rare. Only 7 cases of congenital pleural effusion associated with ELS have been described in the literature [6-12]. The other ELS patient reported herein developed hemothorax. To our knowledge, spontaneous hemothorax in ILS is exceedingly rare [13], and in ELS only one case has been previously described [14].

Plain radiographs of the chest in pulmonary sequestration often show abnormal lung or vascular shadows that suggest the diagnosis. The usual presentation is a single homogeneous opacity or a cystic mass involving the base of one lung. In fact, any persistent abnormality in the posteromedial basal segment of a lower lobe in a

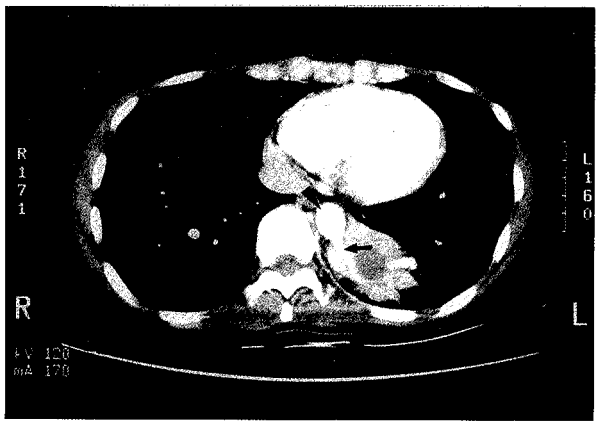

Fig. 1. Spiral CT of patient 5 shows a systemic artery (arrow) from the thoracic aorta (arrowhead) feeding the pulmonary lesion in the left lower lobe

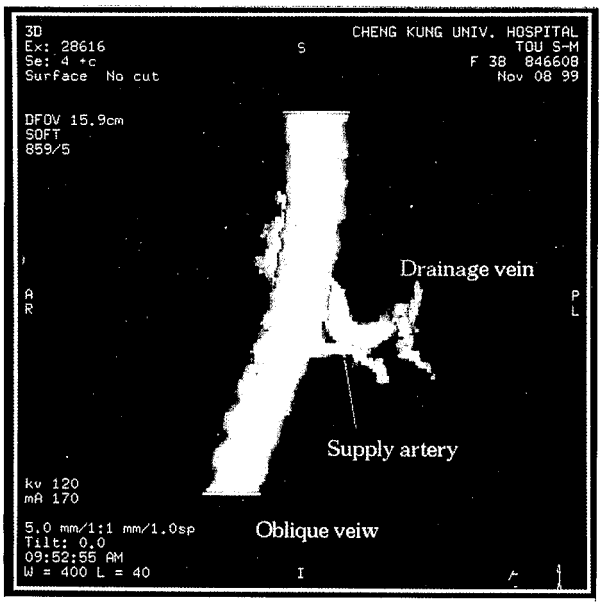

Fig. 2. Three-dimentional reconstruction of the descending aorta shows the supply artery and drainage vein in patient 5.

child or young adult should suggest sequestration [4]. Traditionally, the diagnosis of pulmonary sequestration has been made definitively with angiography to demonstrate aberrant blood vessels supplying the sequestered lung. Ultrasound was proved to be useful in evaluating chest mass in children, and several reports have even demonstrated the prenatal sonographic diagnosis of pulmonary sequestration. However, the sonographic detection of the feeding artery may be technically problematic with difficulty arising if the feeding arteries are from the thoracic aorta above the diaphragm or from an intercostal artery [15]. Some papers have advocated MRI or MR angiography instead of traditional angiography for diagnosing pulmonary sequestration [16,17]. However, the MRI may have some clinical limitations, such as those patients with a pacemaker or metallic device, greater expense, or a longer examination time with poor tolerability. Our patient 1 had received a MRI, but the aberrant feeding artery was not shown due to motion artifact.

Furthermore, with the advent of helical technology, which allows rapid acquisition through an entire anatomic region during the holding of a single breath, the role of CT in evaluating suspected pulmonary sequestration is being reconsidered [18, 19]. Helical CT has several advantages over conventional CT, Doppler sonography, and MR imaging :volume acquisition (slice reconstruction, multiplanar and three-dimensional reformation), faster scanning (reduced need for sedation and IV contrast media), and the ability to evaluate lung parenchyma and the airways. Helical CT coupled with dynamic intravenous contrast material bolus enhancement has enabled the development of CT angiography, a well-recognized and reliable technique for the obtaining of excellent anatomic detail of the aorta and its branches. In our experience of these 5 patients, conventional CT was performed in all 5 of our patients and only 2 patients' CT scans disclosed the anomalous artery. One patient (patient 5) received spiral CT angiography after a non-diagnostic conventional CT, and the spiral CT showed 2 anomalous feeding arteries and one draining vein (Fig 1-3).

In conclusion, pulmonary sequestration is rare despite the progress of imaging techniques. The preoperative finding of an anomalous feeding artery to the lung lesion is diagnostic and essential to prevent unexpected massive bleeding during operation. Spiral CT angiography is considered to be the diagnostic technique of choice in pulmonary sequestration and prognosis

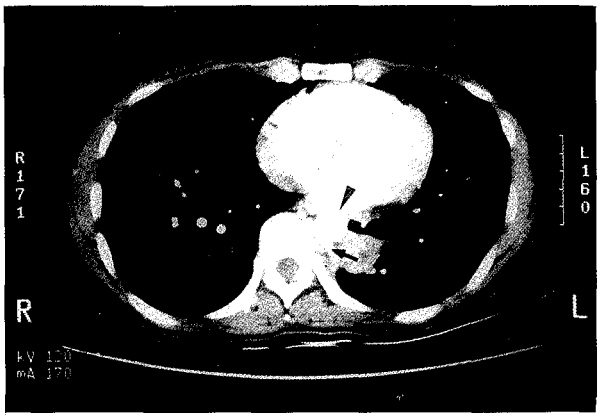

Fig. 3. Spiral CT shows the drainage vein (arrow) to the hemiazygus vein in the same patient.

is usually good after operation.

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游離肺之臨床和影像學上之表現

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游離肺是一種少見的先天性肺部異常，它是一種無功能的肺組織而有異常的系統性動脈血流供應。解剖上它可分為 (1)肺葉內型: 游離肺存在正常的肺葉之內 (2)肺葉外型: 游離肺在正常的肺葉之外，並有其個別的肋膜包覆。我們醫院 11 年來經開刀及病理證實共有 5 名確定病例，其中 2 例是肺葉外型，3 例是肺葉內型。全部肺葉內型病例均位於左下肺葉，其中兩人表現為慢性咳嗽，另一人表現為復發性咳血。此三人之年齡在 26-38 歲間。2 個肺葉外型病人年紀都很輕，一為剛出生，一為 13 歲。這新生兒是以先天性肋膜腔積水來表現，並且在母體內時即曾接受過 4 次抽胸水; 另外那 13 歲男孩是以血胸來表現。此五位病人有三位在手術前經由電腦斷層攝影已診斷為游離肺。全部病人接受手術後預後均良好。*(胸腔醫學 2000; 15: 183-188)*

關鍵詞：游離肺，咳血，水胸，血胸，電腦斷層

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哮喘或慢性阻塞性肺疾之門診患者不正確使用霧氣治療之評估

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霧氣治療對於氣喘患者是相當經濟、方便且有效的治療。治療效果的好壞取決於吸入器的設計和人為操作的正確性。常用之吸入器有兩種: 1) 定量噴霧吸入器 (metered-dose inhaler，MDI)；與 2) 乾粉式吸入器(dry-power inhaler，DPI)。有研究報告指出患者常有明顯誤用吸入器的情形。本研究之目的是在評估患有哮喘或慢性阻塞性肺疾之門診患者對於定量噴霧吸入器與乾粉式吸入器是否能正確的操作。

研究對象為南部某醫學中心胸腔科門診患有哮喘或慢性阻塞性肺疾之患者 75 人。實施方法為觀察與記錄患者對於定量噴霧吸入器與乾粉式吸入器 (包括準納乾粉定量吸入器, Accuhaler 及易吸乾粉定量吸入器, Easyhaler)的各個操作步驟，能否正確達成，而予以評分。並依操作評比將受測者區分為良好、普通與不好之等級，來比較不同吸入器的差異。

結果顯示有相當高比率的患者 (定量噴霧吸入器 76%，乾粉式吸入器 58%)未能良好的操作各種吸入器。常見之共同錯誤步驟是在吸藥前未能將氣儘量吐出以及吸藥後未能閉氣；操作定量噴霧吸入器另外之缺點在於未能達到手啓動-吸氣協調；而乾粉式吸入器則是未能快速的深吸氣。統計上，患者能良好操作乾粉式吸入器(Accuhaler)的比率比其使用定量噴霧吸入器者有顯著的增加 (48% vs 24%, p=0.002)；反之，在操作不好的患者中，其使用定量噴霧吸入器的比率比使用乾粉式吸入器(Accuhaler)者亦有顯著的增加 (17% vs 7%, P=0.044)。

要正確使用吸入器需仰賴於正確的衛教示範與個人的反覆練習。研究顯示氣喘患者對於吸入器的操作確有加強的必要。面對推陳出新的吸入器，醫護人員當把握各進修機會充實霧氣治療的技能，才能提供患者正確的衛教，而獲得最有效的治療。*(胸腔醫學 2000; 15: 189-194)*

關鍵詞：霧氣治療，定量噴霧吸入器，乾粉式吸入器

前　言

霧氣治療(aerosol therapy)指呈液態或固態微粒狀態的藥物懸浮在空氣中，經呼吸道吸入用來治療肺部疾病[1]。霧氣治療對於呼吸道疾病的作用較口服藥物更快速，所需要的劑量比口服或注射途徑少得多，也較不會引起不必要的副作用，因此在哮喘(asthma)及慢性阻塞性肺疾(chronic obstructive pulmonary disease，COPD)的患者，霧氣治療均被視爲一方便、有效的給藥方式。目前常使用之吸入器(inhaler)有兩種: 1)定量噴霧吸入器 (metered-dose inhaler，MDI)；與 2)乾粉式吸入器 (dry-power inhaler，DPI) [2]。一個好的吸入器需具備以下特點：所有患者均容易使用、且可隨拿隨用、多劑量型、容易攜帶與有藥物餘量顯示。影響吸入藥物在呼吸道沉積的因素包括有吸入粒子的大小，呼吸型態與呼吸道疾病等[3]。臨床上有效的吸入粒子大都介於 1-10 微毫米之間[4]，而呼吸的型態包括吸氣的速度、吸氣後的閉氣、和呼吸的潮氣容積都會影響吸入藥物到達呼吸道的位置。因此要增加藥物粒子沉積在呼吸道內的機會，就需要正確且熟練的操作技巧，才可將約 8-15% 的噴出藥物吸到肺部[5]。

研究報告指出無論門診或住院患者均有明顯誤用(misuse)吸入器的情形[6-7]，也有報告指出醫護人員亦有不適當使用吸入器的可能[8-9]。誤用的結果可導致降低效力、增加副作用及增加非必要使用之藥物浪費。本研究是對於門診之哮喘或慢性阻塞性肺疾患者，探討其對

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表一 各吸入器操作步驟的評估表

步驟	定量噴霧吸入器(MDI)	乾粉式吸入器(DPI)	
		Accuhaler	Easyhaler
1	取下蓋子、搖晃噴霧器	旋轉開蓋子	取下蓋子、垂直握住
2	垂直握住	拉下把桿	先按下吸入器乙次
3	儘量將氣呼出[1]	儘量將氣呼出[1]	儘量將氣呼出[1]
4	噴霧器置於口腔前 2-4 公分或用嘴含住銜口器[2]	含住銜口器	含住銜口器
5	開始吸氣並壓下噴霧器乙次	用力且快速深吸氣	用力且快速深吸氣
6	持續緩慢且深吸氣	離開銜口器，	離開銜口器，
7	摒住呼吸 5-10 秒	摒住呼吸 5-10 秒	摒住呼吸 5-10 秒
8	緩慢吐氣，必要時待 30 秒再作第二次吸入治療	緩慢吐氣，必要時待 30 秒再作第二次吸入治療	緩慢吐氣、必要時待 30 秒再作第二次吸入治療

[1]吐氣到功能性殘餘肺容積(FRC) 或 殘餘肺容量(RV)

[2] 另可加一儲藥腔(spacer)在銜口器上

於霧氣治療之各種吸入器的使用情形，以強調正確衛教與操作指導的重要性。

方 法

本研究是於南部某醫學中心胸腔科門診所作之評估。對象爲七十五位罹患有哮喘或慢性阻塞性肺疾之患者。所有受測者的診斷均基於臨床表徵與肺功能檢查而確立。醫師於門診開立霧氣治療 (定量噴霧吸入器或乾粉式吸入器)之處方後，門診護士均有對患者實施吸入性治療之衛教。所使用之定量噴霧吸入器爲 Atrovent (Boehringer Ingelheim，Germany) 或 Ipradol (Hafslund Nycomed，Austria)；所使用之乾粉式吸入器爲 Accuhaler (準納乾粉定量吸入器，GlaxoWellcome, UK) 及 Easyhaler (易吸乾粉定量吸入器；Orion, Finland)。每一患者至少均有使用定量噴霧吸入器或乾粉式吸入器兩個月的經驗後，於門診回診時，再予以測試評估其對定量噴霧吸入器或乾粉式吸入器實際操作之情形。

受測患者均由受過專業訓練的護理師來實施評估，其評估是依各吸入器使用之標準程序來訂定。(表一) [10] 測試步驟爲直接觀察受測者操作不同吸入器 (定量噴霧吸入器、乾粉式吸入器) 的情形。依據受測者在不同吸入器操作中實際正確完成的步驟數來評分。若受測者能正確完成每一步驟，則該項目給與 1 分；反之，不正確操作、或跳過某一項步驟，則該項目給與 0 分。對於各吸入器的操作評比可分爲三個等級：良好 (正確步驟達到 7 或 8 個)、普通 (正確步驟達到 4 或 5 或 6 個)以及不好 (正確步驟在三個或以下)。

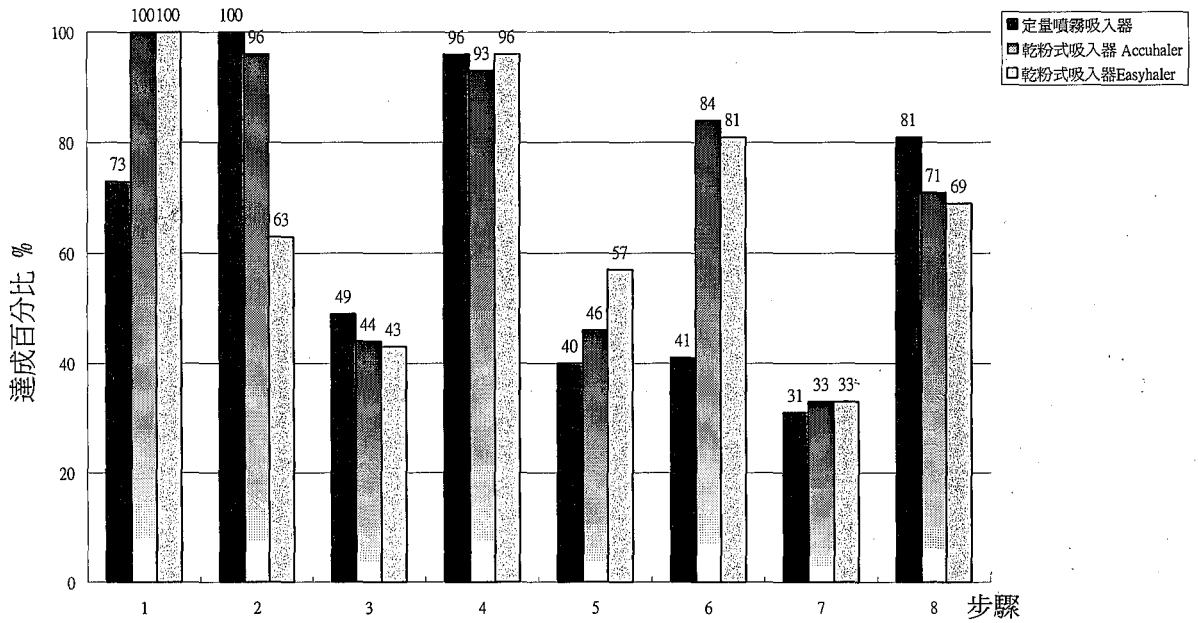
不同吸入器操作得分的評比(良好、普通、不好)是以 Chi-Square tests (SPSS v8.0)分析來比較； p 值小於 0.05 視爲有意義差別。

結 果

研究對象計有 75 個患者，包括 35 個哮喘與 40 個慢性阻塞性肺疾，平均年齡爲 57 歲 (範圍 18-74 歲)。觀察患者在使用定量噴霧吸入器 (Ipradol 或 Atrovent) 與乾粉式吸入器 (Accuhaler 與 Easyhaler)時，各操作步驟能正確達成的百分比如（圖一）所示。結果顯示使用定量噴霧吸入器最常呈現的問題是 1) 吸氣後沒有摒住呼吸；2) 吸氣-啓動之間無法協調配合；3) 吸藥前未能盡量把氣吐出；以及 4) 使用前未能搖混均勻。而使用乾粉式吸入器主要的問題在於 1) 吸氣後沒有摒住呼吸；2) 未能快速且深吸氣；以及 3) 吸藥前未能盡量把氣吐出。Easyhaler 的使用亦可發現不必要之吸氣-啓動協調。無論定量噴霧吸入器或 Easyhaler 的使用，在步驟八均可發現的錯誤爲含住銜口器後連續吸入藥物而沒有間斷，而造成藥物不當的使用。

受測者對於不同吸入器之正確操作步驟數的評比如（表二）所示。就使用定量噴霧吸入器而言，只有近 24% 患者能達到操作良好的程度，甚至有近 17 % 的患者根本無所適從，錯誤百出。至於乾粉式吸入器，其操作程序較爲簡單，因此平均有 42% (Easyhaler，36%；Accuhaler，48%) 患者能達到操作良好的程度，而操作不良者約爲 9% (Accuhaler 7%；Easyhaler 12%)。統計上，

圖一　使用不同吸入器時，正確操作各步驟的百分比



患者能良好操作乾粉式吸入器(Accuhaler)的比率比其使用定量噴霧吸入器者有顯著的增加 (48% vs 24%, p=0.002)； 反之，在操作不好的患者中，其使用定量噴霧吸入器的比率比使用乾粉式吸入器(Accuhaler)者亦有顯著的增加 (17% vs 7%, P=0.044)。兩種乾粉式吸入器(Accuhaler 與 Easyhaler)在操作評比上，無統計上差異。

討　論

在 1956 年，第一個定量噴霧吸入器 (metered dose inhaler，MDI) 的商品- Medihaler 問世，爲哮喘與慢性阻塞性肺疾的治療開創新的紀元[2]。爾後針對患者吸入動作無法協調配合與推進劑 (propellant) 所造成的污染等問題逐漸改進，而有新的產品，如各式吸入輔助器 (auxiliary device 或稱 spacer 儲藥腔、延長腔)、呼吸引動式定量噴霧器 (breath-actuated MDI)、非氟氯化碳定量噴霧器 (non-chlorofluorocarbon MDI) 以及乾粉式吸入器 (dry-powder inhaler，DPI)等。

定量噴霧吸入器的優點爲體積小、攜帶方便且價格低。其缺點在於藥物的吸入必需要病患能夠吸氣協調與閉氣，此對於急性氣喘發作的患者、手關節炎者以及年幼或年長者會有使用上的困難。利用一些輔助器例如延長腔[11]、或呼吸引動式定量噴霧吸入器等改變操作方法，使吸入的霧氣更容易進入肺內。在正確使用方法下，約 9-12%的噴出藥物能進到下呼吸道[12]。一般定量噴霧吸入器所使用的推進劑爲氟氯碳化物 (chlorofluorocarbon，CFC)，但氟氯碳化物會破壞大氣之臭氧層及造成溫室效應，故依據蒙特婁公約，將予以全

表二　不同吸入器之正確操作的評比

操作評比	數目(百分比)		
(正確操作步驟數)	MDI[1]	DPI[2] (Accuhaler)	DPI (Easyhaler)
良好 (7 or 8)	18 (24 %)#	36 (48 %)#	27 (36 %)
普通 (4 or 5 or 6)	44 (59 %)	34 (45 %)	39 (52 %)
不好 (≦ 3)	13 (17 %)@	5 (7 %)@	9 (12 %)

[1]MDI(metered dose inhaler):定量噴霧吸入器;

[2] DPI (dry powder inhaler):乾粉式吸入器，包括 Accuhaler, Easyhaler

操作 Accuhaler 評比良好的比率多於操作 MDI 者(p= 0.002)

@操作 MDI 評比不好的比率多於操作 Accuhaler 者 (p = 0.044)

面禁止使用[13]。

基於氟氯碳化物的污染與手啓動-吸氣不易協調的原因，所以乾粉式吸入器的發展迅速而倍受注意。目前市面上常見的乾粉式吸入器產品包括 Sphinhaler、Turbuhaler、Diskhaler、Accuhaler 及 Easyhaler。乾粉式吸入器的優點爲呼吸引動式 (breath-activated) 吸入器及不含氟氯碳化物。其缺點爲部分產品爲單一劑量裝置（如 Sphinhaler），較不方便；其次完全依靠吸力把藥粉吸入，有時對於年紀小、老年人或急性患者會造成吸入困難以及有些藥粉在潮濕環境下易凝結，故不宜對著銜口器吹氣，以免阻塞出口。研究顯示，定量噴霧吸入器與乾粉式吸入器的藥物吸入效果相當[13]。

目前霧氣治療已成爲哮喘及慢性阻塞性肺疾患者舒緩氣喘症狀的主要方法。由於治療效果與各種吸入器的操作是否正確有很密切的關係，所以如何加強患者對霧氣治療的認知與正確操作乃爲重要之課題。患者在使用各類吸入器之前，應先清楚所使用藥物的種類、作用、劑量、使用頻率，並能判定藥物存量。事實上臨床觀察常可發現在門診或病房看到許多病患不正確的使用各種吸入器。文獻報告在住院的氣喘患者中約有 47-79%的患者沒有能夠正確使用定量噴霧吸入器[6,15-17]；而門診中亦有 62-69% 的患者未能適當使用吸入器[9,15]。吾等的評估亦顯示門診之哮喘或慢性阻塞性肺疾患者有相當高的比率是不正確的使用霧氣治療，平均只有約 24% (定量噴霧吸入器) 到 42% (乾粉式吸入器) 的患者能良好使用吸入器。究其原因爲缺乏對患者做正確的衛教與示範或患者本身習慣於錯誤之操作步驟而不自覺。

一般定量噴霧吸入器與乾粉式吸入器常見之錯誤步驟是在吸藥前未能將氣儘量吐出以及吸藥後未能閉氣；而定量噴霧吸入器另外之主要缺點在於使用前未能充分搖混和未能達到手啓動-吸氣協調。雖然上市時間較久，較爲一般病患所熟悉操作，即使如此，能完整且正確操作者並不多。因此定量噴霧吸入器改進的方向包括加上儲藥腔(spacer)，使用呼吸引動式定量噴霧器 (breath-actuated MDI)以及改用非氟氯碳化物 (non-CFC) 推進劑，以減少污染。至於使用乾粉式吸入器之主要缺點在於未能快速的深吸氣以及容易對著銜口器吹氣。對於單一儲藥腔設計之乾粉式吸入器，如果對著銜口器吹氣，水氣容易造成藥物凝集而影響藥物吸出；另外 Easyhaler 也常出現多餘之手啓動-吸氣配合的步驟。整體而言，如同本研究結果所示，乾粉式吸入器的操作步驟較簡單而容易配合，因此較適用於對傳統式定量噴霧吸入器不適應之患者，然而面對多樣式的吸入器產品（如 Accuhaler、Easyhaler、Turbuhaler 與 Diskhaler 等），如果不熟悉就不能正確的使用，因此醫護人員必須負起正確指導之責任。

曾有多篇報告指出醫師、護理人員或藥師常不能正確的使用定量噴霧吸入器或乾粉式吸入器，即使是他們也常常開立或執行這一類的處方[8,18-20]。如果醫護人員對於完整的霧氣治療觀念及各種吸入器之正確操作步驟，本身尚且模糊又不熟悉，更遑論對病患作正確的示範，也就不能達到預期之治療效果。護理人員在門診常擔負起第一線之衛教工作，但文獻報告指出，只約 57-83% 護理人員能良好操作量噴霧吸入器[8,20]。因此護理人員除加強霧氣治療之知識與技能外，應如研究結果所顯示，針對患者容易疏忽的步驟加強衛教示範。另一提供住院或門診患者有關吸入器衛教的途徑爲採用衛教錄影帶，有研究顯示衛教錄影帶的效果並不會亞於個人衛教[21]。醫護人員對霧氣治療的認知與正確的衛教指導，無疑是達到有效霧氣治療所必需。

由於霧氣治療使用之劑量小、副作用低、肺部作用時間快且攜帶方便，因此很受臨床醫師與患者的歡迎與信賴，而吸入器操作正確與否則全視有否正確的衛教示範與個人的反覆練習。如同文獻所報告，本研究顯示的確有相當高比率的患者未能正確操作各種吸入器，尤其是定量噴霧吸入器。顯示患者在霧氣治療的認知與實際操作的正確性有再加強的空間。面對推陳出新的吸入器，醫護人員當保握各研討會與進修機會充實霧氣治療的知識與技能，以便能提供患者正確的衛教知識，而獲得最有效的治療。

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Evaluation of Misuse of Aerosol therapy by Patients with asthma or COPD in Outpatient settings

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Aerosol therapy is an economic, convenient and effective treatment for patients with dyspnea. The efficiency of the aerosol therapy depends on the design of the inhalers and correct performance of the patients. The major inhaler devices include 1) metered-dose inhaler (MDI), and 2) dry-powder inhaler (DPI). Many studies have demonstrated the misuse of aerosol therapy by the patients. The aim of present investigation was to evaluate the knowledge and skill of the patients with dyspnea in the proper use of aerosol therapy.

Seventy-five patients of asthma or COPD in the chest medicine clinic of a medical center in Southern Taiwan were included. They were assessed as to their proficiency in the use of MDI (including Ipradol and Atrovent) or DPI (including Accuhaler and Easyhaler). We recorded correct steps of each inhaler achieved by the patients and divided the patients into three groups: good, fair and poor according to the achievement. Statistical analysis was carried out to evaluate the difference between inhalers.

The study confirms that a large percentage of patients used MDI (76%) or DPI (58%) incorrectly. The most common problems were a) failing to keep breath–holding after inspiration, and b) failing to exhale out before drug inhalation. The other major problem in MDI was discordance between actuating and breathing; however, the problem in DPI was failing to breathe-in forcefully and deeply. Statistically, the incidence of good score in the performance of DPI (Accuhaler) was much higher than that in the MDI performance (48% vs 24%, p=0.002). Similarly, significant difference was also demonstrated between MDI and DPI (Accuhaler) performance in the groups of poor score.(MDI 17% vs DPI 7%, p=0.044)

Both correct demonstration and repeated practice are necessary to achieve proper performance of the inhalers. The physicians and nurses should try hard to learn each kind of new inhaler devices before the can demonstrate correctly to the patients. ***(Thorac Med 2000; 15: 189-194)***

Key words: aerosol therapy, metered-dose inhaler, dry-powder inhaler

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Pulmonary Nocardiosis—A Case Report

Chun-Chieh Yang, Jiunn-Min Shieh, Kuo-Hwa Chiang, Shiann-Chin Ko

Pulmonary nocardiosis is an infrequent but severe infection presenting with a variety of radiographic abnormalities. It is most common in immunocompromised patients or in those being treated with corticosteroid for chronic obstructive pulmonary disease or other systemic disease, but otherwise it may occur in healthy persons. Pulmonary nocardiosis is mainly acquired by direct inhalation of Nocardia spp. from contaminated soil, and presents as a subacute or chronic suppurative pulmonary disease. Norcardia is relatively difficult to culture and nocardiosis can coexist with diseases that are more easily diagnosed, so it is essential to make a proper diagnosis on the basis of a high level of suspicion and the full acknowledgement of the patient.

We report a patient with pulmonary nocardiosis who improved after sulfa drug and minocycline treatment. ***(Thorac Med 2000; 15: 195-199)***

Key words: pulmonary nocardiosis, corticosteroid, sulfa drug

Introduction

Nocardia species are a group of soilborne aerobic gram-positive and partially acid-fast branching, filamentous rods which cause a subacute or chronic suppurative disease, mimicking a lung carcinoma, tuberculosis or abscesses. There is no clinical syndrome that is pathognomonic of nocardiosis. Norcardia species are important members of the soil microflora worldwide and pulmonary nocardiosis is often acquired by direct inhalation of Norcardia spp. from contaminated soil.

Pulmonary nocardiosis is typically encountered in immunocompromised patients or in those being treated with anti-inflammatory drugs, especially corticosteroids or azathioprine for chronic obstructive pulmonary disease or other systemic disease. Nocardia asteroides is responsible for at least 80% of pulmonary nocardiosis. The treatment for nocardiosis includes sulfonamides, and more recently, trimethoprim-sulfamethoxazole (TMP-SMX), associated with surgical drainage when required. The combination of amikacin and imipenem is usually reserved for resistant strains or for patients allergic to sulfa drugs. Minocycline and amoxicillin-clavulanic acid are alternative medications.

Prognostic factors related to high mortality are associated with corticosteroid treatment and dissemination of the infection.

Mortality rates of 70% have been reported in patients with disseminated infection , especially when the central nervous system was

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involved, despite appropriate antibiotic treatment. Herein we describe a case of pulmonary nocardiosis in which the patient improved after sulfa drug and minocycline treatment.

Case Report

A 65-year-old male patient, who had had chronic obstructive pulmonary disease treated with theophylline and beta-2 agonist since July 1997, was admitted into the medical ward on March 10, 1999, due to dyspnea, fever, cough, and purulent sputum for 2 days.

Physical examinations showed a temperature of 38.5℃, a BP of 120/80 mmHg, pulse rates of 108 beats per minute, and a respiratory rate of 24 breaths per minute. Examination of the head, eyes, ears, nose, and throat showed anemic conjunctiva. The neck was supple with no enlarged lymph nodes. The heart sound was rapid and breathing sounds were rales over bilateral lower lung fields. The abdomen and lower extremity examinations were normal.

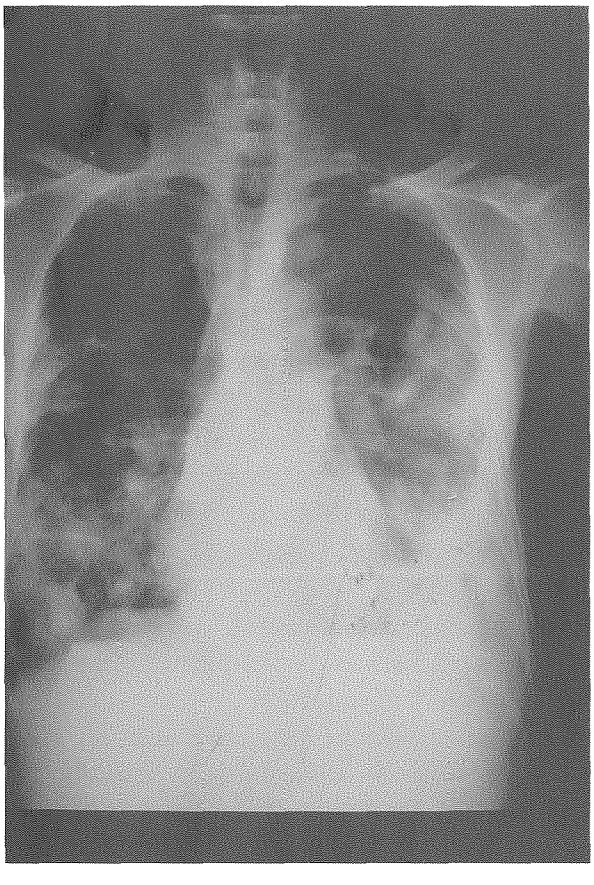

Fig.1. CXR Showed multiple nodular lesions and confluent alveolar infiltration in both lungs.

The laboratory data showed WBC 29,600/uL with a shift to a left differential count; Hct 27.0%; platelets 368,000/uL; blood sugar, liver function and electrolytes normal except for the renal function; blood urea nitrogen 43 mg/dl; and creatinine 1.7 mg/dl.

The chest X ray showed multiple nodular lesions and confluent alveolar infiltration in both lungs, with a predominance in both lower lung fields (Figure 1).

He received antimicrobial therapy with cefuroxime and gentamicin for 4 days, which was replaced by vancomycin due to a persistent high fever and previous bacteremia of methicillin-resistant staphylococcus epidermidis 4 years ago.

His clinical condition still progressed despite strong antibiotic treatment. We arranged an echo-guided pleural tapping and lung aspiration, then the specimens were sent for cytology, acid-fast bacillus stain, Gram's stain, and bacterial culture 7 days post-admission. The only positive result was the isolation of Nocardia from the pleural effusion.

Finally, we changed our antibiotic regimens to TMP-SMX and minocycline. His clinical symptoms gradually improved after this antimicrobial therapy (Figure 2), so he was discharged in stable condition on March 31, 1999.

Discussion

Nocardia can infect any individual but is more common in immunocompromised patients [1]. Several species have been documented to be pathogenic in man, including N asteroides, N brasiliensis, N farcinica, N otitidis caviarum, N nova, and N transvalensis [2].

Most cases begin as pulmonary infection and disseminate hematogenously with abscess

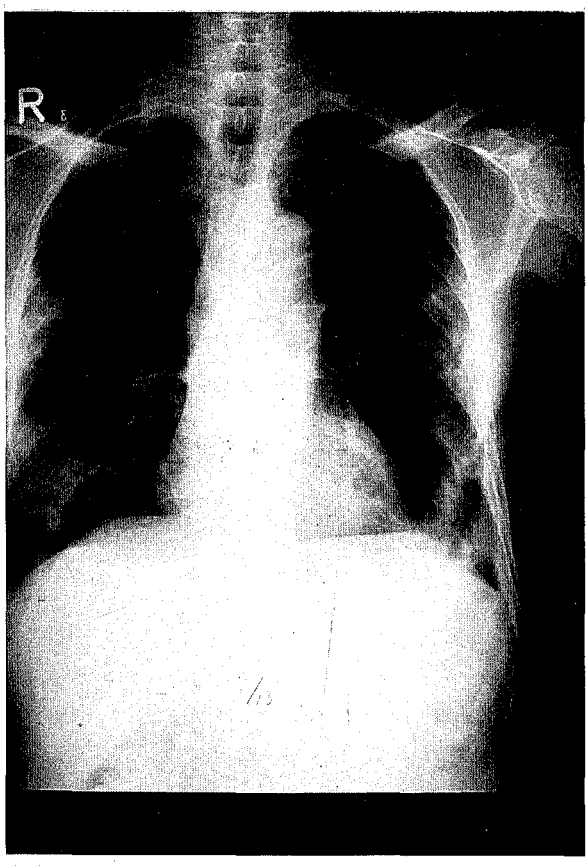

Fig.2. CXR Showed resolution of nodular lesions and alveolar infiltration post treatment.

formation in the brain, liver, kidney, and other organs. Infection may also begin as skin or subcutaneous abscesses [3,4].

The clinical manifestations of pulmonary nocardiosis are cough, purulent sputum, and fever [5]. In general, the clinical course is chronic with a duration of symptoms before diagnosis of 3 weeks or more.

The chest radiographic manifestations of nocardiosis, like those of tuberculosis, are pleomorphic. Consolidations and large irregular nodules, often cavitary, are most common; nodules, masses, and interstitial patterns also occur. Pleural effusions are quite common and lymph nodes may be enlarged [1].

Pulmonary nocardiosis is difficult to diagnosis on the basis of clinical and radiologic findings [5]. Moreover, Nocardia is difficult to culture as it often requires 3 weeks to grow and there is no reliable serologic test for its presence [1].

The definite diagnosis should be made by isolating Nocardia spp., using an aggressive approach such as bronchoscopic lavage, fine-needle aspiration of the affected region, CSF examination, or aspiration of pus from the abscesses [6].

Therapy with sulfonamides and, more recently, TMP-SMX, is thought to be optimal for nocardial infections. Sulfonamides are the most effective and best-studied drugs for the treatment of nocardiosis. Alternatives to sulfonamide therapy include imipenem, amikacin, minocycline, and amoxicillin-clavulanic acids. Although the optimal dose and duration of sulfonamide therapy is unknown, treatment with three to six double-strength TMP-SMX tablets daily is recommended [7].

The duration of sulfonamide therapy is 6 weeks for the localized form of nocardiosis, and 6 months to 1 year for disseminated nocardiosis [5]. The clinical outcome of pulmonary nocardiosis is related to the dissemination of the infection and the immune status of the host. In immunocompetent patients with localized infections, the outcome is generally favorable.

On the other hand, the outcome is poor in immunocompromised patients with disseminated infection [7].

In summary, pulmonary nocardiosis is difficult to diagnose, diagnosis is usually delayed, and a high index of suspicion for nocardiosis is required in susceptible hosts presenting with radiographic pleomorphism [1-10].

In this case, the isolation of Norcardia from pleural effusion, and antimicrobial therapy with TMP-SMX and minocycline, achieved a satisfactory outcome in the treatment of this patient.

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肺部奴卡氏菌病－病例報告

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肺部奴卡氏菌病是一種不常見且具有多種肺部病狀表現的嚴重感染，主要發生在免疫功能低下或接受類固醇治療的慢性阻塞性肺疾病及其他內科疾病患者，但亦能在正常之宿主上造成感染。其傳染途徑主要是存在土壤中的奴卡氏菌經由空氣吸入肺部而呈現出亞急性或慢性肺部發炎。因奴卡氏菌不易培養且能伴隨其他較易診斷之肺部疾病共同發生，故診斷不易，唯有高度的警覺配合對病患的了解，方能獲致正確之診斷。

在此我們報告一例肺部奴卡氏菌病經磺胺藥物治療痊癒的經過。*(胸腔醫學 2000; 15: 195-199)*

關鍵詞：肺部奴卡氏菌，類固醇，磺胺藥物

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瀰漫性囊狀病變合併自發性氣胸

邱國欽　賴永發　王瑞隆　林安伸　趙東瀛

一位 17 歲男性，有抽煙病史，主訴乾咳及左側胸痛已三天，前來求診。其胸部放射線檢查如下圖一、二、三。

請問：

1.胸部 X 光片及高解析度電腦斷層掃描(HRCT)有何發現？

2.鑑別診斷應包括哪些疾病？

3.正確診斷爲何？

4.如何診斷？

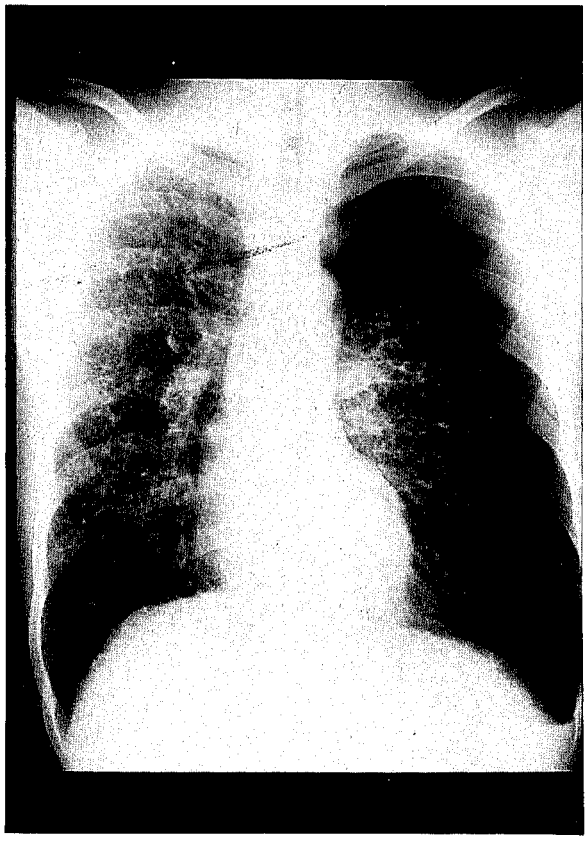

Fig. 1

1.胸部 X 光片顯示兩側多發性囊狀病灶，合併左側氣胸，無肋膜積水，肺容積無明顯減少；HRCT 可見兩側肺野大小不一的囊狀病灶，以上及中肺葉居多。

2.鑑別診斷：主要包括 X 組織球增生症(histiocytosis-X)，淋巴管肌瘤症(lymphangioleiomyomatosis)，結節性硬化症(tuberus sclerosis)，及原發性肺纖維化症(idiopathic pulmonary fibrosis)。

3.正確診斷爲：X 組織球增生症

4.診斷方法有：高解析度電腦斷層掃描，支氣管鏡肺泡灌洗術(bronchial alveolar larvage)，及胸腔鏡檢查或施行胸廓切開術，以取得組織切片，做病理學檢查。

討　論

肺部組織球增生症是少見但重要之疾病，多發生於年輕人，以 20 至 40 歲爲發病高峰期，男女比例相近或男明顯多於女(6:4)[1]，此病並無明顯的地理或職業分佈影響，但多數病人有抽煙史。

臨床上，病人多因常規的胸部 X 光檢查被發現，或自發性氣胸而就醫；此外，也可能有下述症狀：乾咳(56-70%)、喘(40-87%)、疲勞(30%)、體重下降(20-30%)、

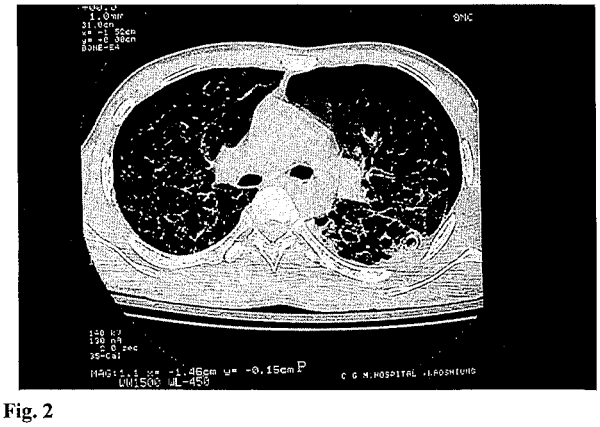

Fig. 2

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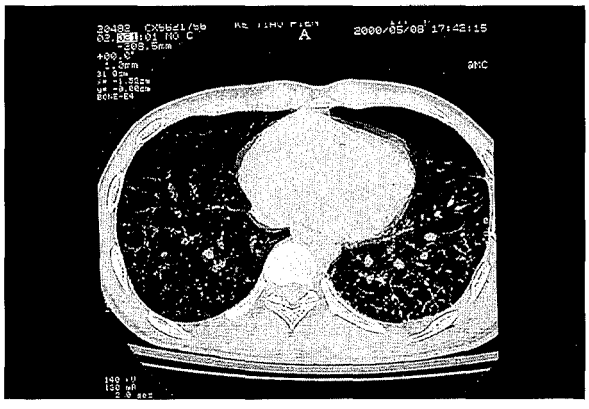

Fig.3

胸痛(10-21%)、發燒(15%)[2,3]。

在影像學上，常見兩側合併多發性結節及囊狀病變，以上肺葉及中肺葉爲主。此病初發以多發性結節爲多，若持續演進，則變成兩側多發性囊泡病灶[4]，其特點有[5,6]：

1.病灶多發生於上及中肺葉。

2.肺容積早期正常,晚期則常有肺氣腫的現象。

3.囊泡大小不一。

4.兩側肋膈角常不受侵犯。

本病須與淋巴管肌瘤症、結節性硬化症，及原發性肺纖維化症做鑑別診斷，如下表：

	X 組織球增生症	淋巴管肌瘤症	結節性硬化症	原發性肺纖維化症
性　別	男女相近	女性爲主	女性爲主	男略多於女
好發位置	上中肺葉	下肺葉	下肺葉	肺底部及外側肺野
合併氣胸	+	+	+	+
肺外病灶	腦下垂體、骨骼、皮膚	乳糜胸、腎臟	腦、腎臟、皮膚	無
好發年紀	20 至 40 歲	生育期女性	生育期女性	50 至 70 歲

此病有可能產生下列數種併發症：

1.復發性氣胸(25%) [7]。

2.咳血(13%)[8]。

3.骨骼空泡病灶(4-20%)，以扁平骨爲主[2]。

4.尿崩症(8%)[2]。

診斷方法如下：

1.若有典型胸部 X 光片且高解析度電腦斷層掃描具下列特徵即可診斷[6]，如圖二、圖三：

(1) 兩側多發性囊泡狀病灶

(2) 上及中肺葉爲主

(3) 兩側肋膈角少有侵犯

(4) 肺容積無明顯下降

2.可做支氣管鏡肺泡灌洗術，取得檢體，做細胞學檢查，若發現超過 5%Langerhans cell [9,10]，且這些細胞可被 S-100 protein、MT-1 單株抗體所染色，或 CD-1[11,12]爲陽性，亦可診斷。

3.最後，也可施行胸腔鏡手術或胸廓切開術，取得組織切片，做病理學診斷。

在治療方面，仍以戒菸爲首要[13]。類固醇的使用並無明顯的效果顯現；而放射線治療可用於骨骼之病變，對於肺部病灶則沒有作用。

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