

PCCU

Lesson 1, Volume 12—Inhalation Fever

By Paul D. Blanc, MD, MSPH, FCCP

Objectives

1. Understand the concept of inhalation fever as a flu-like, self-limited syndrome caused by a heterogeneous group of stimuli.
2. Define the pathophysiology of inhalation fever in the context of its inflammatory manifestations.
3. Identify the major groups of inhalation fever syndromes due to metal fumes, polymer fumes, contaminated water sources, and organic dusts.
4. Recognize the contradistinctions between inhalation fever and other pulmonary syndromes occurring after related exposures, but with differing pathophysiology.
5. Delineate the role of prevention to reduce the exposures that cause inhalation fever.

Key words

inhalation fever; metal fume fever; occupational lung disease; organic dust toxic syndrome; polymer fume fever

Inhalation fever is a syndrome marked by a flu-like illness including fever, chills, myalgia, and malaise. This syndrome, however, is not due to acute infection with a viral or bacterial organism, but occurs following inhalation of any of a number of different substances. Onset is acute, typically 4 to 8 h after initial exposure. Substances linked to inhalation fever are surprisingly heterogeneous, can be encountered in both occupational and environmental settings, and include metal oxide fumes from welding,¹⁻³ heat breakdown products of certain synthetic polymers,⁴ organic dusts,⁵ and contaminated water sources such as from humidifiers.⁶ These seemingly unrelated exposures understandably led clinicians and researchers initially to consider each of these febrile syndromes to be entirely distinct processes. A variety of different common names for the various inhalation fever syndromes underscores this traditional view: silo unloader's disease, mill fever, metal fume fever, polymer fume fever, and humidifier fever are examples. In more recent years, however, the unifying classification of "inhalation fever" has gained wider acceptance. The term inhalation fever was first proposed in 1978 and has come into broader use as investigators have come to appreciate the common features that appear to link all of the inhalation fevers, despite their differing proximal causes.⁶⁻¹⁰

The key shared clinical, epidemiologic, and experimental features of inhalation fever regardless of the exposure involved are delineated in Table 1. Inhalation fever is associated with a high attack rate among those having greater exposure. This attack rate can be 70% or higher given sufficient exposure. This is a pivotal feature of the disease, and is all the more notable because those previously naive to the inhalant involved are equally if not even more responsive than those who may have been previously challenged with it. In other words, inhalation fever is not idiosyncratic, nor does it rely on prior sensitization dependent on a humoral or cellular amnestic response. The high attack rates of inhalation fever also differentiate it from most infectious processes.

Table 1 — Key Features of Inhalation Fever

1. Self-limited, flu-like syndrome

2. Onset 4 to 8 h after heavy exposure to causative agent
3. High attack rates in those exposed
4. Not idiosyncratic; no prior sensitization
5. Blunted response with repeated exposure (tachyphylaxis)
6. Lung is portal of entry and target organ mediating response
7. Inflammatory lung infiltrate (polymorphonuclear leukocytes)
8. Peripheral blood leukocytosis
9. Proinflammatory cytokines play a pivotal role

Not only is sensitization not a part of the inhalation fever response, but, in contrast, the syndrome commonly manifests tachyphylaxis or a blunted response after frequent repeated exposures. This is the hallmark of inhalation fever in specific occupational settings. In both brass foundries and textile mills, high-level repeated exposures can occur such that workers have been most likely to experience the inhalation fever response when returning to the job after a few days off. Because of this tachyphylaxis, the same name, "Monday morning fever", was popular for inhalation fever in both brass foundries (for metal fume fever) and in textile mills (for mill fever).^{11,12} The exposures were very different, but the epidemiologic pattern of disease was the same.

The pathogenic mechanisms underlying inhalation fever have not been delineated with precision. Nonetheless, experimental laboratory animal and human exposure studies have provided important insights into some of the pivotal aspects of inhalation fever. Most importantly, the lung appears to be the target organ in inhalation fever.¹³ In this regard, the lung serves more than a route of entry for the various exposures linked to this response. The lung also appears to provide the stimulatory source of the specific signals that mediate the syndrome's local lung and systemic features. For example, in both animal and human models of inhalation fever, a dramatic neutrophil influx in the lung is observed. Bronchoalveolar lavage (BAL) 18 to 24 hours after zinc oxide inhalation has shown 35% polymorphonuclear leukocytes; grain and swine-room dust inhalation exposures have yielded similar BAL data.^{1,14,15} Consistent with these inflammatory cellular findings, increases in BAL proinflammatory cytokines, in particular tumor necrosis factor, interleukin-6, and the neutrophil chemotactic factor interleukin-8, have also been observed in experimental models of inhalation fever.^{2,16,17} The major types of inhalation fever are summarized in Table 2.

Table 2—Major Types of Inhalation Fever

Exposure	Type	Syndrome Name
Metal fumes	Generic	Metal fume fever
Zinc oxide	Specific	Smelter shakes
Organic dust	Generic	Organic dust toxic syndrome ODTS
Silage	Specific	Silo unloader's disease
Cotton dust	Specific	Mill fever
Flax	Specific	Heckling fever
Wood trimmings	Specific	Wood-trimmer's disease
Grain dust	Specific	Grain fever
Humidifying	Generic	Humidifier fever

Legionella	Specific	Pontiac fever
Polymer breakdown	Generic	Polymer fume fever

Metal Fume Fever

Metal fume fever caused by zinc oxide fume is the most well-recognized form of inhalation fever. It was first reported over 150 years among the brass foundries of Birmingham, England.¹⁸ Metal fume fever is caused by high levels of exposure to zinc oxide fumes. Brass making, by adding zinc to molten copper, is an ideal work process for generating such fumes. The most common modern industrial activity associated with zinc oxide fume inhalation is electric arc welding on galvanized (zinc-coated) steel.¹⁹ Routine galvanizing itself, which involves dipping steel in molten zinc, does not typically occur at a temperature high enough to generate dense concentrations of zinc oxide. The typical symptoms of metal fume fever, as with the inhalation fevers generally, are chills, fever, and malaise.^{13,20} Minor respiratory and gastrointestinal complaints can also accompany the syndrome. A transient leukocytosis is common, but the chest radiograph should be clear. There is no routine clinical role for measuring blood zinc levels.

Although it is often stated that only freshly formed zinc oxide fume induces inhalation fever, there have been well-documented, albeit infrequent, case reports of fume fever after heavy exposure to finely ground zinc oxide dust in the absence of a fresh fume exposure.^{21,22} It is also important to note that although inhalation fever is by far the most common response to zinc oxide inhalation, other syndromes may occur. These include bronchospasm, contact urticaria, and hypersensitivity-like responses associated with exposure to zinc oxide fumes; although all are limited to a few case reports.²³⁻³⁰ Of interest, zinc oxide ingestion can cause gastroenteritis, but does not induce the metal fume fever syndrome.³¹ This further supports the view that inhalation is a key aspect of the fever syndrome.¹³

Even though many reviews and textbooks state that a number of metal oxides in addition to zinc oxide cause metal fume fever, the data to support this are sparse. The metals cited include magnesium, copper, cadmium, chromium, antimony, and iron. There is human experimental data from the 1920s indicating that magnesium oxide inhalation can cause fume fever, although there is limited epidemiologic data to support this association.³²⁻³³ Industrial exposure to magnesium oxide fumes is extremely uncommon. Copper may be a potential cause of metal fume fever, but data in this regard are limited. There are occasional citations in the scientific literature describing a copper-associated febrile response.³⁴⁻³⁵ Inhalation fever from other metal oxides has not been documented.

There is often confusion in relation to cadmium inhalation as a cause of metal fume fever. Cadmium forms a toxic metal fume that is an established cause of acute lung injury.^{36,37} In that context, the acute lung injury of cadmium can be accompanied by fever, but is not otherwise consistent with the clinical criteria of inhalation fever syndrome. Indeed, the term "cadmium fume fever", although sometimes used, is inappropriate and misleading. The lung injury after cadmium inhalation is not self-limited but progressive and often fatal. Respiratory compromise, marked by hypoxemia or pulmonary infiltrates, is not consistent with inhalation fever. The issue of cadmium exposure is particularly germane to the welding or flame-cutting of sheet metal or of previously soldered metals.¹⁹ This latter work practice can lead to significant cadmium fume exposure because "silver solder" can be cadmium-based. Another area of confusion arises with a different metal inhalation, zinc chloride. Zinc chloride, unlike zinc oxide, but like cadmium, can also cause severe lung injury.³⁸⁻³⁹ Exposures can occur through the use of zinc chloride-containing smoke bombs in military or police training exercises. It is important not to confuse such exposures with the far more common zinc oxide-caused metal fume fever.

Organic Dust Toxic Syndrome

Organic dust toxic syndrome (ODTS) includes inhalation fever after the exposure to dusts from moldy or damp silage or hay⁵ and after exposure to other agricultural dusts such as woodchips in mulching processes. ODTS has also occurred after "environmental" exposures, one famous example being an "indoor hayride" sponsored by a college fraternity.⁴⁰ Agricultural dusts, unlike the simple metal oxides, are complex mixtures containing bacteria, fungi, and their byproducts in addition to many other contaminants. In the past, ODTS has been referred to as "pulmonary mycotoxicosis."⁴¹ Because the proximal cause of ODTS is not known, the term mycotoxicosis is no longer preferred. Another term, "silo unloader's syndrome", encompasses one of the activities associated with

ODTS but is not inclusive and can lead to confusion with "silo filler's disease" an acute lung injury due to nitrogen dioxide.⁴²

Like metal fume fever, ODTS typically occurs 4 to 8 h after exposure and is marked by fever, chills, and myalgia that may be accompanied by cough, nausea, and headache.^{5,41,43} Eye and mucous membrane irritation is common, potentially because of the amount and size of the dust particle exposures involved. Acutely, a peripheral leukocytosis is common. Serum precipitins to thermophilic bacteria and mold species are typically negative.

□

Other Organic and Vegetable Dusts

Workers exposed to the dusts of cotton and certain other fibers can experience an illness clinically indistinguishable from ODTS. Mill fever is the most common term for this condition to describe inhalation fever among cotton workers; and "heckling fever" describes the same condition among flax workers.¹² The best described outbreak of mill fever occurred among self-employed mattress makers during World War II, who used contaminated ("stained") cotton.⁴⁴ Grain fever is an inhalation fever associated with exposure to massive concentrations of grain dust.⁴⁵ Dusts include wheat, corn, and sorghum. It is common among grain handlers. Like zinc oxide-caused metal fume fever, grain fever has been reproduced in human exposure models. Pulmonary inflammatory cellular infiltrates and increased proinflammatory cytokines have been documented by BAL in these subjects.^{14,17}

Wood trimmer's disease describes an inhalation fever syndrome that occurs in sawmill workers exposed to dust from microbial-contaminated wood, especially bark.⁴⁶ Inhalation fever also occurs frequently in swine confinement workers, an occupation in which a variety of dust and gas exposures occur because the animals are raised in tightly enclosed structures.^{15,16} With all forms of organic dust-related inhalation fever, endotoxin has long been suspected as a key element of cause. However, a co-factor role for other exposures has not been excluded.

Inhalation Fever From Contaminated Water Sources

Humidifier fever refers to an inhalation fever syndrome associated with exposure to contaminated aerosols from humidifying systems, usually in industrial settings. A similar illness can occur among sewage workers. Humidifier-related inhalation fever was well documented in 1976, after a series of similar outbreaks in Great Britain.⁶ The printing industry has been at high risk for outbreaks, in part because of its technical requirement for ambient humidity. Environmental exposures causing humidifier fever have occurred in contaminated home heating units. Humidifiers that draw water from stagnant sources contaminated with bacterial sludge which is then nebulized through forced-air systems are the most problem-ridden. Overgrowth of *Naegleria gruberi* and *N pseudomonad* have been specifically implicated.⁴⁷⁻⁵⁰

Another waterborne inhalation fever is associated with exposure to aerosols contaminated with the bacterium *Legionella pneumophila*. Unlike Legionella pneumonia, this syndrome called Pontiac fever, is a self-limited, influenza-like illness similar to humidifier fever. A number of Pontiac fever outbreaks have been identified retrospectively on the basis of serologic data. Implicated *Legionella pneumophila* types have included serogroups 1 and 7 as well as the micdadei and anisa species.⁵¹⁻⁵⁵ Industrial and commercial cooling systems, whirlpools, and fountains have been implicated as sources of this specific inhalation fever syndrome.

Polymer Fume Fever

Polymer fume fever was first described in 1951.⁵⁶ It is caused by the inhalation of the thermal breakdown byproducts of polytetrafluoroethylene (PTFE; Teflon) and related synthetic polymers.⁴ When these polymers are heated to temperatures between 300 and 750 C, a variety of different byproducts can be formed. The precise identification of the cause or causes of polymer fume fever has not been made. Industrial practices associated with these fumes include welding metal coated with PTFE, molding or extruding PTFE, and smoking PTFE-contaminated cigarettes.⁵⁷⁻⁶⁰

Unfortunately, higher temperature breakdown of PTFE and related polymers produces highly irritant fumes that can cause acute lung injury rather than inhalation fever. Severe, acute noncardiogenic pulmonary edema has been reported after such exposures.⁶¹⁻⁶³

Occasionally, overheated PTFE-coated cooking utensils have been associated with irritant lung injury.⁶⁴

Differential Diagnosis

The principal differential diagnosis relevant to inhalation fever includes acute lung injury, infection, hypersensitivity pneumonitis, and other immunologic responses. These are summarized in Table 3.

Table 3—Inhalation Fever Differential Diagnosis

Alternative Diagnosis	Related Exposures(Source)
Acute Lung Injury	Cadmium fumes (welding) Nitrogen dioxide (welding, silo-filling) Polymer byproducts (heat breakdown)
Infection	Legionella pneumonia (contaminated water) Other pneumonias (bacteria and molds)
Hypersensitivity pneumonitis	Humidifier lung (humidifier contaminants) Farmer's lung (thermophilic species)
Asthma	Organic dusts (including aspergillus) Metal fumes (welding)

It is critical to differentiate between inhalation fever and acute lung injury. It is important to acknowledge their potential similarities. Both can occur soon after a high level, acute exposure through inhalation. Fever can be present in toxin-related acute lung injury due to toxic inhalation, further blurring the distinctions between these two syndromes. Even more confusing, the exposure situations in which inhalation fever occurs can be similar to those leading to acute lung injury. Welding may be associated with cadmium fumes or nitrogen dioxide gas exposure, both of which can lead to pulmonary edema.¹⁹ High temperature fluoropolymer breakdown may also release byproducts that cause lung injury rather than polymer fume fever.⁴ Fresh silage can release nitrogen dioxide causing silo filler's disease, an acute lung injury syndrome.⁴² Even moldy materials that might otherwise be associated with ODTS can occasionally be contaminated with what appear to be toxic fungal byproducts, although these have been poorly characterized.⁶⁵

It is important to note, however, that the clinical differences between inhalation fever and acute lung injury are quite distinct. Inhalation fever, by definition, is self-limited and benign. Significant respiratory compromise with chest radiographic infiltrates or hypoxemia suggest an alternative diagnosis. Adult respiratory distress syndrome (ARDS) is not a part of the spectrum of illness subsumed under the designation "inhalation fever". With the symptoms or signs of acute lung injury, the diagnosis of inhalation fever should not be invoked; a toxic inhalant causing lung injury should be suspected.

For both ODTS and humidifier fever, infectious disease may need to be ruled out. This may become most confusing in differentiating between Pontiac fever and pneumonia. Epidemiologically, the former is marked by an extremely high attack rate among those highly exposed with a brief period between exposure and symptoms, while the latter is sporadic, has an incubation period of days, and strikes groups at higher risk of infection. Clinically, Legionella infection is also quite distinct from Pontiac inhalation fever. Pontiac fever is not associated with pneumonic infiltrates or respiratory compromise.⁵¹

Hypersensitivity pneumonitis (HP) can occur after chronic exposures to many of the same organic dusts and bioaerosols associated with ODTS and humidifier fever.⁶⁶ HP, in its classic manifestation, includes granulomatous lung changes with corresponding radiographic abnormalities, a restrictive ventilatory defect by pulmonary function, and a lymphocytic inflammatory infiltrate by BAL analysis. None of these findings should be present in simple inhalation fever. It is important to note, however, that both

processes can occur in the same individual in the context of chronic exposure complicated by a superimposed, high intensity acute exposure. Other immunologic processes may also be included in the differential diagnosis of inhalation fever. A late-phase asthmatic response may be accompanied by constitutional symptoms that could raise a question of inhalation fever. However, airway obstruction is not a clinical feature of inhalation fever and indicates an alternative diagnosis.

Medical Management

The treatment of inhalation fever is conservative and supportive. There are no specific therapies for any of the syndromes. If acute lung injury is a consideration, adequate evaluation and follow-up should address the potential for subsequent pulmonary edema. Concomitant inhalation fever and hypersensitivity pneumonitis may also require further diagnostic evaluation. The key to the management of inhalation fever is prevention. As a group, all of these syndromes are linked to very high exposures that can usually be quickly pinpointed through a targeted occupational and environmental history.⁶⁷ Although inhalation fever itself is self-limited, the poor hygienic conditions in which they occur often indicate shared risk for other, less benign conditions such as those delineated in Table 3.

References

1. Blanc P, Wong H, Bernstein MS, et al. An experimental model of metal fume fever. *Ann Int Med* 1991; 114:930-36
2. Blanc PD, Boushey HA, Wong H, et al. Cytokines in metal fume fever. *Am Rev Respir Dis* 1993; 147:134-39
3. Gordon T, Chen LC, Fine JM, et al. Pulmonary effects of inhaled zinc oxide in human subjects, guinea pigs, rats and rabbits. *Am Ind Hyg Assoc J* 1992; 53:503-09
4. Shusterman D. Polymer fume fever and other fluorocarbon pyrolysis-related syndromes. *Occup Med* 1993; 8:519-31
5. National Institute for Occupational Safety and Health (Centers for Disease Control). NIOSH alert: Preventing organic dust toxic syndrome. DHHS Publication No. 94-102. Cincinnati, Ohio: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, 1994
6. Anonymous. Inhalation fevers (Editorial). *Lancet* 1978; 1(8058):249-50
7. Rask-Anderson A, Pratt DS. Inhalation fever: a proposed unifying term for febrile reactions to inhalation of noxious substances (Letter). *Br J Ind Med* 1992; 49:40
8. Rask-Anderson, A. Inhalation fever. In: Harber P, Schenker M, Balmes J, eds. *Occupational and environmental respiratory diseases*. St. Louis: Mosby, 1995; 243-58
9. Taylor, G. Acute systemic effects of inhaled occupational agents. In: Merchant JA, ed. *Occupational respiratory diseases*. Pub. No. DHHS (NIOSH) 86-102. US Department of Health and Human Services, National Institute for Occupational Safety and Health: Cincinnati:1986; 607-25
10. Rose C. Inhalation fevers. In: Rom W, ed. *Environmental and occupational medicine*. 2d ed. Boston: Little, Brown & Co, 1992; 373-91
11. Turner JA, Thompson LR. Health hazards of brass foundries. *Pub Health Bul* 1925; 157:1-71
12. Harris TR, Merchant JA, Kilburn KH, et al. Byssinosis and respiratory diseases of cotton mill workers. *J Occup Med* 1972; 14:199-206

13. Blanc P, Boushey HA. The lung in metal fume fever. *Semin Respir Med* 1993; 14:212-25
14. Von Essen SG, O'neill DP, McGranaghram S, et al. Neutrophilic respiratory tract inflammation and peripheral blood neutrophilia after grain sorghum dust extract exposure. *Chest* 1995; 108:425-33
15. Larsson KA, Eklund AG, Lars-Olof H, et al. Swine dust causes intense airways inflammation in healthy subjects. *Am J Respir Crit Care Med* 1994; 150:973-77
16. Wang Z, Malmberg P, Larsson P, et al. Time course of interleukin-6 and tumor necrosis factor-alpha increase in serum following inhalation of swine dust. *Am J Respir Crit Care Med* 1996; 143: 147-52
17. Clapp WD, Becker S, Quay J, et. al. Grain dust induced airflow obstruction and inflammation of the lower respiratory tract. *Am J Respir Crit Care Med* 1994; 150: 611-17
18. Thackrah CT. *The Effects of Arts, Trades, and Professions, and of Civic States and Habits of Living on Health and Longevity*. Second Edition. London: Longman, Rees, Orme, Brown, Green, and Longman, 1832: 101-02
19. National Institute for Occupational Safety and Health. *Criteria for a Recommended Standard: Welding, Brazing and Thermal Cutting*. Cincinnati: US Dept HHS, 1988
20. Volgelmeier C, Konig G, Bencze K, et al. Pulmonary involvement in zinc fume fever. *Chest* 1987; 92:946-48
21. Batchelor RP, Fehnel JW, Thomson RM, et al. A clinical and laboratory investigation of the effect of metallic zinc, of zinc oxide, and of zinc sulfide upon the health of workmen. *J Ind Hyg* 1926; 8:322-63
22. Rohrs LC: Metal fume fever from inhaling zinc oxide: *Arch Int Med* 1957; 100:44-48
23. Malo JL, Cartier A. Occupational asthma due to fumes of galvanized metal. *Chest* 1987; 92:375-77
24. Farrell FJ. Angioedema and urticaria as acute and late phase reactions to zinc fume exposure, with associated metal fume fever-like symptoms. *Am J Ind Med* 1987; 12:331-37
25. Kawane H, Soejima R, Umeki S. Metal fume fever and asthma (Letter). *Chest* 1988; 93:116
26. Malo J-L, Malo J, Cartier A, et al. Acute lung reaction to zinc inhalation. *Eur Respir J* 1990; 3: 111-14
27. Nemery B, Demedts M. Respiratory involvement in metal fume fever. *Eur Respir J* 1991; 4:764-65
28. Langley RL. Fume fever and reactive airways dysfunction syndrome in a welder. *South Med J* 1991; 84:1034-36
29. Ameille J, Brochard P, Dore MF. Occupational hypersensitivity pneumonitis in a smelter exposed to zinc fumes. *Chest* 1992; 101:862-63
30. Castet D, Bouillard J. Pneumopathie aigue au cours d'une exposition a l'oxyde de zinc. *Rev Mal Respir* 1992; 9:632-33
31. Murphy JV. Intoxication following ingestion of elemental zinc. *JAMA* 1970; 212: 2119-20
32. Drinker P, Thomson RM, Finn JL. Metal fume fever: III. The effects of inhaling magnesium oxide fume. *J Ind Hyg* 1927; 9:187-92
33. Hartmann AL, Hartmann W, Buhlmann AA. Magnesiumoxid als ursache des Metallrauchfiebers.(Magnesium oxide as cause of

metal fume fever). *Sweiz Med Wschr* 1983; 113: 766-70

34. Koelsch F. Metal-fume fever. *J Ind Hyg* 1923; 5:87-91

35. Gleason RB. Exposure to copper dust. *Am Ind Hyg Assoc J* 1968; 29:461-62

36. Fuortes L, Leo A, Ellerbeck PG, et al. Acute respiratory fatality associated with exposure to sheet metal and cadmium fumes. *J Toxicol Clin Toxicol* 1991 ;29:279-83

37. Barnhart S, Rosenstock L. Cadmium chemical pneumonitis. *Chest* 1984; 86:789-91

38. Evans EH. Casualties following exposure to zinc chloride smoke. *Lancet* 1945; 2:368-70

39. Schenker MR, Speizer FE, Taylor JO. Acute upper respiratory symptoms resulting from exposure to zinc chloride aerosol. *Environ Res* 1981; 25:317-24

40. Brinton WT, Vastbinder EE, Greene JW, et al. An outbreak of organic dust toxic syndrome in a college fraternity. *JAMA* 1987; 258:1210-12

41. May JJ, Stallones L, Darrow D, et al. Organic dust toxicity (pulmonary mycotoxicosis) associated with silo unloading. *Thorax*. 1986; 41:919-23

42. Douglas WW, Hepper NGG, Colby TV. Silo filler's disease. *Mayo Clin Proc* 1989; 64; 291-304

43. Rask-Andersen A. Organic dust toxic syndrome among farmers. *Br J Ind Med*. 1989; 46:233-38

44. Neal PA, Schneiter R, Carminita BH. Report on acute illnesses among rural mattress makers using low-grade stained cotton. *JAMA*. 1942; 119:1074-82

45. doPico GA, Flaherty D, Bhansali P, et al. Grain fever syndrome induced by inhalation of airborne grain dust. *J Allergy Clin Immunol* 1982; 69:435-43

46. Rask-Anderson A, Land CJ, Enlund K, et al. Inhalation fever and respiratory symptoms in the trimming department of Swedish sawmills. *Am J Ind Med* 1994; 25:65-67

47. Edwards JH, Griffiths AJ, Mullins J. Protozoa as sources of antigen in "humidifier fever." *Nature*. 1976;264:438-39

48. Rylander R, Haglind P, Lundholm M, et al. Humidifier fever and endotoxin exposure. *Clin Allergy*. 1978;8:511-16

49. Edwards JH. Microbial and immunological investigations and remedial action after an outbreak of humidifier fever. *Br J Ind Med* 1980; 37:55-62

50. Anderson K, Watt AD, Sinclair D, et al. Climate, intermittent humidification, and humidifier fever. *Br J Ind Med* 1989; 46:671-74

51. Fraser DW, Deubner DC, Hill DL, et al. Nonpneumonic, short-incubation period legionellosis (Pontiac fever) in men who cleaned a steam turbine condenser. *Science*. 1979; 205:690-91

52. Friedman S, Spitalny K, Barbaree J, et al. Pontiac fever outbreak associated with a cooling tower. *Am J Public Health* 1987; 77:568-72

53. Goldberg DJ, Wrench JG, Collier PW, et al. Lochgoilhead fever: Outbreak of nonpneumonic legionellosis due to *Legionella micdadei*. *Lancet*. 1989; 1:316-18
54. Fenstersheib MD, Miller M, Diggins C, et al. Outbreak of Pontiac fever due to *Legionella anisa*. *Lancet*. 1990;336:35-37
55. Mori J, Hoshino K, Sonoda H, et al. An outbreak of Pontiac fever due to *Legionella pneumophila* serogroup 7. I. Clinical aspects. *Kansenshigaku Zasshi, Japan Assoc Inf Dis* 1995; 69:646-53
56. Harris DK. Polymer fume fever. *Lancet* 1951;2:1008-11
57. Goldstein M, Weiss H, Penek J, et al. An outbreak of fume fever in an electronics instrument testing laboratory. *A J Occup Med* 1987; 29:746-49
58. Centers for Disease Control: Polymer-fume fever associated with cigarette smoking and the use of tetrafluoroethylene-Mississippi. *MMWR Morb Mortal Wkly Rep* 1987; 36:515-516, 521-22
59. Goldstein M, Weiss H, Wade K, et al. An outbreak of fume fever in an electronics instrument testing laboratory. *J Occup Med* 1987; 29:746-49
60. Williams N, Smith FK. Polymer fume fever. An elusive diagnosis. *JAMA* 1972; 219: 1587-89
61. Williams N, Atkinson W, Patchefsky AS. Polymer-fume fever: not so benign. *J Occup Med* 1974; 16:519-22
62. Robbins JJ, Ware RL. Pulmonary edema from Teflon fumes: Report of a case. *N Engl J Med* 1964; 271:360-61
63. Evans EA. Pulmonary edema after inhalation of fumes from polytetrafluoroethylene (PTFE). *J Occup Med* 1973; 15:599-601
64. Zanen AL, Rietveld AP. Inhalation trauma due to overheating in a microwave oven. *Thorax* 1993; 48:300-02
65. Yoshida K, Masayki A, Araki S. Acute pulmonary edema in a storehouse of moldy oranges; a severe case of the organic dust toxic syndrome. *Arch Environ Health* 1989; 44:382-84
66. Von Essen S, Robbins RA, Thompson AB, et al. Organic dust toxic syndrome: an acute febrile reaction to organic dust exposure distinct from hypersensitivity pneumonitis. *J Toxicol Clin Toxicol* 1990; 28:389-420
67. Blanc PD, Balmes JR. History and physical examination. In: Harber P, Schenker M, Balmes J, eds. *Occupational and environmental respiratory diseases*. St. Louis: Mosby, 1995; 28-38

Lesson 2, Volume 12—Bronchiolitis Obliterans and Bronchiolitis Obliterans Organizing Pneumonia (BOOP)

By Gary R. Epler, MD, FCCP

Objectives

1. Review the anatomic and structural aspects of the bronchiolar airways.
2. Update the pathologic and clinical classification of bronchiolar disorders.
3. Understand the clinical, radiographic, and physiologic features of bronchiolitis obliterans.
4. Understand the clinical, radiographic, and physiologic features of bronchiolitis obliterans organizing pneumonia (BOOP).
5. Compare the distinctive differences between bronchiolitis obliterans and BOOP.

Key words

bronchiolitis obliterans; bronchiolitis obliterans organizing pneumonia, BOOP ; constrictive bronchiolitis; obliterative bronchiolitis

Bronchiolar lesions are an important cause of airflow obstruction and diffuse infiltrative lung diseases. Recognition of the distinctive differences between the two major disorders of bronchiolitis obliterans and bronchiolitis obliterans organizing pneumonia (BOOP) is essential for appropriate and effective patient care. This lesson reviews current information regarding the clinical, physiological, radiographic, and pathologic findings associated with these two entities.

Bronchioles are small airways, 1 to 2 mm in diameter, without cartilage or submucosal glands. There are an estimated 28,000 terminal bronchioles which represent the final conducting bronchioles at the 16th generation, with diameters of 0.6 mm. The 224,000 respiratory bronchioles are distinctive because in their walls they contain alveolar sacs. The bronchioles terminate at the 13.8 million alveolar ducts and 300 million alveoli.

Ciliated cells predominate on the surface of the proximal airways, while Clara cells compose the majority of cells in the bronchiolar mucosa.¹ Apically, Clara cells contain membrane-bound secretory granules that probably are active in the secretion of proteins and may be active in surfactant secretion. Neuroendocrine cells reach maximal density in the proximal bronchioles. They occur singly or in clusters and tend to be concentrated at the bifurcations of the conducting airways. These cells are a source of bioactive secretory products, including bombesin-like activity (gastrin-releasing peptide), somatostatin, endothelin, serotonin, and calcitonin.

Airway Bronchiolar Disorders

The pathologist distinguishes several distinct airway lesions (Table 1):

Table 1—Pathologic Lesions of the Bronchioles

Airway lesions

- Cellular bronchiolitis
 - Follicular bronchiolitis
 - Mineral dust bronchiolitis
 - Cigarette smoke respiratory bronchiolitis
 - Diffuse panbronchiolitis
 - Constrictive bronchiolitis
 - Bronchiolitis obliterans with intraluminal polyps
- Interstitial lesions
- Respiratory bronchiolitis-interstitial lung disease
 - Bronchiolitis obliterans organizing pneumonia (BOOP)

Cellular bronchiolitis is acute or chronic inflammation of the bronchioles. The inflammation may be submucosal, mural, or peribronchiolar. This is a common finding histologically in the adult. A distinct corresponding clinical process is not well defined, however, because biopsy material is usually not available and appropriate epidemiologic studies are lacking. In adults, the lesion probably corresponds to the clinical syndrome in patients who develop a persistent cough of 1 to 2 weeks after a viral illness. There may or may not be wheezing and airflow obstruction. The cough usually subsides after 3 weeks. Occasionally, a course of corticosteroid therapy is needed for resolution.

Follicular bronchiolitis is a descriptive term for a subset of cellular bronchiolitis associated with lymphoid hyperplasia and reactive germinal centers along the small airways and bronchioles. This lesion may occur in patients with rheumatologic disorders such as rheumatoid arthritis.²

Mineral dust bronchiolitis is fibrotic thickening of the walls of the terminal and respiratory bronchioles, in some instances with extension of the process into alveolar ducts.³ This lesion has been described in workers exposed to a wide variety of inorganic dusts such as iron oxide, aluminum oxide, asbestos, talc, mica, coal, and silica.

Respiratory bronchiolitis secondary to cigarette smoke is defined as bronchioles that are thickened as a result of inflammatory edema and cellular infiltrates, sometimes with fibrous tissue scarring. There may be early airway collapse on expiration secondary to destruction of the peribronchiolar alveolar attachments. Clinically, the patients may have a cough, wheezing, and in some, an abnormal chest high-resolution CT (HRCT) scan.

Diffuse panbronchiolitis is a distinct clinical disorder affecting terminal and respiratory bronchioles associated with symptoms of progressive shortness of breath, episodes of cough and purulent sputum, and chronic sinusitis. The disorder is largely restricted to Japan, although it has been reported among Chinese, Koreans, in Europe, and in the United States.⁴ The 10-year mortality can be high, but erythromycin has been found to be an effective treatment.

Constrictive bronchiolitis (see Table 2) is a lesion of the conducting bronchioles with histologic changes varying from mild bronchiolar inflammation and scarring to late concentric fibrosis with complete obliteration of the bronchioles.⁵

Table 2—Histologic Features of Constrictive Bronchiolitis Obliterans

- Concentrically-scarred or obliterated bronchioles
- Irreversible scarring and alteration of bronchioles
- Spectrum of complete fibrous obliteration of bronchioles
- Stenosis from mural or adventitial scarring
- Dilation of airways with mucus stasis

Acute or chronic inflammation in the bronchiolar wall
Acute luminal inflammation

The clinician adds additional information regarding the underlying causes of the lesions or associated systemic disorders to develop a clinical classification of the bronchiolar disorders (Table 3).

Table 3—Clinical Classification of the Disease of the Bronchioles: Bronchiolar Disorders With Airflow Obstruction

Acute or chronic bronchiolitis

Diffuse panbronchiolitis

Constrictive bronchiolitis (bronchiolitis obliterans)

- Idiopathic
- Postfume exposure
- Nitrogen dioxide
- Sulfur dioxide
- Postinfection
- Mycoplasma
- Rheumatologic or connective-tissue disorders
- Rheumatoid arthritis
- Scleroderma
- Ankylosing spondylitis
- Drug reaction
- Penicillamine
- Gold
- Post bone marrow transplantation
- Post heart-lung and lung transplantation
- Miscellaneous
- Aspiration of activated charcoal
- Stevens-Johnson syndrome
- Neuroendocrine cell hyperplasia-carcinoid
- Gastro-esophageal reflux
- Primary biliary cirrhosis

Idiopathic (cryptogenic) bronchiolitis obliterans is a rare disorder that occurs in patients who have no obvious inciting agent or associated systemic disorder, yet who have airflow obstruction clinically, and constrictive bronchiolitis histologically.⁶ Typical clinical findings of idiopathic bronchiolitis obliterans include several weeks or months of dyspnea and a nonproductive cough. Bilateral early inspiratory crackles are often heard. The vital capacity may be decreased. The FEV₁ or FEV₁/FVC may be severely decreased. The diffusing capacity may be variable, from normal to increased or decreased values. The chest roentgenogram may show small reticular-nodular opacities at the bases, but is often normal. Response to therapy is poor. Early antibiotics for infections and corticosteroid therapy for severe and life-threatening exacerbations are recommended. Lung transplantation may be effective

for some patients.

Toxic fume bronchiolitis obliterans may occur as a result of exposure to irritant inhalants such as nitrogen dioxide or sulfur dioxide. A three-phase pattern is typical of responses to these exposures. First, there is a 4- to 6-hour time period with upper airway symptoms predominantly for water soluble irritants such as sulfur dioxide, or minimal symptoms for less soluble gases such as nitrogen dioxide. Then acute respiratory distress develops, which is associated with diffuse alveolar damage and ARDS. After resolution, there is a third phase of 7 to 10 days minimal respiratory symptoms, then a gradual onset of shortness of breath. During this final phase, there are corresponding early inspiratory crackles, severe airflow obstruction, hyperinflation radiographically, and typical constrictive bronchiolitis with obliteration of many airways pathologically. The development of new chemicals is increasing throughout the world resulting in an increased possibility of exposed workers developing bronchiolar disorders. For example, two workers in a lithium battery factory were accidentally exposed to thionyl-chloride, a compound that produces sulphur dioxide and hydrochloric acid fumes when hydrated. One of them developed a prolonged clinical course consistent with bronchiolitis obliterans.⁷

Postinfectious bronchiolitis obliterans continues to be a rare condition in adults and may occur after a viral or mycoplasma infection. It is more common in children, especially after respiratory syncytial virus (RSV) and adenovirus. Swyer-James syndrome is a variant of postinfectious bronchiolitis obliterans characterized radiographically by unilateral hyperlucent lung. It usually emanates from an acute viral bronchiolitis in infancy or early childhood. Adults with Swyer-James syndrome may be asymptomatic or may have cough, recurrent respiratory infections, and hemoptysis. HRCT imaging of the lung shows bronchiectasis, decreased size of the vessels, and air trapping on expiratory films.⁸

Connective tissue bronchiolitis obliterans occurs most commonly in women with rheumatoid arthritis. It has also been reported in scleroderma, lupus erythematosus, ankylosing spondylitis, and Sjogren's syndrome. The clinical features are identical to idiopathic bronchiolitis obliterans. Histologically, a pattern of constrictive bronchiolitis or intraluminal granulation tissue polyps is seen. The latter has a more favorable course. The finding of constrictive bronchiolitis in patients with rheumatoid arthritis has usually been associated with a poor prognosis; however, a favorable 2-year outcome was recently reported among a group of seven patients treated with erythromycin.²

Drug-related bronchiolitis obliterans generally has been reported in association with rheumatoid arthritis in patients receiving gold or penicillamine. The penicillamine-related lesion is usually constrictive bronchiolitis with a poor prognosis, sometimes requiring lung transplantation for management.⁹ Bronchiolitis obliterans with intraluminal polyps may also be seen as a drug-related lesion and is associated with a better outcome. Although cause and effect is difficult to confirm, the possibility of drug-related bronchiolitis obliterans continues to be important clinically. Patients with a connective tissue disorder receiving these medications who develop unexplained cough or dyspnea should be evaluated promptly.

Bone marrow transplantation bronchiolitis obliterans probably reflects irreversible pulmonary graft-vs-host disease. It is preceded by typical findings of graft-vs-host disease such as skin rash, mucositis, sicca, and angiitis, which usually occurs within 3 months after transplantation. Then 6 months later, obliterative bronchiolitis begins with cough followed by progressive dyspnea. The chest radiograph is normal in 80% of these patients. The FEV₁ is severely reduced with no improvement after bronchodilator inhalation. Response to therapy is poor once severe airflow obstruction has been established. Among a group of bone marrow recipients who had graft-vs-host disease, Yousem found five with constrictive bronchiolitis.¹⁰ The histologic findings indicated that airway lumens were obliterated by dense fibrous scar tissue, and the atretic airways were identified only by their location adjacent to arterioles. Prognosis was poor. Two of the patients died, two underwent double lung transplants, and one was alive with disease.

Lung transplant bronchiolitis obliterans probably represents a form of chronic rejection. It continues to occur in about 20 to 50% of long-term survivors with high mortality. Among 135 heart-lung transplants and 61 lung transplants in 184 patients, the prevalence of obliterative bronchiolitis was 64% for heart-lung transplantation and 68% after lung transplantation.¹¹ Obliterative bronchiolitis occurred in 28%, 49%, 56%, and 71% of these patients at 1, 2, 3, and 5 years respectively after lung transplantation. The frequency and severity of the acute rejection episode was the highest risk factor. Treatment consisted of augmented immunosuppression. Analysis of the 73 patients with obliterative bronchiolitis indicated a 10-year survival of only 17% compared to 56% for patients without obliterative bronchiolitis.

Among a group of lung retransplantation 160 patients, those who underwent retransplantation because of obliterative bronchiolitis had a poor prognosis.¹² Only 31% were free of the bronchiolitis obliterans syndrome at the third year compared to 83% of patients

who underwent retransplantation because of other indications.

Seasonal variation was found in a group of 49 patients who developed bronchiolitis obliterans.¹³ The mean onset of the lesion was 507 days after transplantation. Onset of this complication occurred in 47% of patients during the first quarter of the year compared to 27%, 24%, and only 2% for subsequent quarters.

The secondary pulmonary lobule visualized by the HRCT scan has become an important diagnostic finding for the assessment of transplantation-related obliterative bronchiolitis. The structure is a polyhedral-shaped unit measuring 1.0 to 2.5 cm on each side.¹⁴ The pulmonary veins and lymphatics are located at the periphery of the lobules. The center of the lobule contains the pulmonary artery and a bronchiole of about 1 mm in diameter. Abnormalities in the periphery can be utilized to diagnose an interstitial process or lymphangitic carcinomatosis, while abnormalities in the center of the lobule are utilized for the diagnosis of a bronchiolar disorder. For transplantation-related obliterative bronchiolitis, HRCT findings include central bronchodilatation, hyperlucency, mosaic phenomenon, peribronchial, and perivascular infiltrates.¹⁵

Effective therapeutic options continue to be explored. Augmented immunotherapy may alter the decrease in FEV₁ in a rapid and sustained manner.¹⁶ In a study of aerosolized cyclosporine, seven of nine patients showed improvement in rejection histology and stabilization of FEV₁.¹⁷ Larger, randomized control trials may be needed to confirm efficacy.

Miscellaneous bronchiolitis obliterans may result from aspiration and also has been associated with Stevens-Johnson syndrome. *Neuroendocrine cell hyperplasia-carcinoid-related bronchiolitis obliterans* has been reported in eight patients among 25 consecutive patients undergoing lung resection for peripheral carcinoid.¹⁸ This lesion usually is not associated with symptoms; however, multiple tumorlets and microcarcinoids occurring within the bronchioles can result in a progressive obliterative bronchiolitis and severe airflow obstruction.¹⁹ *Primary biliary cirrhosis bronchiolitis obliterans* has been reported in a 39-year-old woman.²⁰ BAL showed 73% neutrophils. There was some improvement with corticosteroid therapy, but the condition worsened later. The patient developed acute respiratory failure and died of septic shock. *Sauropus androgynus constrictive bronchiolitis* has been reported among a group of patients who developed progressive dyspnea and cough after ingesting *S androgynus* juice in Taiwan.²¹ *S androgynus* is a leafy vegetable cultivated in India, Malaysia, Indonesia, Southwest China, and Vietnam. The leaf of the vegetable normally is ingested after being cooked. It has been blended with pineapples or guavas to make a mixed vegetable-fruit juice and consumed for its alleged effects of body weight reduction and blood pressure control. Many of these patients have remained with chronic dyspnea, severe airflow obstruction with FEV₁ values less than 1 L, and severely decreased diffusing capacity, despite corticosteroid therapy.

Interstitial Bronchiolar Disorders (BOOP)

The pathologist distinguishes two interstitial lesions (Table 4). *Respiratory bronchiolitis-interstitial lung disease* is characterized by mild interstitial infiltrates, fibrosis, and airspace accumulations of macrophages around respiratory bronchioles and alveolar ducts occurring almost exclusively in smokers. *Bronchiolitis obliterans organizing pneumonia (BOOP)* is defined pathologically as granulation tissue plugs within the lumens of distal bronchioles extending into alveolar ducts and alveoli with connective tissue polyps, while the lung architecture is maintained (see Table 5). The classification of BOOP is expanded by adding a clinical setting of causes or associated disorders (Table 5).

Table 4—Clinical Classification of the Diseases of the Bronchioles: Interstitial Bronchiolar Disorders

Postinfection

Mycoplasma
Legionella
Cytomegalovirus
Adenovirus
Influenza
Chlamydia

Drug-related

Amiodarone
Bleomycin
Gold

Focal nodule

Rheumatologic or connective-tissue disorders

Lupus erythematosus
Rheumatoid arthritis
Dermatomyositis
Sjogren's syndrome

Immunologic disorders

Common variable immunodeficiency syndrome
Essential mixed cryoglobulinemia

Bone marrow transplantation

Lung transplantation

Miscellaneous

HIV infection
Radiation therapy
Myelodysplastic syndrome
Lymphoma and cancer
Chronic thyroiditis
Alcoholic cirrhosis
Seasonal syndrome with cholestasis
Inflammatory bowel disease
Tryptophan
Textile printing dye

Respiratory bronchiolitis-interstitial lung disease

Bronchiolitis obliterans organizing pneumonia (BOOP)

Idiopathic

Postinfection

Mycoplasma

Legionella

Cytomegalovirus

Adenovirus

Influenza

Chlamydia

Drug-related

Amiodarone

Bleomycin

Gold

Focal nodule

Rheumatologic or connective-tissue disorders

Lupus erythematosus

Rheumatoid arthritis

Dermatomyositis

Sjogren's syndrome

Immunologic disorders

Common variable immunodeficiency syndrome

Essential mixed cryoglobulinemia

Bone marrow transplantation

Lung transplantation

Miscellaneous

HIV infection

Radiation therapy

Myelodysplastic syndrome

Lymphoma and cancer

Chronic thyroiditis

Alcoholic cirrhosis
Seasonal syndrome with cholestasis
Inflammatory bowel disease
Tryptophan
Textile printing dye

Table 5—Histologic Features of Bronchiolitis Obliterans Organizing Pneumonia (BOOP)*

Major features

Granulation tissue plugs within lumens of distal bronchioles extending into alveolar ducts and alveoli

Additional features

Connective-tissue polyps
Fibrinous exudates
Alveolar accumulations of foamy macrophages
Inflamed alveolar walls
Lung architecture is maintained

*Information from Colby and Myers, reference 5.

□

Idiopathic BOOP affects men and women equally. There is no relationship to smoking. A flu-like illness, fever, and increased sedimentation rate occur in 30 to 50% of patients and generally indicates a steroid responsive process. Cough is common; dyspnea is mild. Wheezing and hemoptysis are rare.

On examination, finger clubbing is not seen and crackles occur in two thirds of patients. Pulmonary function studies show a decreased vital capacity, normal flow rates except in smokers, and a decreased diffusing capacity.²²

Radiographically, bilateral patchy (alveolar) infiltrates are the most common finding. Cavitory nodules and effusions are rare.²³ Sometimes the infiltrates can be "fleeting" in nature—coming and going in different parts of the lung. In one study of 15 patients, the infiltrates were classified as "mobile" in one third.²⁴

Chest CT findings show airspace consolidation, generally located peripherally.²⁵ Costabel²⁶ noted a characteristic CT finding of triangular-shaped patchy infiltrates, with the base of the triangle located along the pleura. Crescent and ring-shaped opacities sometimes can be seen.²⁷

BAL in idiopathic BOOP often shows an increase in lymphocytes, which also corresponds to a positive response to corticosteroid therapy. Yamamoto found a predominance of lymphocytes, sometimes as high as 80 to 95%, and a decrease in the CD4/CD8 ratio.²⁸

An open lung biopsy has been the preferred method for a definitive diagnosis, but video-assisted thoracoscopic biopsies should also provide sufficient tissue to establish a diagnosis. In selected situations, a transbronchial biopsy may be sufficient if both bronchiolar and alveolar elements are seen in the tissue specimen and if there are typical clinical and radiographic findings.

Prednisone continues to be the recommended therapy for patients with symptomatic and progressive BOOP. The dosage is generally 1 mg/kg for 1 to 3 months, then decreasing dosage to 40 mg for 3 months, then 10 to 20 mg daily for 1 year. A shorter 6-month course of 40 mg daily dosage may be sufficient in certain situations. Relapse may occur if an insufficient amount or duration of corticosteroid therapy is given, but fortunately BOOP will respond to the previous steroid responsive level. Total and permanent recovery is seen in 65 to 80% of patients treated. Mortality remains about 5%.

Erythromycin orally, 600 mg/d, has been utilized in six patients with idiopathic BOOP and improvement was seen in all patients.²⁹ The patients were women aged 18 to 83 years, four with patchy infiltrates and two with interstitial infiltrates radiographically and three with lunge lymphocytosis. There was some clinical and radiologic improvement within 2 to 4 weeks; one patient recovered completely at 2 months. The remaining five patients recovered after 3 months. In a report of one patient, inhaled triamcinolone (3 inhalations 4 times daily) for 8 months, resulted in complete resolution of the disease.³⁰ Randomized control trials are needed for confirmation of the effectiveness of these agents.

There is an accelerated or rapidly progressive form of BOOP in a small percentage of patients.³¹ Among a group of five patients with this fulminate variant, the duration of illness was 3 to 14 days in most.³² Four patients presented with respiratory failure requiring mechanical-assisted ventilation and two died. The authors suggest that early recognition and prompt initiation of corticosteroid therapy in the three surviving patients was instrumental in preventing death.

Post-infection BOOP has been reported after adenovirus, cytomegalovirus, or influenza pneumonias. It also occurs after Legionella infection. It was successfully treated with corticosteroid therapy in a 70-year-old man reported to have had Chlamydial pneumonia.³³

Drug-related BOOP has been associated with several anti-inflammatory and immunosuppressive agents such as gold, methotrexate, and sulphasalazine. Other agents include cephalosporins, amiodarone, bleomycin, and illicit use of cocaine. The clinical features and response to therapy are similar to idiopathic BOOP.

Focal nodular BOOP can be classified as a solitary pulmonary nodule. For example, there is a report of a 54-year-old man whose chest radiograph and chest CT scan showed a 3-cm nodule with a cavity suggestive of lung cancer.³⁴ The mass was completely removed surgically and microscopically consisted entirely of BOOP. Two weeks later, two new lesions were seen in the right lung associated with cough and an increased sedimentation rate. Prednisone therapy resulted in normal findings after the first month of treatment. Focal lesions may be curative from exploratory surgical excision, or they may eventually develop into typical patchy infiltrates requiring steroid therapy for resolution.

Rheumatologic (connective tissue) BOOP has been reported in virtually all connective tissue disorders, most commonly found in association with lupus erythematosus, polymyositis/dermatomyositis, and rheumatoid arthritis. The clinical findings and radiographic features are similar to idiopathic BOOP. The disorder may be responsive to corticosteroid therapy, but it may not be as effective as in idiopathic BOOP.

Immunologic disease BOOP has been reported in common variable immunodeficiency syndrome and essential mixed cryoglobulinemia.

Bone marrow transplantation BOOP has been reported rarely. It may occur as a result of an infection with Mycoplasma, cytomegalovirus, or other viral agents. Too few reports are available to determine whether it is a complication of bone marrow transplantation or represents a manifestation of chronic graft-vs-host disease. For example, there is a report of a 23-year-old bone marrow recipient who developed acute graft-vs-host disease at 1 month that rapidly responded to therapy.³⁵ Five months post-transplant, she developed respiratory failure requiring mechanical ventilatory support. Her chest radiograph showed patchy infiltrates, and an open lung biopsy showed BOOP. Despite aggressive management the patient died from respiratory insufficiency 20 days later. Postmortem examination confirmed BOOP.

Lung transplantation BOOP was reported on a sporadic basis, usually associated with a viral infection until recently when it was reported in 10 to 25% of lung recipients.^{36,37} One study showed BOOP in 17 of 163 lung transplantation recipients.³⁶ The lesion was found between 1 and 43 months posttransplantation. Eleven patients had an associated acute rejection, seven developed bronchiolitis obliterans later, and three had bronchiolitis obliterans before the BOOP. Although the histologic features of BOOP

were no different from the idiopathic form, the prognosis in lung transplant recipients was significantly less favorable. Eight patients died. These authors suggested that BOOP is a nonspecific reaction to an injury. Rejection is the most common injury in these patients. Among another group of 115 lung transplant recipients, 32 developed BOOP.³⁷ The authors concluded that this lesion probably results from acute epithelial injury either secondary to acute rejection or to ongoing infection, and not as a component of chronic rejection.

Miscellaneous BOOP is common, and new disorders are being reported continually.²⁴ *HIV infection BOOP* has been reported and controlled by corticosteroid therapy. *Radiation therapy BOOP* may have a fatal outcome in unusual situations, but corticosteroid therapy can result in a rapid, sustained, and complete clinical and radiologic resolution of the opacities. *Myelodysplastic syndrome BOOP* was reported in one patient whose symptoms and hypoxemia resolved 4 days after prednisone was started. *Lymphoma and other cancer-related BOOP* has been reported in several patients; the outcome may be poor. *Chronic thyroiditis-related BOOP* has been reported, one patient recovered without corticosteroid therapy; an *alcoholic cirrhosis-related BOOP* has also been reported in one patient who recovered without corticosteroid therapy. *Chronic interstitial cystitis (Hunner's ulcer) with concomitant BOOP* has been reported in one patient whose pulmonary illness resolved with corticosteroid therapy. *Inflammatory bowel disease-related BOOP* has been reported in patients with ulcerative colitis and Crohn's disease. There was rapid and sustained clinical and roentgenographic improvement in the patients treated with corticosteroid therapy. *Tryptophan-related BOOP* has been reported after ingestion of 2.7 g of L-tryptophan daily during a 25-month period. Treatment with intravenous methylprednisolone resulted in prompt resolution of symptoms and radiographic improvement. *Seasonal BOOP syndrome with cholestasis* was reported in England among 12 patients with intrahepatic cholestasis who developed recurring pulmonary symptoms histologically—some with organizing pneumonia and some with BOOP.³⁸ These features occurred every year in most patients during the last weeks of February and resolved by early May. The cause was not determined, although it was thought to be an inhaled agent present in the general environment. It was probably due to an immunologically-mediated hypersensitivity response, rather than an infection. *Textile printing dye-related BOOP* was reported in 22 textile air-brushing company workers among 257 in eight textile printing factories.³⁹ Six of the patients died. It was related to the spraying procedures that delivered a respirable aerosol of a specific chemical, Acramin FWN, to distal airways and alveoli.

BOOP is a distinctively different pathologic and clinical syndrome compared to *constrictive bronchiolitis (bronchiolitis obliterans)* (see Table 6). Chest physical findings differ, with early inspiratory crackles in bronchiolitis obliterans, and late inspiratory crackles in BOOP. Chest radiographic findings differ, often being normal in bronchiolitis obliterans, while bilateral patchy infiltrates are present in BOOP. Pulmonary function shows airflow obstruction with decreased FEV₁/FVC in the former and abnormal diffusing capacity in the latter. Response to therapy and prognosis differ markedly as well. Minimal-to-moderate response to corticosteroid therapy and a disabling disorder is expected in patients with bronchiolitis obliterans. In contrast, complete recovery can be anticipated in 65 to 80% of patients with BOOP.

Table 6—Distinctions Between Bronchiolitis Obliterans and BOOP

Description	Bronchiolitis Obliterans	BOOP*
General	Airflow disorder	Interstitial disorder
Chest exam	Early crackles	Late crackles
Chest radiograph	Normal	Patchy infiltrates
Pulmonary function	Reduced FEV ₁ , FEV ₁ /FVC%	Reduced TLC and DCO
Bronchoalveolar lavage	Neutrophils	Lymphocytes
Therapy response	Poor	Good
Prognosis	Poor	Good

*TLC = total lung capacity; DCO = diffusion of carbon monoxide.

References

1. Thompson AB, Robbins RA, Romberger DJ, et al. Immunological function of the pulmonary epithelium. *Eur Respir J* 1995; 8:127-49
2. Hayakawa H, Sato A, Toyoshima M, et al. Bronchiolar disease in rheumatoid arthritis. *Am J Respir Crit Care Med* 1996; 154:1531-36
3. Churg A. Mineral dust induced bronchiolitis. In: Epler GR, ed. *Diseases of the bronchioles*. New York: Raven Press. 1994, 139-51
4. Fitzgerald JE, King TE Jr, Lynch DA, et al. Diffuse panbronchiolitis in the United States. *Am J Respir Crit Care Med* 1996;154:497-503
5. Colby TV, Myers JL. Clinical and histologic spectrum of bronchiolitis obliterans, including bronchiolitis obliterans organizing pneumonia. *Semin Respir Med* 1992;13:119-33
6. Kraft M, Mortenson RL, Colby TV, et al. Cryptogenic constrictive bronchiolitis. *Am Rev Respir Dis* 1993;148:1093-1101
7. Konichezky S, Schattner A, Ezri T, et al. Thionyl-chloride-induced lung injury and bronchiolitis obliterans. *Chest* 1993; 104:97:1-73
8. Muller NL, Miller RR. Diseases of the bronchioles: CT and histopathologic findings. *Radiology* 1995;196:3-12
9. Boehler A, Vogt P, Speich R, et al. Bronchiolitis obliterans in a patient with localized scleroderma treated with D-penicillamine. *Eur Respir J* 1996, 9:1317-19
10. Yousem SA. The histological spectrum of pulmonary graft-versus-host disease in bone marrow transplant recipients. *Hum Pathol* 1995; 26:668-75
11. Reichenspurner H, Girgis RE, Robbins RC, et al. Stanford experience with obliterative bronchiolitis after lung and heart-lung transplantation. *Am Thorac Surg* 1996; 62:1467-73
12. Novick RJ, Stitt L, Schafers HJ, et al. Pulmonary retransplantation. *J Thorac Cardiovasc Surg* 1996;112:1504-14
13. Hohlfeld J, Niedermeyer J, Hamm H, et al. Seasonal onset of bronchiolitis obliterans syndrome in lung transplant recipients. *J Heart Lung Transplant* 1996; 15:888-94
14. Webb WR. High-resolution lung computed tomography: normal anatomic and pathologic findings. *Radiologic Clinics of North America* 1991;29(5):1051-63
15. Ikonen T, Kivisaari L, Harjula ALJ, et al. Lung and heart-lung transplantation: Value of high-resolution computed tomography in routine evaluation of lung transplantation recipients during development of bronchiolitis obliterans syndrome. *J Heart Lung Transplant* 1996; 15:587-95
16. Snell GI, Esmore DS, Williams TJ. Cytolytic therapy for the bronchiolitis obliterans syndrome complicating lung

transplantation. *Chest* 1996; 109:874-878.

17. Iacono AT, Keenan RJ, Duncan SR, et al. Aerosolized cyclosporine in lung recipients with refractory chronic rejection. *Am J Respir Crit Care Med* 1996; 153:1451-55

18. Miller RR, Muller NL. Neuroendocrine cell hyperplasia and obliterative bronchiolitis in patients with peripheral carcinoid tumors. *Am J Surg Pathol* 1995; 19:653-58

19. Sheerin N, Harrison NK, Sheppard MN, et al. Obliterative bronchiolitis caused by multiple tumourlets and microcarcinoids successfully treated by single lung transplantation. *Thorax* 1995; 50:207-09

20. Chatte G, Streichenberger N, Boillot O, et al. Lymphocytic bronchitis/bronchiolitis in a patient with primary biliary cirrhosis. *Eur Respir J* 1995; 8:176-79

21. Chang H, Wang JS, Tseng HH, et al. Histopathological study of *Sauropus androgynus* associated constrictive bronchiolitis obliterans. *Am J Surg Pathol* 1997; 21:35-42

22. Epler GR. Bronchiolitis obliterans organizing pneumonia. *Semin Respir Infect* 1995; 10:65-77

23. Froudarakis M, Bouros D, Loire R. BOOP presenting with haemoptysis and multiple cavitary nodules. *Eur Respir J* 1995; 8:1972-74

24. Boots RJ, Mowat P, McEvoy JDS. Bronchiolitis obliterans organising pneumonia. *Aust NZ J Med* 1995; 25:140-45

25. Preidler KW, Szolar DM, Moelleken S, et al. Distribution pattern of computed tomography findings in patients with bronchiolitis obliterans organizing pneumonia. *Invest Radiol* 1996; 31:251-55

26. Costabel U, Teschler H, Schoenfeld B, et al. BOOP in Europe. *Chest* 1992; 102:14S-20S

27. Voloudaki AE, Bouros DE, Froudarakis ME, et al. Crescentic and ring-shaped opacities: CT features in two cases of bronchiolitis obliterans organizing pneumonia (BOOP). *Acta Radiol* 1996; 37:889-92

28. Yamamoto M, Ina Y, Kitaichi M, et al. Clinical features of BOOP in Japan. *Chest* 1992; 102:21S-25S

29. Ichikawa Y, Ninomiya H, Katsuki M, et al. Low-dose/Long-term erythromycin for treatment of bronchiolitis obliterans organizing pneumonia (BOOP). *The Kurume Med J* 1993; 40:65-67

30. Watson D, Fadem JJ. Bronchiolitis obliterans organizing pneumonia cured by standard dose inhaled triamcinolone. *South Med J* 1995; 88:980-83

31. Costabel U, Guzman J, Teschler H. Bronchiolitis obliterans with organising pneumonia. *Thorax* 1995; 50:S59-S64

32. Nizmi IY, Kissner DG, Visscher DW, et al. Idiopathic bronchiolitis obliterans with organizing pneumonia. *Chest* 1995; 108:271-277.

33. Diehl JL, Gisselbrecht M, Meyer G, et al. Bronchiolitis obliterans organizing pneumonia associated with chlamydial infection. *Eur Respir J* 1996; 9:1320-22

34. Domingo J, Perez-Calvo J, Carretero J, et al. Bronchiolitis obliterans organizing pneumonia. *Chest* 1993; 103:1621-23

35. Przepiorka D, Abu-Elmagd K, Huaranga A, et al. Bronchiolitis obliterans organizing pneumonia in a BMT patient receiving

FK506 [letter]. Bone Marrow Transplant 1993; 11:502

36. Chaparro C, Chamberlain D, Maurer J, et al. Bronchiolitis obliterans organizing pneumonia (BOOP) in lung transplant recipients. Chest 1996; 110:1150-54

37. Siddiqui MT, Garrity ER, Husain AN. Bronchiolitis obliterans organizing pneumonia-like reactions. Hum Pathol 1996; 27:714-19

38. Spiteri MA, Klenerman P, Sheppard MN, et al. Seasonal cryptogenic organising pneumonia with biochemical cholestasis. Lancet 1992; 340:281-84

39. Moya C, Anto JM, Taylor AJN. Outbreak of organising pneumonia in textile printing sprayers. Lancet 1994; 343:498-502

Copyright 1997 American College of Chest Physicians

Lesson 3, Volume 12—Immunotherapy and Allergen Avoidance for Allergic Airway Disorders

By John W. Georgitis, MD, FCCP

Objectives

1. To list common categories and types of allergens
2. To describe early and late phase responses and importance of mast cells in the allergic response
3. To list the measures of allergen avoidance
4. To examine the benefits and risks of immunotherapy
5. To identify the advantages and disadvantages of immunotherapy in asthma.

Key words

airway disorders; allergen avoidance; allergen immunotherapy

Medical management of rhinitis and asthma have been reviewed recently, especially in the revised National Heart, Lung and Blood Institute Expert II Panel Report on asthma guidelines,¹ so this discussion will cover the indications and methodology of allergen avoidance and immunotherapy. Immunotherapy and allergen avoidance are highly successful for aeroallergen-induced allergic airway disorders, especially allergic rhinitis. Allergic airway diseases, rhinitis, and asthma are fairly common along with chronic disorders. Allergic rhinitis by conservative estimates affects at least 20% of the general population.² An additional 7 to 10% of people can develop allergic rhinitis over the years.³ Allergic rhinitis classically affects people in their peak productive years of 10 to 35 years but can affect infants and geriatric individuals. There is a high morbidity and cost associated with allergic rhinitis: \$500 million per year in health-care costs, 2 million lost school days, 3.5 million lost work days, and 2.8 million days in restricted activity. Allergic rhinitis is also associated with other disorders such as chronic or recurrent sinusitis, acute and chronic otitis media, asthma, and atopic dermatitis. In fact, 20% of rhinitis patients also have concomitant asthma.

Asthma is thought to affect 5% of the population or 10 million of the US population. It is a far more serious disorder since mortality rates are rising nationally and internationally in select populations. Costs for treatment for asthma average \$3.6 billion in 1990 for hospital and physician expenses and \$1.1 billion in medications.⁴ The indirect expenses for asthma were \$2.6 billion, which included lost school days and days absent from work. Allergic asthma is one of many triggers for asthma and may be the major cause for underlying bronchial hyperreactivity present in asthma. Of note, 60% of asthmatics also suffer with concurrent rhinitis symptoms.

The patient obviously must manifest symptoms after allergen exposure and have demonstrable allergen-specific IgE either by skin testing or serologic testing before instituting allergen avoidance or utilizing immunotherapy for the disorder. Allergen avoidance is not a 100% reduction of the aeroallergen exposure, but is in fact a reduction hopefully at levels below the threshold dose which initiates symptoms. Immunotherapy is best described as a slow immunization to a specific aeroallergen or allergens, yet has intrinsic risks associated with the treatments. Immunotherapy addresses the underlying allergic reaction and attempts to modify the response to aeroallergens that induce the reaction.

Aeroallergens include pollens, molds, and animal particles such as hair, saliva, dander, urine, feces, and body parts (mammals, mites, birds, insects). An aeroallergen must be sensitizing and must be present in the ambient air in ample quantities to cause

symptoms in an allergic individual. Ragweed pollen is probably the most cited example of a seasonal aeroallergen in that people allergic to ragweed have significant exposure during the months of August and September. Examples of other seasonal allergens include grasses (late spring exposure); oak, birch, hickory, maple, walnut, cedar, willow (early spring); and Russian thistle, pigweed, plantain, chenopodium or sage (summer and fall). The most often-cited perennial allergens are house dust mites: *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*, yet cockroach antigen is also a prevalent allergen in inner-city housing complexes.

Pathophysiology of Allergic Reactions

The basic mechanism of the allergic response involves allergen-specific IgE, which is bound on the surface of mast cells^{5,6} and which reacts to a specific aeroallergen resulting in cross-linkage of IgE receptors and subsequent mast cell activation. The mast cell is a keystone cell in this response. Other inflammatory cells such as neutrophils, basophils, and eosinophils are important in this reaction, but the mast cell is the first cell activated in the allergic reaction. Mast cells are located on the mucosal surface, interspersed among epithelial cells and in the submucosal space. With aeroallergen exposure and mast cell activation, preformed and newly formed mediators are released rapidly into the surrounding tissues. The preformed mediator, histamine, is found in high concentrations inside the mast cell and with release activates histamine receptors responsible for mucosal vasodilation, itching, edema, secretory gland, and goblet cell mucin release. Newly formed mediators are created in this allergic reaction from phospholipase A₂ activation resulting in arachidonic acid formation, which in turn is metabolized to leukotriene C4 or prostaglandin D₂.^{6,7,8} In addition, platelet activating factor (PAF) is formed. Chemotactic factors and cytokines are also produced causing cellular influxes of neutrophils, eosinophils, and basophils to the site of the allergic reaction. This immediate response to aeroallergens involving mast cells is called the early allergic reaction.

Two to 8 hours later, there is another allergic reaction referred to as the late-phase reaction (LPR),⁹ which is characterized by an influx of inflammatory cells. Predominantly neutrophils and eosinophils appear at the site and there is further leukotriene and histamine release into nasal secretions during the LPR indicating alternative sources of these inflammatory mediators other than the mast cell. In addition, the tissues are hyper-responsive to other nonaeroallergen stimuli such as irritant gases, perfumes, or odors for example. In terms of reactivity, the tissues during the LPR also respond to lower doses of the aeroallergen than the first initial exposure.

During natural exposure to aeroallergens, the allergic individual exhibits a seasonal rise in allergen-specific IgE, eosinophilia of the tissues and secretions, hypersecretion, inflammation and increased hyperreactivity of the airway tissues.¹⁰ There is also an increase in histamine in nasal secretions and inflammatory mediators during the aeroallergen exposure.

Allergen Avoidance

Americans in the United States spend 30 to 60% of daily living in their homes, so reduction or control of allergen exposure at home should be the natural first intervention for treating allergic airway disorders. These interventions are simple and inexpensive compared to pharmacologic options. Yet actual institution of these controlling measures is dependent upon the individual's motivation. Analysis of home or work dust samples can characterize and quantitate the specific environmental allergens. Furthermore, postinterventional dust analyses may provide a measure of the specific intervention's effectiveness. Table 1 lists the common indoor allergens and known threshold levels for specific allergens. Tables 2-5 are specific interventions for identified allergens. Der f 1 and Der p 1 levels greater than 2,000 ng/g of dust collected and Fel d 1 higher than 8,000 ng/g delineate levels where there should be environmental intervention.^{11,12}

Table 1—Indoor Allergens

Source	Allergen	Molecular Weight	Action Level
Animals			
<i>Felis domesticus</i> (cat)	Fel d 1	35	8,000 ng/g

<i>Felis domesticus</i> (cat)	Fel d 1	35	8,000 ng/g
<i>Canis familiaris</i> (dog)	Can f 1	25	□
<i>Mus musculus</i> (mouse)	Mus m 1	19	□
Insects			
<i>Blattella germanica</i> (German cockroach)	Bla g 1	28	> 1 unit/g
	Bla g 2	36	□
	Bla g 4	21	□
<i>Peripaneta americana</i> (American cockroach)	Per a 1	20-25	□
House dust mites			
<i>Dermatophagoides farinae</i>	Der f 1	25	2,000 ng/g
	Der f 2	14	□
<i>Dermatophagoides pteronyssinus</i>	Der p 1	25	2,000 ng/g
	Der p 2	14	□
<i>Euroglyphus maynei</i>	Eur m 1	25	□
<i>Bloma tropicalis</i>	Blo t 5	14	□
Fungi			
<i>Aspergillus fumigatus</i>	Asp f 1	18	10,000 colonies
<i>Alternaria alternata</i>	Alt a 1	32	□
Penicillium	□	□	□
Cladosporium	□	□	□

Table 2—Pollen Control Measures

Close windows and doors
 Install window filters
 Avoid hanging laundry outdoors
 Avoid early morning outdoor activities
 Wear facemask when mowing
 Clean up immediately after extended periods outdoors
 Use air conditioning in car and home
 Use HEPA filters in rooms

Table 3—Animal Danders

Control where pet sleeps Treat pet's coat Bathe animal regularly Clean home regularly and thoroughly

Table 4—Molds and Fungi

Keep humidity low Install exhaust fan Use safe yet strong household cleaners Limit number of household plants Store firewood outdoors Remove old wallpaper Take up carpeting from damp areas
--

Table 5—House Dust Mites

Cover/encase bedding Wash sheets and pillowcases often (>140F hot water) Clean carpet and rugs or treat with tannic acid Do not steam clean Avoid upholstered furniture Keep clothing away in closets and drawers
--

Recent studies have demonstrated that simple environmental intervention such as changing to new bedding, removal of an animal, regular vacuuming and dusting, or hot water washing of bedding and pillows can reduce the amount of specific allergens present in homes.^{13,14} In terms of clinical efficacy, Ehnert and associates have shown that reduction of house dust mite levels below 2 ng/g of dust collected increases the PC₂₀ to histamine in asthmatic children.¹⁵ Other simple measures such as use of HEPA filters, which reduce dust amounts, result in symptomatic improvement in individual allergic subjects.¹⁶ Unfortunately, effective reduction in cockroach allergen has been difficult and requires further study.

Mechanisms of Immunotherapy

Several general principles are needed before instituting immunotherapy. IgE-mediated sensitivity should be documented to a specific aeroallergen by either cutaneous testing or by *in vitro* testing. There also needs to be an extract of the aeroallergen. Immunotherapy needs to be given in relatively high doses for a long period of time. The dose must be close to that dose that produces local and systemic reactions. A favorable response results in a reduction in symptoms, yet there is a fine line between effective dose and injections resulting in significant reactions. This is the major reason that allergen immunotherapy should be administered in an office setting.

Effective immunotherapy alters skin test response, basophil histamine release, release of mediators into nasal secretions during challenge, and bronchial reactivity. The favorable clinical effect is often seen before alteration of these immunologic findings. The clinical response is often associated with an increase in allergen-specific IgG identified as "blocking antibody." Although there are exceptions where some patients have a favorable response but no IgG antibody production. With immunotherapy, there is an initial rise in serum allergen-specific IgE, then blunting of the seasonal rise in IgE and ultimately a fall in IgE titers. Immunotherapy may also reduce mast cell sensitivity to aeroallergens independent of its effects on B cell production of IgE and IgG.

The rationale for immunotherapy is that in nature, avoidance of pollens, molds, and house dust mites is extremely difficult and unrealistic at times. Alternatively, some aeroallergens such as animal danders from dogs or cats and urine from laboratory animals can be avoided. The goal of immunotherapy is to increase the individual's tolerance to natural exposure of the aeroallergen resulting in symptom control and decrease in medication use.

Efficacy of immunotherapy for allergic rhinitis has been well documented.^{17,18} In placebo-controlled trials, ragweed immunotherapy demonstrated efficacy based upon symptom-medication scores. This effect was dose-related whereby maintenance doses of 1 g or more of antigen E (Amb a I) were effective and lower doses ranging from 0.00024 to 0.006 g were ineffective. Immunologic findings were a rise in serum IgG, an initial rise in serum IgE then decline to pretreatment levels, no seasonal rise in IgE, an increase in ragweed-specific IgA and IgG in nasal secretions, a decrease in lymphocyte responsiveness to ragweed, an increase in threshold allergen dose on nasal challenge for release of inflammatory mediators (histamine, PGD₂, leukotrienes, and kinins) and suppression of late-phase skin reactions to intradermal ragweed extract. Similar double-blind studies have shown clinical efficacy for grass, mountain cedar, and house dust mite immunotherapy for allergic rhinitis.

Efficacy for allergic asthma is not as extensive as for rhinitis, inherent in identification of aeroallergen-induced asthma without other complicating factors. One study was unable to identify adequate numbers of patients to investigate ragweed immunotherapy in asthma.¹⁹ In grass-sensitive asthmatics given immunotherapy, older studies noted a reduction in symptoms with treatment. A recent study by Creticos and associates²⁰ involving ragweed-allergic asthmatic adults did show some benefit in asthma symptoms and medication use, yet Adkinson and colleagues²¹ were unable to show superiority of immunotherapy to conventional "appropriate medical treatment" in children with perennial asthma.

Cat-induced asthma has been the best model for allergic asthma. In elegant studies, cat immunotherapy was shown to be as safe as ragweed immunotherapy.^{22,23} Double-blind trials using cat immunotherapy demonstrated a decrease in bronchial reactivity to cat dander, a reduction in skin prick test response, an increase in IgG to the major cat allergen, Fel d 1, and the expected response of an initial rise in IgE then fall to pretreatment levels. One study by Ohman and associates²³ used deliberate exposure to cats in a confined area to demonstrate that patients on active immunotherapy had a significant delay before onset of eye and pulmonary symptoms. Similar studies²⁴ have shown efficacy for dog immunotherapy in asthma.

Immunotherapy to house dust-induced asthma has had conflicting results, with two positive studies and one negative study. This is not surprising since house dust contains a variety of allergens ranging from mites, cockroaches, cats, dogs, other animal danders to pollens and molds. Immunotherapy to house dust mite shows a significant decrease in asthma symptoms, decrease in medications, and decrease in response to both immediate and late-phase responses during bronchoprovocation.

There are, however, immunotherapy procedures that are not effective. Low dose regimens (Rinkel technique) are proven ineffective in several double-blind, placebo-controlled studies. Immunotherapy based upon provocation-neutralization and sublingual immunotherapy have not undergone the rigors of placebo-controlled, double-blind investigations as other immunotherapy regimens, so efficacy of these types is purely anecdotal.

Immunotherapy Regimens

There are certain basics to immunotherapy. In selecting patients, they need to have symptoms of allergic rhinitis or asthma, demonstrate IgE by skin testing or *in vitro* testing, and inability to control symptoms through avoidance and/or medications. Immunotherapy should be used with other general treatment regimens, *ie*, continuing asthma medications, and controlling their environment. A practical consideration is limiting the allergens to 6 to 10 for each treatment vial. Therefore, the testing should identify the selective aeroallergens to be used in the individual. Treatment with irrelevant allergens is not advised, wasteful, and may induce sensitivity to that allergen.

Allergenic extracts require careful storage in order to maintain potency. Extracts will lose 50% of their initial potency when kept at room temperature or by going through repeated freezing and thawing. Extracts containing 50% glycerin are stable for 3 years at 4° C as are freeze-dried extracts kept at the same temperature. Concentrated aqueous extracts without glycerin stored at 4° C lose their potency slowly over time such that it is at 50% potency after 6 months. Diluted aqueous extracts lose potency more rapidly. Use of standardized extracts is highly desirable and the FDA now utilizes the allergy unit (AU) to characterize these extracts. For other extracts, the old method for extracts utilizes protein nitrogen units (PNU) or weight per volume (w/v).

The recommended starting dose for sensitive patients is 0.5 AU, 0.4 PNU or 0.1 mL of a 1:200,000 w/v dilution. Doses may be safely increased by two-fold dilutions at weekly or twice a week intervals. If local or systemic reactions occur, the dose should be reduced to the previously tolerated dose. Rush or clustered schedules have been developed to expedite the immunization process but have not undergone extensive trials for aeroallergen use.

Maintenance dose is that concentration resulting in clinical reduction of symptoms and administered safely without systemic reactions. This is usually an individual response but most patients can achieve a dose of 1,000 AU with the exception of cat extract, which is 25,000 AU. The interval of maintenance dose is 3 to 4 weeks. Duration of therapy is dictated by the patient, but is commonly given for 2-3 years during which there is gradual clinical symptom control. Discontinuation of immunotherapy may be considered after this interval weighing the risk of reappearance of symptoms. In situations without clinical improvement, one must consider either modification of the immunotherapy or cessation of the regimen.

Most patients on immunotherapy will experience local reactions such as localized swelling and erythema that resolve over hours. However, local reactions can be large (>4 cm in diameter) causing considerable discomfort and lasting greater than 24 h. Systemic reactions are a distinct risk for patients on immunotherapy.²⁵ These may range from simple hives to severe life-threatening anaphylaxis. In some instances, systemic reactions have been fatal.¹⁸ Systemic reactions may be generalized urticaria and/or angioedema, swelling of the airway (tongue, throat, and lower airway) with impaired swallowing or breathing, or cold, damp skin, rapid pulse, and low blood pressure. In addition, there may be exacerbation of allergic symptoms such as sneezing, rhinorrhea, nasal congestion, wheezing, coughing, and shortness of breath. These must be differentiated from the vasovagal reactions of low blood pressure with low heart rate.

Table 6—Guidelines for Administration of Immunotherapy

1. Observe the patient for 15 min.
2. Personnel familiar with a) adjustment of dose to minimize reactions, b) recognize and treat local reactions and systemic reactions, c) be trained in CPR.
3. Have available resuscitative equipment including stethoscope, sphygmomanometer, tourniquets, syringes and needles, epinephrine, oxygen, oral airway, intravenous fluids, and tracheostomy setup.

The American Academy of Allergy and Immunology has published recommended guidelines for practitioners giving immunotherapy. These are listed in Table 6. In addition, some physicians observe highly allergic individuals for 25-30 min with each injection. For asthmatic patients, immunotherapy should be administered only if the patient's peak flow or FEV₁ is greater than 75% of their personal best. In addition, immunotherapy probably should not be administered to patients on chronic beta-blockers or having significant cardiovascular disease. In pregnant patients, immunotherapy should not be started and for those patients already on immunotherapy but not a maintenance dose, the current dose should be used until the pregnancy is completed.

Future of Immunotherapy

The future of immunotherapy is difficult to predict, but in the foreseeable future, the regimens and/or agents will be vastly different than they are today. Local nasal administration for immunotherapy has been tried and found to be effective in ragweed and grass-sensitive individuals. The advantages of such a program are that treatment can be given at home, it is relatively safe, and it is cost-effective. However, further studies are needed to elucidate the mechanism(s) of action and use of other aeroallergens. Recent work²⁶ has indicated that anti-cytokine or anti-IgE therapy may be highly effective in altering the allergic response and is undergoing clinical trials.

Summary

In summary, allergen avoidance is the first intervention used in the allergic individual, whereas immunotherapy is best given for

patients who are unresponsive to avoidance/environmental control and pharmacotherapy management. Immunotherapy is proven effective for allergic rhinitis and allergic asthma. Therapy however involves 2-3 years and has inherent risks of anaphylaxis and local reactions that the patient needs to be made aware of before instituting the injections.

References

1. National Asthma Education and Prevention Program: Expert Panel Report 2: Guidelines for the Diagnosis and Treatment of Asthma. NIH Publication #55-4051 Bethesda, Md. February, 1997
2. Hagy GW, Settipane GA. Rhinitis. 2nd Ed. Providence, RI: Oceanside Publishing Inc. 1991
3. Settipane RJ, Hagy GW, Settipane GA. Long term risk factors for developing rhinitis: a 23 year follow-up study of college students. *Allergy Proc* 1994; 15: 21-25
4. Weiss KB, Gergen PJ, Hodgson TA. An economic evaluation of asthma in the United States. *N Engl J Med* 1992; 326: 862-66
5. Ishizaka K, Ishizaka T. Identification of gE antibodies as a carrier of reagenic activity. *J Immunol* 1967;99:118797
6. Barnes PJ. Pathophysiology of allergic inflammation. In: Middleton EM Jr, Reed CE, Ellis EF, et al, eds. *Allergy: principles and practice*. St. Louis: CV Mosby Co. 1993; 243-66
7. Mayatepek E, Hoffman GF. Leukotrienes: biosynthesis, metabolism, and pathophysiologic significance. *Pediatr Res* 1995; 37: 1-9
8. Henderson WR, Jr. The role of leukotrienes in inflammation. *Ann Int Med* 1994; 121: 684-97
9. Lemanske RF, Kaliner MA. Late phase allergic reactions In: Middleton EM Jr, Reed CE, Ellis EF, et al, eds. *Allergy: principles and practice*. St. Louis: CV Mosby Co. 1993; 320-61
10. Van Metre TE Jr, Adkinson NF Jr. Immunotherapy for aeroallergen disease. In: Middleton EM Jr, Reed CE, Ellis EF, et al, eds. *Allergy: principles and practice*. St. Louis: CV Mosby Co. 1993; 1327-43
11. Hamilton RG, Chapman MD, Platts-Mills TAE, et al. House dust aeroallergen measurements in clinical practice: a guide to allergen-free home and work environments. *Immunol Allergy Pract* 1992; 14: 96-112
12. Platts-Mills TAE, Woodfolk JA, Chapman MD, et al. Changing concepts of allergic disease: the attempt to keep up with real changes in life styles. *J Allergy Clin Immunol* 1996; 98: S297-306
13. Christiansen SC, Martin SB, Schleicher NC, et al. Exposure and sensitization to environmental allergen of predominantly Hispanic children with asthma in San Diego's inner city. *J Allergy Clin Immunol* 1996; 98: 288-94
14. Sakaguchi M, Inouye S, Sasaki R, et al. Measurement of airborne mite allergen exposure in individual subjects. *J Allergy Clin Immunol* 1996; 97: 1040-44
15. Ehnert B, Lau-Schadendorf S, Weber A, et al. Reducing domestic exposure to house dust mite allergen reduces bronchial hyperreactivity in sensitive children with asthma. *J Allergy Clin Immunol* 1992; 90: 135-38
16. Reisman RE, Mauriello PM, Davis GB, et al. A double-blind study of the effectiveness of a high-efficiency particulate air (HEPA) filter in patients with perennial allergic rhinitis and asthma. *J Allergy Clin Immunol* 1990; 85: 1050-57

17. Rocklin RE, Sheffer AL, Greineder DK, et al. Generation of antigen-specific suppressor cells during allergy desensitization. *N Engl J Med* 1980; 302: 1213-19
18. Norman PS. Safety of allergen immunotherapy. *J Allergy Clin Immunol* 1989; 84: 438-89
19. Bruce CA, Norman PS, Rosenthal RR, et al. The role of ragweed pollen in autumnal asthma. *J Allergy Clin Immunol* 1977; 59: 449-59
20. Creticos PS, Reed CE, Norman PS, et al. Ragweed immunotherapy in adult asthma. *N Engl J Med* 1996; 334: 501-06
21. Adkinson NF, Jr, Eggleston PA, Eney D, et al. A controlled trial of immunotherapy for asthma in allergic children. *N Engl J Med* 1997; 336: 324-31
22. Taylor WW, Ohman JL, Lowell TC. Immunotherapy in cat-induced asthma. Double-blind trial with evaluation of bronchial responses to cat allergen and histamine. *J Allergy Clin Immunol* 1978; 61: 283-87
23. Ohman JL, Findlay SR, Leiterman M. Immunotherapy in cat-induced asthma. Double-blind trial with evaluation of in vivo and in vitro responses. *J Allergy Clin Immunol* 1984; 74: 230-39
24. Valovirta E, Koivikko A, Vanto T, et al. Immunotherapy in allergy to dog: a double-blind clinical study. *Ann Allergy* 1984; 53:85
25. Tinkelman DG, Cole WQ, Tunno J. Immunotherapy: a one-year prospective study to evaluate risk factors of systemic reactions. *J Allergy Clin Immunol* 1995; 95: 8-14
26. Kepron W, Jackson C-J, Ceton HA. A canine model for the study of hapten-specific suppression of IgE-mediated bronchoconstriction and anaphylaxis. *Int Arch Allergy Immunol* 1987; 82:468-70

Copyright 1997 American College of Chest Physicians

Lesson 4, Volume 12—Preoperative Pulmonary Evaluation

By Juliette Wait, MD

Objectives

1. To know the risks of pulmonary complications in relation to the type of surgical procedure
2. To understand the value of preoperative pulmonary function testing, which patients should be studied, and how the results should be used
3. To know the guidelines for assessment of patients before surgical resection of the lung
4. To be familiar with the issues concerning the evaluation of patients for lung reduction surgery or transplantation
5. To fully understand postoperative management

Key words

preoperative assessment; preoperative PFTs; pulmonary complications; surgery

The Types of Surgical Procedures and Pulmonary Complications

The types of surgery performed and anatomical location of the surgery are major determinants of risk factors in the development of postoperative pulmonary complications. The greatest complications are found with surgery to the thorax and upper abdomen, with additional considerations for resection of the lung for any reason. The types most commonly associated with complications will be addressed first.

Upper Abdominal Surgery

The pulmonary complication rate after surgery to the upper abdomen is as great as 20%, which is significantly more than that of surgery to the lower abdomen. The difference is due in part to the effect of upper abdominal surgery on the respiratory muscles. Several studies have described breathing patterns with either increased use of the ribcage muscles or increased use of abdominal expiratory muscles (to lengthen the diaphragm during exhalation) due to decreased use of the diaphragm after upper abdominal surgery. This has been attributed to a reflex inhibition of diaphragmatic stimulation. In anesthetized animals, reflex inhibition of neuronal stimulation to the diaphragm has been demonstrated during manipulation of abdominal viscera or distention of the esophagus.¹ In humans this reflex inhibition is reversed by administration of epidural anesthesia. Following abdominal surgery, patients develop a breathing pattern that maintains an adequate minute ventilation but with a smaller tidal volume and an increased respiratory rate. This breathing pattern persists for several days up to 1 week and is associated with a decrease in measured vital capacity. These breathing patterns are likely to promote atelectasis, which may in turn, lead to hypoxemia, retained secretions, and possibly pneumonia in the postoperative patient. Other factors may contribute to increased respiratory complications or to poor function of the respiratory muscles. These include acute bronchitis, hypophosphatemia, hypocalcemia, and a general debilitated state. A diagnosis of chronic obstructive pulmonary disease, *per se*, has not proven to be an independent predictor of postoperative pulmonary complications in patients after elective abdominal aortic surgery, in which the overall pulmonary complication rate was 16%. However, prolonged anesthesia time and use of large volumes of crystalloid did. Similarly, several studies have identified other factors that contribute to increased pulmonary complications after upper abdominal surgery. These factors do not have a good

negative predictive value, but they do have a relatively good positive predictive value.² These nonpulmonary risk factors include: duration of surgery greater than 2 hours, age greater than 60 years, presence of significant medical disease (*ie*, American Society of Anesthesiology [ASA] classification >1), male gender, and positive smoking history. The ASA score is used by anesthesiologists to determine preoperative risks based on simple clinical criteria. Although this scoring system is rather subjective, most critics agree that any score of more than 1 is relatively easy to identify. An ASA score of 1 is a healthy individual, with scores of 2-5 indicating levels of severity of disease.

Liver Transplantation

Liver transplantation is associated with a greater risk for postoperative pulmonary complications due to the nature of the underlying disease being treated and long anesthesia time required for the surgery. Not surprisingly, more than other operations to the upper abdomen these patients have a higher incidence of pulmonary infections and postoperative adult respiratory distress syndrome (ARDS), usually due to sepsis or occasionally attributed to intravenous cyclosporine.³ Preoperative hypoxemia is often related to intrapulmonary vascular dilatations which are best documented by perfusion lung scanning or contrast echocardiography that demonstrate shunting.³ Since severe hypoxemia may pose an additional risk in these patients, a poor preoperative response to 100% oxygen may preclude transplantation.

Laparoscopic Abdominal Surgery

Laparoscopic cholecystectomy has become so common, it is almost the norm rather than the exception. The laparoscope is now used for many other abdominal procedures, but the preponderance of case studies regard the complication rate following cholecystectomy. Direct comparisons with open procedures are difficult because there are differences in patient selection and follow-up with different studies. Nevertheless, laparoscopic surgery is associated with fewer postoperative pulmonary abnormalities and shorter hospital stays.^{4,5} The mean stay for a cholecystectomy is less than 1.2 days, and some cases are handled in day surgery.⁴ The early ambulation and discharge from the hospital probably contribute significantly to the decreased incidence of postoperative complications. The technique uses small incisions in the abdominal muscles and less manipulation of the abdominal organs, hence minimizing the adverse effects of surgery on the respiratory muscles. Although these procedures involve smaller incisions, the anesthesia time is often longer. Intraoperative hypercarbia and acidosis from absorption of intraperitoneal carbon dioxide may cause problems during surgery, but these reverse quickly with removal of the gas.

Thoracic Surgery

By causing injury to the thoracic muscles, thoracotomy decreases the compliance of the chest wall, reducing the vital capacity and predisposing the patient to alveolar hypoventilation and hypoxemia. The decrease in compliance and vital capacity is most pronounced at 2 to 3 days postoperatively, and is often aggravated by pain. However, attempts to control the pain with narcotics may cause further respiratory distress and atelectasis. An approach to the thorax via a median sternotomy tends to lessen these problems, but does not avoid them.

Cardiac Surgery

Atelectasis of the left lower lobe after cardiac surgery is a common finding that is often not listed as a complication unless other factors coexist such as fever, sputum production, or hypoxemia that may adversely affect the patient's hospital course. The incidence has been reported in as many as 90% of patients and the cause is often attributed to damage to the phrenic nerve from the use of iced slushes to decrease myocardial oxygen demand during bypass.⁶ The nerve injury may last from 30 days to as long as 2 years and is often associated with an elevated left hemidiaphragm on chest x-ray. The incidence is decreased if pericardial insulation is used during surgery. Operative factors associated with this complication are longer bypass times, entrance into the pleural cavity, or direct damage during mobilization of the internal mammary artery. Bilateral phrenic nerve damage is less common but is associated with greater morbidity, often requiring prolonged mechanical ventilation.

There are no studies indicating there is a value of pulmonary function below which cardiac surgery is precluded. Patients with abnormal pulmonary function studies, abnormal chest radiographs, and left ventricular failure are more likely to have complications of prolonged mechanical ventilation, atelectasis, or postoperative pneumonia than are patients with normal pulmonary function and

left ventricular function. The overall incidence of major and minor pulmonary complications in patients after coronary bypass surgery is 7.5%. Although patients with complications had slightly lower preoperative lung function and lower postoperative oxygen levels, routine chest physiotherapy did not prevent complications. Normal pulmonary and left ventricular function does not guarantee that complications will not occur; conversely, patients with abnormal lung function and left ventricular function may do very well. ARDS is a postoperative complication that has been described in association with the preoperative use of amiodarone. In one study, ARDS occurred in 17% of patients who had received preoperative amiodarone and was associated with a 50% mortality rate.⁷ The cause is not known but may be related to the production of oxygen-free radicals through a synergistic effect of high inspired oxygen levels during surgery.

Video-Assisted Thoracoscopic Surgery and Thoracoscopy

Newer technologies such as the videoscope, the staple gun, and the laser knife have allowed thoracic surgeons to operate through much smaller incisions. At this time, almost any surgical procedure that can be performed in or on the chest have been tried with the more limited access using the videoscope. When the technique is successful and a larger procedure is not needed, the hospitalization time is substantially decreased to 3 to 5 days compared to 8 to 10 days for open thoracic procedures. Smaller incisions, performed without spreading the ribs, and the limited manipulation of internal organs may also contribute to the reduced postoperative pain and more rapid recovery. The complication rate overall is less which may be due to early mobilization and discharge from the hospital.⁸

Lung Resection

A recent multicenter study of more than 12,000 thoracotomies, usually for carcinoma, examined the incidence of in-hospital mortality for lung resection. The study found an in-hospital mortality rate of 3.8% after wedge resection, 3.7% after segmental resection, 4.2% after lobectomy, and 11.6% after pneumonectomy.⁹ The significant predictors of in-hospital mortality were age >60 years, male gender, extended resection, chronic lung or heart disease, diabetes, and with larger hospitals having lower rates. Lobectomy, but not pneumonectomy, is associated with a significant early loss of lung function that improves over time. Recently, multivariate analysis has shown that a low predicted FEV₁ and a high LDH were independently associated with postoperative morbidity.¹⁰

Survival

Currently, bronchogenic carcinoma is the most common indication for lung resection; it is usually performed with a standard thoracotomy in patients who often have underlying damage to the lungs secondary to cigarette smoke. For some patients, the risks of curative surgery may include death, incapacitation from loss of lung function, or other severe postoperative morbidity. Complete resection of surgical Stage I or II non-small cell lung cancer gives a predicted 5-year survival rate of approximately 70% and 50% respectively, exclusive of operative mortality.¹¹ However, the mortality rate from chronic obstructive pulmonary disease with a forced expiratory volume in 1 second (FEV₁) of less than 0.8 L/s, which is less than 30% predicted in a male) is relatively high, having a 5-year survival rate of approximately 20 to 30%, particularly if cor pulmonale is present.¹² This figure approaches the survival rate in otherwise relatively healthy individuals with unresectable lung cancer responding to radiation. Thus, including both operative mortality and morbidity, the risks to a patient whose lung function would decline to an FEV₁ of less than 30% predicted after resection are so great that most authorities do not recommend radical curative surgery for patients in this category. Careful evaluation of pulmonary function is imperative in patients scheduled to undergo curative lung resection for cancer.

Postoperative lung function is best predicted by quantitative lung scanning combined with preoperative assessment of the FEV₁. Perfusion scans are performed with quantitation of the radioactive uptake in each lung expressed as a percent of the total uptake by both lungs. It is currently suggested that the estimated postoperative FEV₁ be expressed as a percent of the normal predicted value for that patient, with a minimal accepted value of 30% predicted normal. One suggested method of using the quantitative lung scan to calculate the postoperative FEV₁ after lobectomy is as follows: The expected loss of function = Preop FEV₁ x (% function of the affected lung from the lung scan) x (Number of segments in the lobe to be resected / Total number of segments in the lung). Many studies have confirmed the good correlation between the predicted values and actual values, but this method does not accurately predict postoperative morbidity or mortality.

Lung Volume Reduction Surgery (LVRS)

By improving chest wall and respiratory muscle mechanics, resection of nonfunctioning bullous portions of lungs from patients with advanced emphysema often results in significant improvement of pulmonary function and improved distance walked in 6 min. Ideal patient selection and preoperative evaluation are not yet established. In general, the impairment to lung function in patients chosen for LVRS is not as severe as those listed for lung transplantation ($FEV_1 \leq 30\%$ predicted, vs $FEV_1 \leq 20\%$).¹³ Furthermore, LVRS can serve as a bridging procedure to transplantation by improving lung function for many years. However, this may be the only suitable alternative for some due to advanced age (>65 yr) or the presence of other exclusion criteria for transplantation. Adverse outcomes such as prolonged mechanical ventilation, persistent air leaks (40% have leaks greater than 1 week), and thoracic space problems are not well predicted and are often related to the choice of surgical procedure. Surgical candidates are selected by: 1) diagnosis of advanced emphysema with hyperexpansion of the thorax, 2) severe dyspnea, 3) presence of areas of residual lung with preserved architecture based on chest radiographs and chest CT scintigraphy, 4) general ability to withstand the surgical procedure, and 5) smoking cessation >6 months. CT provides more detailed information of the architecture of the lung than plain chest radiographs and may detect unsuspected lung carcinomas. Quantitative nuclear ventilation-perfusion scintigraphy (SPECT scan) is useful, but not mandatory, to better define the abnormally functioning areas of the lung. Patients with significant cardiac disease, $DCO \leq 15\%$ predicted, pulmonary artery hypertension (PAH) with cor pulmonale, or inability to participate in a pulmonary rehabilitation program are often associated with greater morbidity and mortality.¹⁴ Many centers exclude such patients.

Surgical Procedures With Lower Risk of Pulmonary Complications

A very low incidence of pulmonary complications has been described with surgical procedures to the lower abdomen such as appendix, inguinal hernia, female and male genital tracts. Most complications when they do occur are related to either sedation from pain medications resulting in atelectasis, or postoperative deep venous thrombosis and pulmonary embolism. Similarly, the same precautions apply to surgery to the extremities, particularly the lower limbs where the highest rates of deep venous thrombosis and pulmonary emboli are found. Neurosurgical patients may have an altered mental status with a decreased ability to cough, leading to lower tidal volumes and an increased risk of aspiration of oral contents. Surgical procedures to the head and neck for malignant conditions are often extensive and performed on older patients who may also have underlying pulmonary diseases or a debilitated state. Nevertheless, the incidence of pulmonary complications with these types of surgery are quite low when compared to surgical procedures to the thorax or upper abdomen.

Preoperative Pulmonary Function Studies

The purpose of doing pulmonary function studies in patients undergoing nonthoracic surgical procedures is not to preclude surgery but helps to anticipate and prevent complications. Preoperative pulmonary function studies are usually not needed for low-risk surgical procedures unless the patients are of advanced age (>60 years), have history of pulmonary disease, a history of smoking, or there is anticipation of anesthesia time greater than 2 h (see Table 1).

Table 1—Indications for Preoperative Pulmonary Function Studies

Age >60 years
Positive smoking history
Presence of pulmonary disease
Presence of pulmonary symptoms
Lung resection considered (add DCO)

Because both upper abdominal surgery and thoracotomy are associated with a higher rate of postoperative pulmonary complications, knowledge of the extent of the pulmonary dysfunction before surgery could lead to increased postoperative vigilance. Except for special circumstances, such as lung resection and some solid organ transplantation, denial of necessary surgery should not be based on lung function alone. Pulmonary function studies should include the FEV_1 , the forced vital capacity

(FVC), and sometimes the diffusing capacity of the lung for carbon monoxide (DCO). Routine arterial blood gas analysis does not have predictive value for postoperative complications, except that an arterial carbon dioxide level of more than 45 mm Hg has been noted to be associated with respiratory complications.

The normal pulmonary circulation has a sufficiently expansive capacity to meet the demands of a pneumonectomy in which the remaining lung must suddenly receive the entire cardiac output. However, a significant limitation to the pulmonary circulation even with good spirometry could have a bad outcome after lung resection. The best noninvasive method to assess the pulmonary circulation is the DCO, which is directly related to the volume of the pulmonary capillary bed. It has recently been reported to be a good predictor of morbidity and mortality after surgical lung resection. A retrospective review of patients in a large Chicago hospital who underwent lobectomy, bilobectomy, or pneumonectomy showed the DCO corrected for lung volume and hemoglobin was the best predictor of postoperative mortality and the only predictor of postoperative pulmonary complications.¹⁵ Any abnormality in DCO as a percent of predicted had an increasing association with postoperative mortality. The highest mortality (>24%) was found in those with DCO values below 60% predicted.

The additional value of exercise testing in assessing the risk to patients about to undergo a thoracotomy is still somewhat controversial. The level of the maximal attained oxygen consumption (VO_2) with incremental exercise can be used to assess both cardiac and pulmonary function with lower values associated with greater postoperative complications. Under most conditions, a VO_2 of greater than 20 mL/kg/min indicates good cardiovascular reserve and a low risk for thoracic surgery. More recent studies suggest that an acceptable value may be as low as 15 mL/kg/min. Similarly, an increase in the right ventricular ejection fraction with exercise was a good predictor of no complications following pulmonary resection.

Recommendations for Postoperative Management (see Table 2)

Table 2—Measures to Minimize Pulmonary Complications in Patients at Risk

Preop:

1. Smoking cessation
2. Antibiotics for acute bronchitis
3. Bronchodilators, if needed
4. Start incentive spirometry or chest physiotherapy

Postop:

1. DVT prophylaxis
2. Measures to improve vital capacity
3. Adequate pain control
4. Bronchodilators
5. CPAP or BiPAP if needed for atelectasis
6. Chest physiotherapy for atelectasis

1. Continue preoperative measures: Smoking cessation is important for the patients; delay surgery if acute bronchitis is present; continue bronchodilators; start incentive spirometry or chest physiotherapy in patients with high risk.
2. Measures to improve postoperative FVC: coughing, incentive spirometry, positive end-expiratory pressure (PEEP) or continuous positive expiratory pressure (CPAP) via face mask. Several controlled

studies have shown the lack of effectiveness of intermittent positive pressure breathing (IPPB) in postoperative patients. It also may be detrimental by causing significant abdominal distention, and is currently only indicated for use in patients with significant neuromuscular disorders who cannot cooperate with other respiratory maneuvers. PEEP or CPAP via a mask has been shown to increase postoperative FVC, improve gas exchange and decrease the incidence of atelectasis postoperatively.

3. Pain control: Epidural analgesia has been shown to be very effective in immediate postoperative pain control, and has been shown to be associated with a decreased risk of postoperative respiratory complications. Opiates delivered via patient-controlled analgesia are associated with infrequent episodes of respiratory depression. Caution to monitor for respiratory depression is always necessary when using opiates, particularly in elderly patients.
4. Once acute atelectasis of a lobe or portion of a lung occurs, treatment initially with vigorous chest physical therapy and a bronchodilator has been shown to be as effective as bronchoscopy. Also, CPAP or BiPAP improves postoperative hypoxemia from atelectasis.
5. DVT prophylaxis: Prevention of DVT is important for all major surgeries but more so in operations known to have a high incidence such as hip or knee orthopedic procedures where the incidence may be as high as 50 to 60%. The risk of DVT is also high in patients over 40 years of age with a recent history of DVT or PE and in those undergoing extensive pelvic or abdominal surgery for malignant disease. Mechanical devices such as graduated compression stockings extending above the knee and pneumatic compression devices are effective in patients receiving general and orthopedic surgery. Low molecular weight heparin is better than nonfractionated heparin in prevention of DVT and PE. The forms of DVT prophylaxis are summarized in Table 3. Patients at high risk may need continued prophylaxis for a short time after discharge from the hospital.

Table 3 — Deep Venous Thrombosis Prevention

Type of Surgery	Recommended Prophylaxis	Alternative Prophylaxis
Very high risk for DVT*	Subcutaneous low-molecular weight heparin, or low-dose warfarin and/or intermittent compression device to legs	Graded compression stocking (above knee) plus subcutaneous low-dose heparin or intravenous dextran
Generally at risk for DVT	Subcutaneous low-molecular weight heparin and/or intermittent compression device to legs	Graded compression stocking (above knee) plus subcutaneous low-dose heparin

*High risk includes hip and knee orthopedic surgery and abdomen and pelvis cancer surgery.

References

1. Prabhakar NR, Marek W, Loeschcke HH. Altered breathing pattern elicited by stimulation of abdominal visceral afferents. *J Appl Physiol* 1985; 58:1755-60
2. Hall JC, Tarala RA, Hall JL, et al. A multivariate analysis of the risk of pulmonary complications after laparotomy. *Chest* 1991;

99:923-27

3. O'Brien JD, Ettinger NA. Pulmonary complications of liver transplantation. *Clin Chest Med* 1996; 17:99-114
4. Meyers WC. Southern Surgeons Club: A prospective analysis of 1518 laparoscopic cholecystectomies. *N Engl J Med* 1991; 324:1073-78
5. Frazee RC, Roberts JW, Okeson GC, et al. Open versus laparoscopic cholecystectomy. *Ann Surg* 1991; 213:651-54
6. Curtis JJ, Nawarawong W, Walls JT, et al. Elevated hemidiaphragm after cardiac operations: Incidence, prognosis, and relationship to the use of topical ice slush. *Ann Thorac Surg* 1989; 48:764-68
7. Mickleborough LL, Maruyama H, Mohamed S, et al. Are patients receiving amiodarone at increased risk for cardiac operations? *Ann Thorac Surg* 1994; 58:622-29
8. Daniel TM, Kern JA, Tribble CG, et al. Thoracoscopic surgery for diseases of the lung and pleura. *Ann Surg* 1993; 217:566-75
9. Romano PS, Mark DH: Patient and hospital characteristics related to in-hospital mortality after lung cancer resection. *Chest* 1992; 101:1332-37
10. Mitsudomi T, Mizoue, T, Yoshimatsu, T, et al. Postoperative complications after pneumonectomy for treatment of lung cancer: multivariate analysis. *J Surg Oncol* 1996; 61:218-22
11. Mountain CF. Lung cancer staging classification *Clin Chest Med* 1993; 14:43-51
12. Traver GA, Cline MG, Burrows B. Predictors of mortality in chronic obstructive pulmonary disease *Am Rev Resp Dis* 1979; 119:895-902
13. Gaissert HA, Trulock EP, Cooper JD, et al. Comparison of early functional results after volume reduction or lung transplantation for chronic obstructive pulmonary disease *J Thorac Cardiovasc Surg* 1996; 111:296-307
14. Keenan RJ, Landreneau RJ, Scirba FC, et al. Unilateral thoracoscopic surgical approach for diffuse emphysema. *J Thorac Cardiovasc Surg* 1996; 111:308-16
15. Ferguson MD, Little L, Rizzo L, et al. Diffusing capacity predicts morbidity and mortality after pulmonary resection. *J Thorac Cardiovasc Surg* 1988; 96: 894-900

Copyright 1997 American College of Chest Physicians

Lesson 5, Volume 12—Smoking Initiation

By Elizabeth A. Gilpin, MS, and John P. Pierce, PhD

Objectives

1. Outline the scope of the adolescent smoking uptake problem.
2. Characterize changing trends in smoking initiation.
3. Present a model of the smoking uptake process.
4. Describe the factors that influence adolescents to smoke.
5. Discuss how smoking uptake can be prevented.

Key words

adolescent smoking; smoking initiation; smoking uptake

According to the Surgeon General of the United States, smoking is the major preventable cause of premature death and disability.¹ Each year, an estimated 419,000 people die of smoking-related diseases in the United States.² To put this figure in perspective, it is almost four times higher than all deaths that can be attributed to alcohol, which is the next most frequent preventable cause of death and disability.²

Smoking prevalence in the adult population has been decreasing steadily ever since the mid-1960s, when the health consequences of smoking became widely known.¹ Not only have very few older adults initiated smoking since then, but many have managed to quit successfully. The prevalence of current smoking among adults has decreased, from 45% in 1965 to about 26% in 1994.³ Furthermore, by the early 1980s, smoking initiation among young adults 21-24 years of age was rare; less than 1% in each age from age 21-24 years initiated regular smoking each year.⁴

The situation is not so encouraging for adolescents. Each day in the United States over 4,700 adolescents from ages 11 to 17 (below the legal age for purchasing cigarettes) first experiment with smoking; the modal age for first experimentation is around 12 years.⁵ Also, around 3,000 youth reach adulthood each day as established smokers.⁶ It is estimated that half the youth who become addicted to cigarettes today will smoke for 16 to 20 years before successfully quitting.⁷ Among those who smoke longer than this (or after approximately 35 years of age), half will die of smoking-related diseases.⁸

Although there has been considerable research on the determinants of smoking uptake and how to prevent it,⁹ these efforts have not yielded approaches for the design of successful mass public health prevention programs. This article will summarize what is currently known about the smoking uptake process, including nicotine addiction, trends in smoking uptake, a description of the uptake process, known factors associated with an increased likelihood of smoking uptake, and where work is needed in the future to gain the understanding that will hopefully lead to prevention approaches that work.

Nicotine Addiction

Today it is recognized that nicotine is the drug in tobacco that causes addiction, and that the pharmacologic and behavioral processes that cause nicotine addiction are similar to those that determine addiction to substances such as heroin and cocaine.¹ Typically, a substance is defined as addictive if there are mood-altering effects which reinforce repeated use, physical dependence

occurs after a build-up period of increased tolerance, use continues despite perception of harm and an expressed desire to quit, and withdrawal symptoms are present if the user quits. Indeed, the pattern of relapse following cessation for nicotine, alcohol, and heroin are nearly identical.¹⁰

There are some smokers that never build up tolerance or become physically dependent on nicotine. It is estimated that as many as 15% of current adult smokers do not smoke every day.¹¹ Since the wash-out period for nicotine in the human body is a matter of hours, it is doubtful whether these occasional smokers are truly addicted. However, many express a desire to quit but nevertheless continue to smoke. Also, some occasional smokers will eventually become addicted, just as social users of alcohol and cocaine are always at risk of future dependence.

There is no perfect marker of when addiction occurs. The measure that is generally used to establish that someone is a smoker is self-report of smoking at least 100 cigarettes in their lifetime.¹ Surveys of adults indicate that about 70% of all those to admit to any experimentation reach this level of smoking.¹² Those who reach this level are considered *ever smokers* by the public health community,¹ and generally most continue to smoke for many years before they can successfully quit. Many never quit.

One third or more of all current smokers make a serious attempt to quit each year, but only about 5 to 10% manage to remain abstinent for at least a year.^{1,13,14} Most relapse occurs within the first few days when withdrawal symptoms are the most severe. However, there is significant relapse even beyond the first week when the symptoms have subsided.¹³ A few former smokers, who quit many years ago, relapse, usually in response to a stressful life event.¹⁵

Trends in Smoking Uptake

After the introduction of manufactured cigarettes in the late 1800s, smoking rapidly gained in popularity. Demand for this new product was stimulated vigorously by innovative tobacco industry marketing campaigns which initially aimed at males but then also targeted females beginning in the 1920s. Consequently, trends in smoking initiation increased both in adults and youth of both sexes throughout the first half of the 1900s.¹⁶ The first evidence that smoking caused lung cancer was published in scientific journals in 1950.^{17,18} Over the next dozen or so years, evidence continued to accumulate and led to the Surgeon General's pivotal report on smoking and health in 1964.¹⁹ The attendant publicity in the popular media surrounding the report effectively informed the adult populace about the dangers of smoking. Consequently, the prevalence of *ever smoking* declined among successive birth cohorts that reached adulthood even as early as 1950.^{20,21} As much as 80% of males and 50% of females born in the early part of the 1900s became smokers (*ie*, they reached the 100-cigarette level), but this percentage declined to around 40% or less for those born after 1950. Much of the decline in the prevalence of *ever smoking* during the 1950s and 1960s was because adults heeded the health warnings, and very few initiated smoking. It wasn't until the 1970s that initiation began to decline among people under 21 years of age.⁹

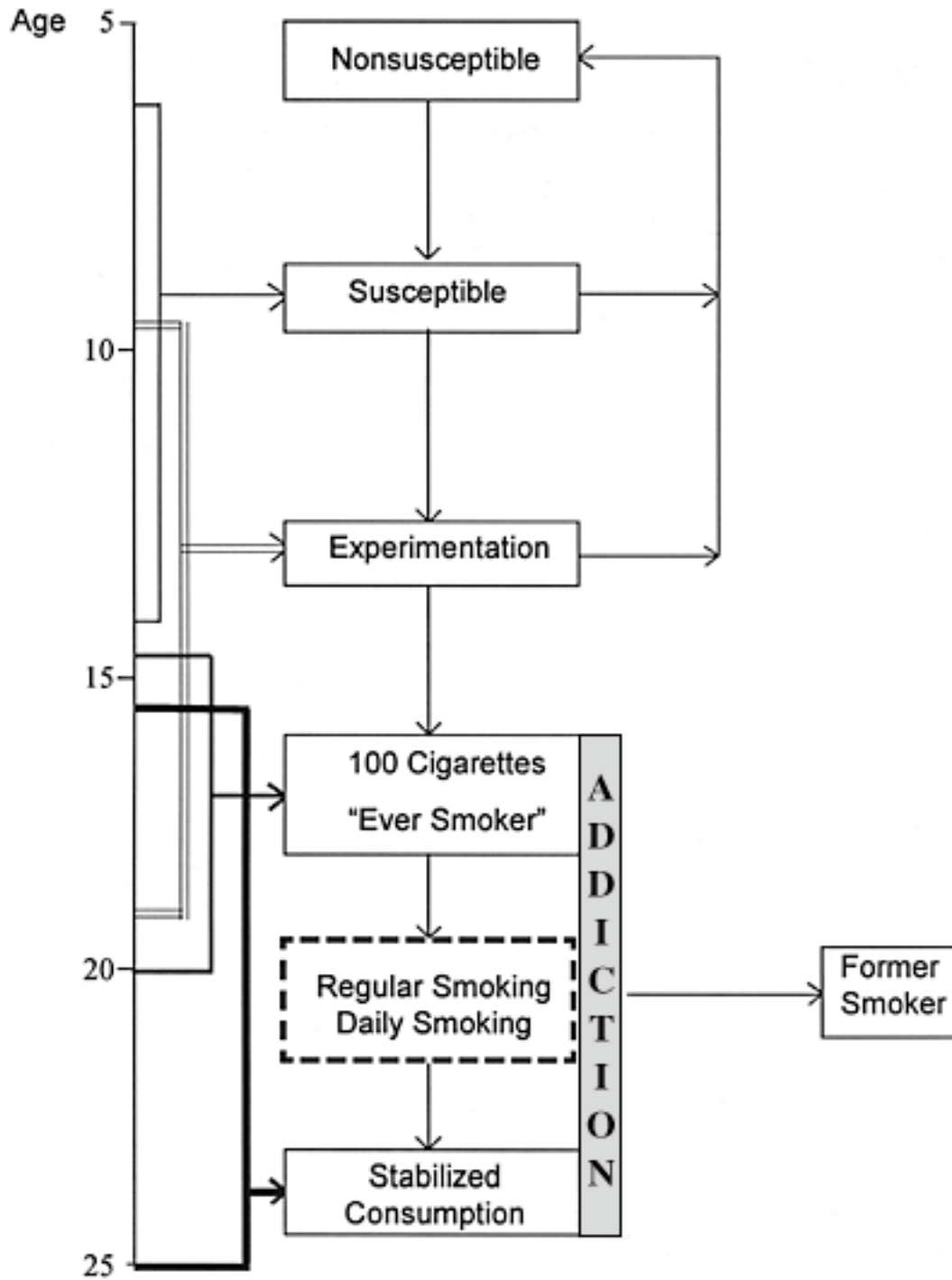
Since 1976, the National Institute on Drug Abuse has conducted annual surveys (Monitoring the Future Project) of high school seniors, which have been extended to surveillance of 8th and 10th graders since 1991.^{22,23} These surveys documented a decline in daily smoking among high school seniors, from about 29% in 1976 that extended until the mid-1980s when it leveled off at about 18%. Daily smoking prevalence among high school seniors hovered around this level until 1992, when it again began to increase. By 1996, it was over 22%. Smoking in the past 30 days among 8th graders has increased each year since 1991, from 14% to 21% in 1996. Although African-American adolescents have a much lower rate of cigarette use than other racial/ethnic groups, the recent increase in smoking was documented for this group as well; smoking in the past 30 days increased among African-American 8th graders from 1.4% in 1991 to 3.0% in 1996. Other studies have verified these recent trends and have shown that the increases in smoking uptake in adolescents 14 to 17 years of age are particularly marked among boys, whites, and those with lower educational aspirations.^{24,25}

One group of young people which has shown a particularly dramatic decline in smoking is medical students. In the 1951 class at Johns Hopkins University Medical School, 65% of the students were smokers: in the class of 1987, only about 2% smoked.²⁶ Other medical schools showed similar low levels of student smoking in the late 1980s. A person motivated to become a physician no doubt has a better understanding than most about the health consequences of smoking and may also have experienced considerable peer pressure not to smoke. Nevertheless, the success in this group indicates that the goal of prevention is possible.

The Smoking Uptake Process

The process of becoming an addicted smoker rarely happens overnight. Instead, it is thought to be comprised of different developmental stages (Fig 1). At the earliest point in the process, the potential future smoker first becomes aware that smoking is something that he or she might choose to do someday.^{6,27} Initially, this awareness may arise from smoking parents, siblings, other adults, or other role models, including those depicted in advertising and entertainment. Eventually, the pre-adolescent or adolescent will likely know a peer who smokes. During this stage, the child or adolescent forms attitudes and beliefs about the utility of smoking. The unwillingness to rule out future smoking has been proposed as a measure of transition to this stage in the uptake process among young adolescents.²⁸ Those who are open to the possibility of smoking are called *susceptible* to smoking and have taken the first step along the uptake process.

Figure 1. The smoking uptake process. The brackets on the age scale at the left show the approximate age range when most individuals are in a given stage. Although it is possible for "experimenters" to regress to being nonsusceptible to smoking, persons who reach the 100-cigarette level are considered former smokers if they quit.



At the next level in the uptake process, the adolescent actually takes a puff on or smokes a cigarette. This first *experimentation* often happens in a social setting. Based on first-hand experience, the adolescent may either reject or become more vulnerable to continued experimentation.²⁹ If the experience wasn't really unpleasant and peers expressed approval, it is likely that the adolescent will try smoking again. The time between the first puff and reaching the *100-cigarette level* can take several years.^{6,30} During this time, the adolescent may smoke sporadically—a cigarette or two at parties or when hanging out with friends. Typically, early

experimenters go for long periods of time without smoking at all.^{29,31}

Eventually, if the adolescent continues experimenting, the *100-cigarette level* will be reached. Studies have shown that it is not until about age 15 that significant numbers of adolescents report having smoked at least 100 cigarettes.^{6,22} Even after this level is reached, the adolescent may continue the intermittent patterns of smoking that characterized the *experimentation* stage. However, the more the behavior is repeated, the more likely it is to be reinforced and to continue. At some point, especially when smoking becomes more frequent, tolerance will begin to develop and the adolescent will begin to smoke because he or she "needs a cigarette." At this point *addiction* is imminent, and smoking becomes more regular, and finally daily smoking commences.³² Even then, tolerance may not be fully developed and the smoker may take several more years before a steady level of usual cigarette consumption is attained. A daily consumption rate of 15 or more cigarettes may not be the norm until over age 24.

The smoking uptake process is completed when *addiction* occurs. However, some people who experiment with cigarettes never become addicted.¹¹ Although the 100-cigarette milestone has been proposed as a marker of addiction, as many as 20% who attain this level may quit smoking altogether before they exhibit any of the characteristics of nicotine addiction (Won S. Choi, PhD, Cancer Prevention and Control, University of California, San Diego, Calif; personal communication). As mentioned earlier, some will become occasional smokers. Also, adolescents will drop out of the smoking uptake process by developing the will not to smoke even if they had been previously susceptible to smoking or even after they have experimented.

Influences on Adolescents to Smoke

Cross-sectional studies can identify correlates of smoking, but cannot support the suggested association by demonstrating that the influence was present before smoking occurred. Nevertheless, results from both cross-sectional and longitudinal studies are similar. Most research has either used a recall outcome measure of any smoking in the past 30 days (which will miss some future smokers and include others who do not become addicted), or used the even broader outcome measure of any cigarette use at all which can range from a single puff to a current daily multi-pack habit. In addition, the studies have analyzed a variety of potential influences using somewhat different measures. For instance, academic achievement could be measured by grade point average from the school record or by self-report of how well the subject does in school compared to peers. And, studies will have measures for some influences and not for others.

Nevertheless, an extensive review of 27 longitudinal studies with different sample sizes, survey methods, and follow-up periods as well as the problems just mentioned, did produce a collection of influences on adolescents to smoke that were significantly related to smoking uptake in the majority of studies that examined them.³³ Demographic characteristics predictive of smoking include older age and lower socio-economic status. Other influences were grouped according to social bonding, social learning, intrapersonal variables, and a category for knowledge, attitudes, and beliefs.

Under social bonding, the degree of family bonding by a variety of measures was associated with future smoking, with those in less-involved families more likely to smoke. Attachment to or agreement with peers, and the level of social involvement with peers (peer bonding) increased the likelihood of uptake. Academic achievement and satisfaction with school (school bonding) diminished the probability of future smoking, whereas problem behavior or truancy increased it. Sports participation and club activities were only examined in one study each, but were not found to be predictive. However, in another study, involvement in "extra-curricular" activities was protective.

Social learning occurs when the child or adolescent has the opportunity to observe the behavior and attitudes of others. Smoking by parents and older siblings appears to increase the likelihood that an adolescent will smoke. The child perceives that some benefit accrues to the smoker and that smoking must be an acceptable behavior if those he or she loves engage in it. Peer smoking was highly predictive of smoking uptake as was friends' approval of smoking. Also predictive were the adolescents' perceptions of how prevalent smoking is among both peers and adults, and the availability of cigarettes.

Another influence included in the social learning category was tobacco marketing. Only two of the studies included measures of this factor, and in only one study was the measure significantly related to uptake. However, evidence from other sources, including cross-sectional studies,³⁴ more recent longitudinal studies, (Won S. Choi, PhD, Cancer Prevention and Control Program, University of California, San Diego; LaJolla, Calif; personal communication) and historical trend analyses,^{16,35} supports the finding that tobacco marketing plays a role in smoking uptake. During periods of intense marketing efforts by the tobacco industry (purportedly

aimed at adults to switch brands), smoking initiation increased among adolescents in the demographic groups targeted.¹⁶ Furthermore, many studies have documented that adolescents smoke the brands of cigarettes that are most advertised.³⁶ A recent tobacco marketing strategy that appears to capture the attention of adolescents is the offering of tobacco promotional items such as tee-shirts, caps, lighters, and other gear that is either available at the point of sale or through coupon redemption.³⁷ Frequently, adolescents will obtain these items from their parents. The adolescents who own these items or who would be willing to use them are in the same demographic groups showing the biggest recent increases in smoking initiation.²⁵

The interpersonal factors associated with smoking uptake were rebelliousness and risk-taking. Also predictive was being either very shy and submissive or being overly aggressive. Thus, it is not surprising that low self-esteem was also predictive of smoking in some studies. The few studies that examined refusal skills indicate that the ability or self-efficacy to refuse offers of cigarettes was protective.

Knowledge of the health consequences of smoking appears to be protective. However, beliefs about potential benefits or positive expectancies of smoking increased the likelihood of future smoking. Adolescents who expressed approval of smoking were also at increased risk for smoking. Most studies that investigated intentions to smoke did find a positive association with future use. Previous experimentation with cigarettes was highly predictive of future use, as were previous alcohol and drug use.

Few of the studies reviewed were based on any model or theoretical framework that related predictors to outcome. Some theories hypothesize that different predictors are relevant to different stages in the uptake process, but very few researchers have investigated this issue.^{6,33} Most studies have focused on the transition from nonsmoker to any use, and they have not attended to the specific transitions (*ie*, from *nonsusceptibility* to *susceptibility*, from *susceptibility* to first *experimentation*, or from *experimentation* to reaching the *100-cigarette level*) in the smoking uptake process. In future multi-wave longitudinal studies, it should be possible to identify the factors that are predictive of transition from each level to the next higher one or, perhaps more importantly, that identify those who do not progress further in the uptake process.

Implications for Prevention

Many of the predictors of smoking uptake are difficult to modify. Socio-economic status, family dynamics, and parental smoking behavior are probably beyond the scope of any specific public health prevention program, but depend on significant changes in society in general. Perhaps a greater understanding of the factors that influence the various transitions along the uptake continuum will add to the meager list of influences that can be modified by public health prevention programs. Also, it may be possible to reinforce the influences that prevent further progress toward nicotine addiction.

One influence that can be modified is tobacco marketing. That adolescents appear to be particularly vulnerable to tobacco marketing tactics may be related to the developmental stages that characterize adolescence.⁶ Some adolescents assert their independence with a symbol, such as a cigarette, which is associated with adulthood. Possession of a promotional item with a brand logo also provides such a symbol. Identity is another concern of this age group and tobacco advertising provides a multitude of images,—the tough independent, the slim sophisticate, the "party animal", and the sportsman or athlete (association of tobacco with sponsorship of sporting events). Adolescents tend to live for the moment, to be self-indulgent, and to think of themselves as invulnerable; consequently, they initiate smoking before they fully understand its dangers; and once addicted, they find it very difficult to quit. Bans on human or cartoon characters in tobacco advertising and bans on promotional items have been proposed and should be adopted as soon as possible.

Potentially, a major tobacco excise tax increase might discourage adolescents from smoking. The price-elasticity of demand for cigarettes is thought to be steeper for adolescents than for adults.^{1,38} However, the inflation-adjusted price of cigarettes in the United States increased throughout the mid 1980s and into the early 1990s when adolescent smoking uptake stopped its decline and began to increase.²⁵ Experimentation often occurs with cigarettes obtained from friends⁶ who may not be as willing to give them away if cigarettes were considerably more expensive. Typically adolescents do not purchase their own cigarettes until they are on the brink of advancing from experimentation to regular smoking and price could influence them to refrain from this transition.⁶ However, a tax increase would need to be large enough that tobacco companies could not absorb it by failing to increase price or only increasing it marginally, which may be why increased taxation by many states in the last decade has not appeared to discourage adolescent smoking initiation. Most prevention programs are school-based, and generally include several components such as education regarding the health consequences of smoking, emphasis on the social undesirability of smoking (*eg*, smells bad, stains

teeth, etc.), and teaching of refusal skills. Those programs, which have been formally evaluated, find only a small positive effect. The effect appears to be greater if the program is part of a larger community-wide effort that seeks to change norms regarding smoking in the entire community.³⁹ Community-wide programs may include passing local smoking ordinances restricting smoking in public and work places, localized media campaigns that depict smoking as an undesirable and dangerous activity, or restricting access by banning vending machines or increasing enforcement of laws prohibiting the sale of cigarettes to those under 18 years of age. Enforcement must approach 100% before it can reduce access effectively; if adolescents can't purchase cigarettes at one store, they will shop around until they find one where they can buy them.

Smoking by actors in movie parts which are role models for children and adolescents promotes the social desirability of smoking. Also, smoking in the movies creates the impression that it is more prevalent than it really is, especially among the types of movie characters who are seen as "positive" role models.⁴⁰ Since both the expectation of benefit and perceived smoking prevalence influence uptake, prevention activists need to confront the entertainment industry and determine what needs to be done to influence the industry to include smoking only when it is contextually important.

The role of the physician in the prevention of smoking uptake is not well defined. A pediatrician might discuss the addictive nature of cigarettes and the health consequences of smoking with pre-adolescents during routine care. They can also inform the parents who are smokers that they are setting a poor example for their children and probably also exposing them to environmental tobacco smoke, which has been documented to cause respiratory problems in children. Parents should also be advised not to give their children tobacco promotional items. There is some recent evidence suggesting that children who witness a parent quit smoking will have a reduced likelihood of future smoking as will children who live with smokers who ban smoking in the household (Arthur J. Farkas, PhD, Cancer Prevention and Control Program, Cancer Center, and Department of Family and Preventive Medicine, University of California, San Diego; LaJolla, Calif; personal communication). These children apparently get the message that smoking is unacceptable. Physicians who treat adults who are parents can pass on this information, and they can emphasize as well that parents can reduce the chance that their child will smoke by working to maintain a healthy parent-child bond throughout adolescence (Janet M. Distefan, BA, Cancer Prevention and Control Program, University of California, San Diego; LaJolla, Calif; personal communication). In addition, physicians can ask all patients about their smoking status and advise smoking patients to quit, and learn how they can provide assistance to those who are interested in quitting.

Summary

Although there has been considerable research on the smoking uptake process, little of the knowledge gained has translated into effective prevention programs. Perhaps future studies which examine factors that influence the transition or lack of transition between levels in the smoking uptake process will prove valuable in this regard. However, it is likely that present state-of-the-art and future prevention approaches will have greater success as part of a sustained public health effort to achieve a smokefree society for everyone by persuading adults to quit. When smoking is no longer perceived as a prevalent and accepted adult activity, adolescents may not find it so attractive.

References

1. US Department of Health and Human Services. Reducing the health consequences of smoking. 25 years of progress. A report of the Surgeon General. Rockville, Md: US Department of Health and Human Service, Public Health Service, Centers for Disease Control, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1989. DHHS Pub. No. (CDC)89-8411, 1989
2. Anonymous. Facing our fears. *Consumer Reports*. 1996; 61:50-53
3. Cigarette smoking among adults, United States, 1994. *MMWR Morb Mortal Wkly Rep* 1996; 45(27):588-90
4. Gilpin EA, Lee L, Evans N, et al. Smoking initiation rates in adults and minors: United States, 1944-1988. *Am J of Epidemiol*

1994;140:535-43

5. Gilpin EA, Choi WS, Berry CC, et al. How many adolescents start smoking each day in the United States. *JAMA* 1997 (in press)

6. Pierce JP, Fiore MC, Novotny TE, et al. Trends in cigarette smoking in the United States. Projections to the year 2000. *JAMA* 1989; 261:61-65

7. Pierce JP, Gilpin E. How long will today's new adolescent smoker be addicted to cigarettes? *Am J Pub Health* 1996; 86:253-56

8. Doll R, Peto R, Wheatley K, et al. Mortality in relation to smoking: 40 years observation on male British doctors. *Br Med J* 1994; 309:901-11

9. US Department of Health and Human Services. Preventing tobacco use among young people. A Report of the Surgeon General. Atlanta, Ga: US Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1994. US Government Printing Office Document N017-001-00491-0, 1994

10. Hunt WA, Barnett LW, Branch LG. Relapse rates in addiction programs. *J Clin Psychol* 1991;27:455-56

11. Gilpin EA, Cavin SW, Pierce JP. Adult smokers who do not smoke daily. *Addiction* 1997; 92:473-80

12. Russell MAH. The nicotine addiction trap: a 40-year sentence for four cigarettes. *Br J Addict* 1990; 85:293-300

13. US Department of Health and Human Services. The health benefits of smoking cessation. A report of the Surgeon General. Atlanta: US Department of Health and Human Service, Public Health Service, Centers for Disease Control, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1990. DHHS Pub. No. (CDC)90-84116, 1990

14. Community intervention trial for smoking cessation (COMMIT): Changes in adult cigarette smoking prevalence. *Am J Pub Health* 1995; 85:193-200

15. Swan GE, Denk CE, Parker SD, et al. Risk factors for late relapse in male and female ex-smokers. *Addict Behav* 1988; 13:253-66

16. Pierce JP, Gilpin EA. A historical analysis of tobacco marketing and the uptake of smoking by youth in the United States: 1890-1977. *Health Psychol* 1995; 14:500-08

17. Doll R, Hill AB. Smoking and carcinoma of the lung: Preliminary report. *Br Med J* 1950; 2:739-48

18. Wynder EL, Graham EA. Tobacco smoking as a possible etiological factor in bronchiogenic carcinoma. *JAMA* 1950; 133:329-36

19. US Department of Health and Human Services. Smoking and health: Report of the Advisory Committee to the Surgeon General of the Public Health Service. Bethesda, Md: Public Health Service, Center for Disease Control, 1964. PHS Pub. No. 1103, 1964

20. Harris J. Cigarette smoking among successive birth cohorts of men and women in the United States during 1900-1980. *J Natl Cancer Inst* 1983; 71:473-79

21. Burns DM, Lee L, Shen LZ, et al. Cigarette smoking behavior in the United States. In: Changes in cigarette-related disease and risks and their implication for prevention and control. Smoking and Tobacco Control Monograph 8. Bethesda, Md: National Cancer Institute, 1997. NIH Pub No 97-4213, 1997

22. Johnston LD, O'Malley PM, Bachman JG. National survey results on drug use from the Monitoring the Future Study, 1975-1992. Vol. 1: Secondary school students. Washington, DC: US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Drug Abuse, 1994
23. Johnston LD. Cigarette smoking continues to rise among American teenagers in 1996. Ann Arbor, Mich: News and Information Agency, University of Michigan, 1996
24. US Centers for Disease Control and Prevention. Trends in smoking initiation among adolescents and young adults - United States, 1980-1989. MMWR Morb Mortal Wkly Rep 1995; 44:521-25
25. Gilpin EA, Pierce JP. Trends in adolescent smoking initiation in the United States: Is tobacco marketing an influence? Tobacco Control 1997; 6:122-27
26. Pierce JP, Gilpin E. Trends in physicians' smoking behavior and patterns of advice to quit. In: Tobacco and the Clinician. Interventions for Medical and Dental Practice. Smoking and Tobacco Control. Monograph 5, Bethesda, Md: National Cancer Institute. NIH Pub No 93-3693, 1993
27. Chassin L, Presson CC, Sherman SJ, et al. Predicting the onset of cigarette smoking in adolescents: A longitudinal study. J Appl Soc Psychol 1984; 14:224-43
28. Pierce JP, Choi WS, Gilpin EA, et al. Validation of susceptibility as a predictor of which adolescents take up smoking in the United States. Health Psychol 1996; 15:355-61
29. Hirschman RS, Leventhal H, Glynn K. The development of smoking behavior: Conceptualization and supportive cross-sectional survey data. J Appl Soc Psychol 1984; 14:184-206
30. Baugh JG, Hunter SM, Webber LS, et al. Developmental trends of first cigarette smoking experience of children: The Bogalusa Heart Study. Am J Pub Health 1982; 72:1161-64
31. Chassin LA, Presson CC, Sherman SJ. Stepping backward in order to step forward: An acquisition-oriented approach to primary prevention. J Consult Clin Psychol 1985; 53:612-22
32. Chassin L, Presson CC, Sherman SJ, et al. The natural history of cigarette smoking: Predicting young-adult smoking outcomes from adolescent smoking patterns. Health Psychol 1990; 9:701-16
33. Conrad KM, Flay BR, Hill D. Why children start smoking cigarettes: Predictors of onset. Br J of Addict 1992; 87:1711-24
34. Evans N, Farkas A, Gilpin E, et al. The influence of tobacco marketing and exposure to smokers on adolescent susceptibility to smoking. J Natl Cancer Inst 1995; 87:1538-45
35. Pierce JP, Lee L, Gilpin EA. Smoking initiation by adolescent girls, 1944 through 1988: An association with targeted advertising. JAMA 1994; 271:608-11
36. Changes in the cigarette brand preferences of adolescent smokers—United States, 1989-1993. MMWR Morb Mortal Wkly Rep 1994; 43:577-81
37. Gilpin EA, Pierce JP, Rosbrook B. Are adolescents receptive to current sales promotion practices of the tobacco industry? Prev Med 1997; 26:14-21
38. Lewit EM, Coate D, Grossman M. The effects of government regulation on teenage smoking. J Law Econ 1981; 24:545-69

39. Johnson CA, Pentz MA, Weber MD, et al. Relative effectiveness of comprehensive community programming drug abuse prevention with high-risk and low-risk adolescents. *J Consult Clin Psychol* 1990; 4:447-56

40. Hazan AR, Glantz SA. Popular films do not reflect current tobacco use. *Am J Pub Health* 1995; 84:116-17

Copyright 1997 American College of Chest Physicians

Lesson 6, Volume 12—Parapneumonic Effusions: Pathophysiology, Diagnosis, and Management

Steven A. Sahn, MD

Objectives

1. To understand the pathogenesis of a parapneumonic effusion and empyema.
2. To understand the value of pleural fluid analysis in the management of parapneumonic effusions.
3. To understand the value of chest CT scanning in evaluating parapneumonic effusions.
4. To understand the role of intrapleural fibrinolytics in management of loculated parapneumonic effusions and empyema.
5. To understand the options for surgical drainage for loculated parapneumonic effusions and empyema.

Key words

decortication; empyema; fibrinolytics; parapneumonic effusions; pleural fluid pH; thoracoscopy

Definitions and Incidence

Pneumonia, a common infection in the community and hospital, is associated with a high incidence (36 to 57%) of pleural effusions.¹⁻³ These figures extrapolate to an estimated 1 million persons in the United States developing parapneumonic effusions yearly. Parapneumonic effusions (pleural fluids associated with pneumonia) are most often free-flowing effusions that resolve spontaneously with antibiotic therapy directed at the pneumonia; these fluids have been termed "uncomplicated effusions." Pleural fluids that require drainage of the pleural space for resolution of the febrile response have been termed "complicated" effusions.^{1,4,5} The natural course of a complicated parapneumonic effusion is to develop a single loculus or multiple loculations and to progress to an empyema cavity. Empyema, from the Greek meaning accumulation of pus in a body cavity, represents the end stage of a complicated parapneumonic effusion (empyema thoracis).

The appropriate analytical approach to diagnosis and the optimal treatment of complicated parapneumonic effusions are controversial because of the lack of prospective, randomized trials. In addition, the value of early pleural fluid analysis to predict the likelihood of risk for development of complicated parapneumonic effusions remains disputed.^{1,4-7} The availability of new options for management of complicated parapneumonic effusions further confounds clinical decision-making as was confirmed by an American College of Chest Physicians interactive session on pleural space infections.⁸

Pathophysiology

Understanding the pathophysiologic progression and time course of an uncomplicated parapneumonic effusion to an empyema helps to explain the varied clinical presentations of these patients. Following aspiration of microorganisms into subpleural alveoli, there is migration and adherence of polymorphonuclear leukocytes (PMNs) to the adjacent endothelium. Oxygen metabolites, granule constituents, and products of membrane phospholipases released by activated PMNs result in endothelial injury of the pulmonary, subpleural, and pleural vessels causing increased capillary permeability. The protein-rich fluid that leaks into the lung parenchyma increases the interstitial pressure resulting in a gradient that drives fluid from the interstitium between mesothelial cells

into the pleural space. Probably with all extensive pneumonias, pleural fluid production increases; however, pleural effusion accumulation will occur only when fluid entry into the pleural space exceeds the absorptive capacity of the parietal pleural lymphatics. The parapneumonic effusion that occurs in the initial hours tends to be small in volume and is a sterile, PMN-predominant exudate; this stage has been labelled the capillary leak or exudative stage. Typically, the pleural fluid pH is >7.30 , the glucose is >60 mg/dL, and the lactate dehydrogenase (LDH) is <500 U/L.^{1,4,9} Patients in this first stage virtually always can be treated successfully with antibiotics without the need for pleural space drainage.

If the pneumonia remains untreated, endothelial injury becomes more pronounced with worsening pulmonary edema and increased pleural fluid formation. Bacteria continue to multiply in the lung with invasion and persistence in the pleural space. As bacteria may be cleared rapidly by parietal pleural lymphatics, finding a positive Gram's stain and culture signifies bacterial persistence for a critical period and probably portends a less favorable clinical course.^{10,11} The pleural fluid in this second stage (bacterial invasion/fibrinopurulent stage) is characterized by an increased number of PMNs, a fall in pleural fluid pH and glucose, and an increase in pleural fluid LDH. Interleukin-8 (IL-8) is a major chemotactic factor for PMNs in empyema; TNF- α may play a role in the local production of IL-8.¹² The pleural fluid/serum glucose ratio decreases to <0.5 with an absolute concentration usually <40 mg/dL because of the increased rate of glycolysis from PMN phagocytosis and bacterial metabolism.¹³ As the end products of glucose metabolism, CO₂ and lactic acid, accumulate in the pleural space, the pH falls. The LDH increases, often to $>1,000$ U/L, because of PMN lysis. Concomitant with these biochemical changes, the pleural fluid becomes clottable as procoagulants from the blood move into the pleural space in conjunction with a loss of pleural space fibrinolytic activity from mesothelial injury.¹⁴ These processes increase the likelihood of deposition of a dense layer of fibrin on both pleural surfaces, and metabolically active fibroblasts move into the pleural space unimpeded by the injured mesothelium and begin to secrete glycoaminoglycans and collagen into the clottable pleural fluid.¹⁵ Both fibrin and collagen compartmentalize the pleural fluid into loculations by bridging the two pleural surfaces and, in addition, limit lung expansion with deposition on the visceral pleura. Pleural fluid volume may increase further because of blockage of the parietal pleural stoma by fibrin and collagen and mesothelial swelling.¹⁶ Early in this stage, antibiotics alone may be effective; but later, pleural space drainage is usually required.

Without treatment, the third stage (organizational/empyema stage) ensues over the next few weeks, resulting in a single cavity or multiple loculations that are formed as fibroblast migration and growth continue in the fibrin-pleural fluid matrix. The resultant inelastic pleural "peel" impairs pleural fluid drainage and inhibits lung expansion. Empyema fluid is a thick, purulent coagulum, which may not be adequately drained by tube thoracostomy. Pus assumes its specific character because of the coagulability of pleural fluid, the abundance of cellular debris, and increased fibrin and collagen deposition. Decreased bacterial opsonization from complement depletion may result in bacterial persistence.¹⁷ Untreated empyema rarely resolves spontaneously. It may drain through the chest wall (empyema necessitatis) or into the lung (bronchopleural fistula). Patients with empyema always require drainage for resolution of pleural sepsis. The rationale for effective management is to identify the pathophysiologic stage and intervene timely and appropriately to prevent progression to empyema.

Diagnosis

The rapid identification of patients who are at high risk of developing complicated parapneumonic effusions should improve clinical outcome by allowing earlier pleural space drainage. Unfortunately, differentiating high- from low-risk patients clinically is problematic, as there is no difference at presentation in age, peripheral leukocyte count, peak temperature, incidence of pleuritic chest pain, or extent of pneumonia.¹ Furthermore, complicated parapneumonic effusions frequently occur in patients with concurrent diseases in which symptoms and treatment (corticosteroids) may influence the presentation.

Pleural fluid analysis is a relatively inexpensive and useful diagnostic test to identify the stage of a parapneumonic effusion and to guide therapy. If pus is aspirated at thoracentesis, diagnosing an empyema, pleural space drainage should be accomplished without delay. Empyema fluid is usually diagnostic for specific pathogens if the specimen is handled expeditiously, appropriate microbiologic technique is applied (including careful anaerobic cultures), the patient has not received prior antimicrobial therapy, and the pleural space is not multiloculated. A positive Gram's stain, even in nonpurulent fluid, implies an advanced stage of disease and suggests the need for immediate drainage.

The pleural fluid protein concentration, nucleated cell count, or percentage of PMNs cannot differentiate a complicated from uncomplicated effusion.⁴ Light and colleagues^{1,5} and Sahn and associates^{4,9} were the first to observe that an appropriately obtained and measured pH from parapneumonic fluid would be helpful in clinical decision-making. A pH of <7.20 and <7.30 were suggested

as pleural space drainage cut points in the bacteriologically negative, nonpurulent, free-flowing effusion. Pleural fluid glucose concentration was found to correlate directly with pleural fluid pH in parapneumonic effusions;⁹ subsequently, it was shown that both PMN phagocytosis and bacterial metabolism were the mechanisms responsible for pleural fluid acidosis and low glucose concentration.¹³ Additional analysis suggested that a pH <7.00, a glucose <40 mg/dL, and an LDH >1,000 U/L indicated a complicated parapneumonic effusion that required drainage.¹ The combined pleural fluid pH data of Light and Sahn from a noncontrolled case analysis of 71 patients supported that a pH of >7.30 on admission virtually always predicted a good outcome with appropriate antibiotic treatment only.^{1,4,9} A pH of <7.10 predicted that pleural space drainage was necessary to resolve pleural sepsis. Eleven of the 71 patients with pleural fluid pH between 7.30 and 7.10 at admission had either complicated or uncomplicated effusions; these patients require careful clinical monitoring with further diagnostic testing (repeat thoracentesis, contrast CT scan) before an informed management decision is made.

Others have questioned the generally accepted guidelines for early pleural space drainage. Berger and Morganroth,⁷ in a retrospective analysis, found that 13 of 16 patients with complicated parapneumonic effusions, defined as a pH <7.20, positive Gram's stain, or positive culture, were effectively treated with antibiotics alone; two patients eventually required chest tube drainage for pleural sepsis and one patient died. Poe and colleagues⁶ retrospectively evaluated 91 patients with parapneumonic effusions using the criteria of Light and colleagues¹ for the decision for surgical drainage. They found that the criteria had relatively high specificity but low sensitivity. When they evaluated their data based on the revised criteria of Sahn and Light¹⁸ for an uncomplicated effusion (pH >7.30 glucose >60 mg/dL, and LDH < 1,000 U/L), 18 of 22 patients recovered without sequelae. Thirteen additional patients had a pleural fluid pH between 7.10 and 7.30 and repeat thoracentesis led to appropriate therapeutic decisions. A recent meta-analysis using receiver operating characteristic (ROC) techniques by Heffner and co-workers¹⁹ found pleural fluid pH to have the highest diagnostic accuracy in identifying complicated parapneumonic effusions that required drainage. Pleural fluid pH decision thresholds varied between 7.21 and 7.29 depending on cost-prevalence considerations.¹⁹

Pleural fluid biochemical parameters were never proposed as an absolute indication for pleural space drainage but as adjunctive data to be used in conjunction with the clinical presentation. The clinician should never advocate an immutable decision based on a single laboratory test without continued vigilance of the patient. On the basis of the available data, however, it is logical to treat a pneumonia with a free-flowing effusion with antibiotics alone if pleural fluid pH is \geq 7.30 (the glucose usually is \geq 60 mg/dL, and the LDH <1,000 U/L). If the pneumonia is treated with appropriate antimicrobials at that stage, the patient appears to be at low risk for requiring pleural space drainage. If the nonpurulent free-flowing fluid has a pH <7.20, pleural space drainage probably should be instituted. Current data support treatment with antibiotics and observation in patients with pH values between 7.21 and 7.29. Clinical parameters, repeat pleural fluid analysis, and contrast chest CT should, in addition to misclassification cost and clinical suspicion, determine management.

It has been suggested that patients with pneumococcal pneumonia and positive pleural fluid bacteriology have a more benign course than patients with infected pleural fluid from other organisms.^{1,2,6} This observation may be related to the earlier presentation of patients with pneumococcal pneumonia compared to anaerobes and, therefore, an earlier stage of the parapneumonic effusion. Thus, consideration of pleural fluid bacteriology may affect therapeutic decision-making.

Management

Antibiotics

Early antibiotic therapy of pneumonia should decrease both the likelihood of development of a parapneumonic effusion and the progression of an uncomplicated to complicated effusion by decreasing the lung capillary leak and clearing bacteria from the pleural space more rapidly. Even when bacterial clearance was similar in an experimental model of empyema, animals receiving antibiotics had significantly less pleural effusion and fibrosis than those not receiving antibiotics.¹⁰ The role of proinflammatory peptides such as TNF- α , an inducer of IL-8 that is chemotactic for PMNs in human empyema, in accelerating the stage of a parapneumonic effusion and the effect of antibiotics on this progression is unclear.¹²

There is little difference in penetration of the penicillins and cephalosporins into empyemas and uninfected parapneumonic fluids.²⁰ Drugs that show excellent pleural penetration include aztreonam, clindamycin, ciprofloxacin, cephalothin, and penicillin with pleural fluid/serum ratios of 79 to 167%, 1 to 4.5 h after single or multiple doses.²¹ With the aforementioned antibiotics, the pleural fluid antibiotic concentrations almost always exceed the accepted minimum inhibitory concentration (MIC) breakpoint for

organisms most likely to cause empyemas.

Aminoglycosides may be inactivated or have poorer penetration into empyemas than uncomplicated parapneumonic effusions. Inactivation may occur in the presence of purulent exudate, pleural fluid acidosis, or a low PO₂ environment.²²

Comparative antibiotic trials in empyema have not been done. Based on the most common organisms that cause empyema (anaerobes, Gram-negative aerobes, and staphylococcus) single agent therapy with imipenem or ticarcillin-clavulanic acid, or combined therapy with clindamycin and ceftazidime or clindamycin and aztreonam are reasonable initial empiric antibiotic choices, if a positive Gram's stain does not provide guidance. Theoretically in empyema, alternatives to aminoglycosides should be sought. The duration of antibiotic therapy should be determined by the clinical setting. Treatment of patients with uncomplicated effusions should be based on the cause of the pneumonia without dose escalation or increased duration of therapy. Patients with empyema should receive a longer duration of therapy (a few weeks), analogous to necrotizing pneumonia and lung abscess, according to the clinical course with antibiotic doses at the high end of the range recommended for pneumonia. Because the majority of empyemas are caused or associated with anaerobes, oral clindamycin or penicillin should be continued for the duration of treatment once parenteral antibiotics are discontinued.²³

Chest Tubes

The standard for drainage of a parapneumonic effusion is tube thoracostomy. A chest tube will be effective only if it can be positioned properly in the pleural space. With a free-flowing effusion, the chest tube can be placed at the bedside. After chest tube insertion, both posteroanterior and lateral chest radiographs should be obtained to assess tube placement; frontal radiographs alone are inadequate. Malposition of a chest tube, best demonstrated by CT, should be suspected if fever does not substantially abate, chest pain persists, and drainage is minimal.²⁴

In the free-flowing, nonpurulent effusion with biochemical markers suggesting a high likelihood of a complicated course, a properly placed chest tube results in rapid and complete evacuation of the pleural space and expansion of the lung, preventing the development of an empyema cavity. The chest tube should be removed when drainage becomes serous and is <50 mL per day.

If the fluid is loculated, a contrast chest CT should be done to define pleural space pathology. With a single loculus without marked pleural enhancement, chest tube drainage usually is effective. However, with multiple loculations, the patient needs different therapy, such as empyemectomy and decortication or image-guided tubes or catheters with fibrinolytics.

Image-guided Percutaneous Catheters

There has been recent interest in image-guided percutaneous catheter drainage of parapneumonic effusions as first-line therapy and following unsuccessful standard chest tube drainage. Van Sonnenberg and colleagues²⁵ found that 15 of 17 patients with failed chest tube drainage for empyema were successfully drained by image-guided percutaneous catheters. Merriam and associates²⁶ retrospectively evaluated 16 patients with empyemas, nine with unsuccessful chest tube drainage, and found that 12 of 15 were cured with catheters. Westcott²⁷ reported successful catheter drainage of 11 of 12 patients with empyemas, five of whom had chest tube drainage as initial therapy.

In a literature review of 104 patients with image-guided catheter (8-14 F) drainage of infected pleural spaces, Ulmer and colleagues²⁸ found an overall cure rate of 81% (range, 72 to 92%) The high success rate presumably relates to more precise placement. Failure from catheter obstruction may be reduced by use of larger bore tubes, frequent irrigation, and fibrinolytics.

Successful pleural space drainage is determined by the stage of the parapneumonic effusion at the time of tube insertion. If the patient comes to medical attention early, the thin, serous fluid of Stage I can be drained effectively by either chest tube or catheter, allowing lung expansion and avoiding loculation and trapped lung. My bias is to drain thick empyema fluid with a large chest tube; however, the data from the interventional radiologists using small catheters is impressive and may be improved further with fibrinolytics.

Computed Tomography (CT)

The value of standard chest radiography in complex pleuropulmonary disease is limited. Although the presence of a free-flowing effusion can be established, identification of loculation is often problematic. In parapneumonic effusions, chest CT is useful in: (1) differentiating pleural from parenchymal disease; (2) evaluating parenchymal disease; (3) determining loculation; (4) characterizing the pleural surfaces; and (5) guiding and assessing therapy.²⁹ The optimal evaluation of patients with pleuropulmonary disease necessitates the use of intravenous contrast, which enables the localization of fluid collections and enhances the pleural membranes and adjacent parenchyma.

In a retrospective study of 26 parapneumonic effusions, including nine empyemas, evaluated by contrast CT, Himmelman and Callen³⁰ found that patients with loculated effusions had larger fluid volumes, longer hospitalization, and more frequent tube thoracostomies than patients with nonloculated effusions. A pH <7.20, LDH >1,000 U/L, and glucose <40 mg/dL correlated with loculation but not with empyema. Waite and associates³¹ found that 24 of 25 patients with empyema had enhancement of the parietal pleura on CT scan after intravenous contrast, and 30 of 35 patients showed parietal pleural thickening. There was an apparent relationship between both parietal pleural thickness and extent of pleural enhancement with the stage of the empyema; those with parietal pleural thickness >4 mm usually required decortication. However, in 10 patients with empyema treated with catheter drainage, serial CT scans showed that the marked pleural thickening at 4 weeks after catheter removal was substantially diminished by 12 weeks,³² attesting to the remarkable reparative capacity of the pleura.

All patients with a complicated parapneumonic effusion do not need chest CT scanning. However, it is probably cost-effective in the patient with a loculated parapneumonic effusion; as the information obtained allows the clinician to proceed with the most rational therapy, which should decrease morbidity, mortality, hospital stay, and cost.³³

Intrapleural Fibrinolytics

With adequate chest tube position, the major reasons for unsuccessful drainage are tube obstruction by organized empyema fluid and multiple pleural space loculations, which have generated interest in fibrinolytic treatment of complicated parapneumonic effusions during the past half century.

Initial enthusiasm for intrapleural fibrinolytics was tempered by systemic adverse effects, until Bergh and colleagues,³⁴ using a purified streptokinase, reported chest radiograph regression in 10 of 12 empyemas without the need for thoracotomy and with trivial adverse effects. Henke and Leatherman³⁵ treated 12 patients with large, loculated, nonpurulent parapneumonic effusions (pH <7.00 and/or glucose concentrations <40 mg/dL) and inadequate drainage by tube thoracostomy with 250,000 units of streptokinase up to 3 times. Chest radiographic and clinical improvement was observed in nine of 12 and eight of 12 patients, respectively.

Moulton and colleagues³⁶ retrospectively reviewed the results of 118 patients treated with image-guided drainage and urokinase instillation. There were 79 empyemas, 27 loculated parapneumonic effusions, and 12 other effusions. Forty-one of the 118 patients had failed prior large-bore thoracostomy tube drainage. Drainage was successful in 111 of 118 patients (94%). The mean total dose of urokinase per case was 466,000 units and no complications were reported.

Park and associates³⁷ evaluated the usefulness of intracavitary instillation of urokinase in 31 patients with loculated pleural effusions (21 with tuberculous pleurisy and 10 with pneumonic empyemas). In 16 of the 31 patients, there was >80% lung expansion, and sonography showed an anechoic appearance in 12. In nine patients, in whom treatment was partially effective (lung expansion 20-80%), an anechoic appearance was seen in six. In the six patients with ineffective lung expansion (<20%) sonography showed a linear septated appearance in one and a honeycomb appearance in five. The authors concluded that urokinase instillation should not be expected to be effective in patients whose pleural fluid had a honeycomb appearance on sonography or whose parietal pleura had a thickness of >5 mm on CT scan.

Bouros and co-workers³⁸ compared the efficacy, safety, and cost of streptokinase and urokinase in 50 consecutive randomized patients with complicated parapneumonic effusions or empyemas who were treated double-blind. All patients had inadequate drainage (<70 mL/24 h) through a chest tube. Response assessed by clinical outcome, fluid drainage, chest radiograph, ultrasound, and/or CT was successful in all but two patients in each group. High fever as an adverse reaction to streptokinase was observed in

two patients. The total cost of the drug in the urokinase group was approximately twice as much as in the streptokinase group (\$320 vs \$180). The authors concluded that both streptokinase and urokinase are effective adjuncts in the management of parapneumonic effusions and may reduce the need for surgery. The clinician must weigh the potential risk of allergic reaction to streptokinase and the slightly higher cost of urokinase.

Fibrinolytic agents should be most effective if used early in the evolution of the parapneumonic effusion before significant collagen is laid down in the pleural space (early in the fibrinopurulent stage).

Thoracoscopy

Ridley and Brainbridge³⁹ reported on 30 patients who received thoracoscopic debridement and pleural irrigation as initial management of empyema; 22 of the 30 patients had pneumonic empyema. The first 12 patients were carefully selected, and success was claimed in all. In the subsequent 18 nonselected patients, 10 required a second drainage procedure, resulting in delayed definitive treatment.

Landreneau and associates⁴⁰ reported on their experience with video-assisted thoracic surgery (VATS) in 76 patients with empyemas who had inadequate chest tube drainage. Sixty-three of 76 (83%) patients were treated successfully with thoracoscopic drainage with or without decortication, while 13 of 76 (17%) patients required subsequent thoracotomy for decortication (including 12 of 36 with chronic empyemas). The authors concluded that VATS has a high success rate in the early management of empyemas; however, conversion to open thoracotomy must be anticipated, especially with chronic empyemas.

In 20 patients with complicated parapneumonic effusions (loculated effusions or pleural fluid pH ≤ 7.20) randomized to VATS or chest tube drainage with streptokinase, Wait and colleagues⁴¹ found that patients treated with VATS had fewer hospital days, shorter chest tube duration, and greater treatment success. Unfortunately, the series was small and the chest tube was not placed with image-guidance. A large multicenter trial is ongoing and is using a more aggressive image-guided arm to compare to surgical drainage.

Empyemectomy/Decortication and Open Drainage

Persistent pleural sepsis, usually associated with the late fibrinopurulent or organizational stage of a parapneumonic effusion, requires aggressive surgical drainage. These patients represent either chest tube failure or delayed presentation. Ashbaugh⁴² reported on the effects of delayed surgical treatment and the choice of operation on morbidity in 122 consecutive patients with empyema—the majority with pneumonia. He found decortication superior to open drainage in patients requiring major operations, with a decrease in total days of illness, days of chest tube drainage, and postoperative hospitalization. Overall morbidity was lowest with decortication when compared with open drainage and chest tube drainage.

Although mortality in empyema remains, empyemectomy/decortication does not contribute to this mortality and is probably the most appropriate treatment for undrained loculations and trapped lung, unless the patient is too debilitated and ill to tolerate a major thoracotomy; in the latter situation, open drainage is preferable. If decortication is accomplished within 2 weeks of pleural space infection, the visceral pleural rind usually is easily extricated from the lung. The patient can usually be discharged from the hospital in 7 to 10 days.

Decortication for the purpose of improving a restrictive ventilatory defect following successful treatment of empyema should not be done immediately due to the remarkable reparative capacity of the pleura. If a restrictive defect persists at 6 months that interferes with the patient's lifestyle, decortication should be considered.

Conclusions

The critical factor determining outcome of parapneumonic effusions is the interval between initial symptoms of pneumonia and seeking of medical attention. Virtually no parapneumonic effusion will become complicated if early, appropriate antimicrobials are given for treatment of the pneumonia. Once the patient is under medical care, the burden falls to the clinician to move swiftly and appropriately in management. Thoracentesis should be done without delay once the presence of a parapneumonic effusion is

established, as the pleural fluid findings provide guidance for clinical decision-making. Pleural space drainage by chest tube or catheter for the high-risk patient with a nonpurulent free-flowing effusion should prevent trapped lung, pleural sepsis, and progression to a complicated parapneumonic effusion or empyema. The multiloculated pleural space needs to be drained aggressively usually with empyemectomy and decortication by thoracoscopy or open thoracotomy, except in the extremely debilitated patient who may benefit from open drainage. Whether image-guided catheters with fibrinolytics can replace surgical drainage of the multiloculated pleural space in the early fibrinopurulent stage awaits an answer from a large randomized trial.

References

1. Light RW, Girard WM, Jenkinson SG, et al. Parapneumonic effusions. *Am J Med* 1980; 69:507-12
2. Taryle DA, Potts DE, Sahn SA. The incidence and clinical correlates of parapneumonic effusions in pneumococcal pneumonia. *Chest* 1978; 74:170-3
3. Bartlett JG, Finegold SM. Anaerobic infections of the lung and pleural space. *Am Rev Respir Dis* 1974; 110:56-77
4. Potts DE, Levin DC, Sahn SA. Pleural fluid pH in parapneumonic effusions. *Chest* 1976; 70:328-31
5. Light RW, MacGregor MI, Ball WC Jr, et al. Diagnostic significance of pleural fluid pH and PCO₂. *Chest* 1973; 64:591-96
6. Poe RH, Marin MG, Israel RH, et al. Utility of pleural fluid analysis in predicting tube thoracostomy/decortication in parapneumonic effusions. *Chest* 1991; 100:963-67
7. Berger HA, Morganroth ML. Immediate drainage is not required for all patients with complicated parapneumonic effusions. *Chest* 1990; 97:731-35
8. Strange C, Sahn SA. The clinician's perspective on parapneumonic effusions and empyema. *Chest* 1992; 103:259-61
9. Potts DE, Taryle DA, Sahn SA. The glucose-pH relationship in parapneumonic effusions. *Arch Intern Med* 1978; 138:1378-80
10. Antony VB, Hadley KJ, Sahn SA. Mechanisms of pleural fibrosis in empyema: pleural macrophage-mediated inhibition of fibroblast proliferation. *Chest* 1989; 95S:230-31
11. Sahn SA, Taryle DA, Good JT Jr. Experimental empyema: time course and pathogenesis of pleural fluid acidosis and low pleural fluid glucose. *Am Rev Respir Dis* 1979; 120:355-61
12. Broaddus VA, Hebert CA, Vitangcol RV, et al. Interleukin-8 is a major neutrophil chemotactic factor in pleural liquid of patients with empyema. *Am Rev Respir Dis* 1992; 146:825-30
13. Sahn SA, Reller LB, Taryle DA, et al. The contribution of leukocytes and bacteria to the low pH of empyema fluid. *Am Rev Respir Dis* 1983; 128:811-15
14. Idell S, Girard W, Koenig KB, et al. Abnormalities of pathways of fibrin turnover in the human pleural space. *Am Rev Respir Dis* 1991; 144:187-94
15. Strange C, Tomlinson JR, Wilson C, et al. The histology of experimental pleural injury with tetracycline, empyema and carrageenan. *Exp Mol Pathol* 1989; 51:205-19
16. Strange C, Allen ML, Harley R, et al. Intrapleural streptokinase in experimental empyema. *Am Rev Respir Dis* 1993; 147:962-66
17. Lew PD, Zubler R, Vaudaux P, et al. Decreased heat-labile opsonic activity and complement levels associated with evidence of C3 breakdown products in infected pleural effusions. *J Clin Invest* 1979; 63:326-34
18. Sahn SA, Light RW. The sun should never set on a parapneumonic effusion. *Chest* 1989; 95:945-47
19. Heffner JE, Brown LK, Barbieri C, et al. Pleural fluid chemical analysis in parapneumonic effusions. *Am J Respir Crit Care Med* 1995; 151:1700-08

20. Taryle DA, Good JT, Morgan EJ, et al. Antibiotic concentrations in human parapneumonic effusions. *Antimicrob Agents Chemother* 1981; 7:171-77
21. Hughes CE, Van Scoy RE. Antibiotic therapy of pleural empyema. *Semin Respir Infect* 1991; 6:94-102
22. Shohet I, Yellin A, Meyerovitch J, et al. Pharmacokinetics and therapeutic efficacy of gentamicin in an experimental empyema rabbit model. *Antimicrob Agents Chemother* 1987; 31:982-85
23. Bartlett JG, Gorbach SL, Thadepalli H, et al. Bacteriology of empyema. *Lancet* 1974; 1:338-40
24. Stark DD, Dederle MP, Goodman PC. CT and radiographic assessment of tube thoracostomy. *AJR* 1983; 141:253-58
25. van Sonnenberg E, Nakamoto SK, Mueller PR, et al. CT-ultrasound-guided catheter drainage of empyemas after chest tube failure. *Radiology* 1984; 151:349-53
26. Merriam MA, Cronan JJ, Dorfman GS, et al. Radiographically guided percutaneous catheter drainage of pleural fluid collections. *AJR* 1988; 151:1113-36
27. Westcott J. Percutaneous catheter drainage of pleural effusion and empyema. *AJR* 1985; 144:1189-93
28. Ulmer JL, Choplin RH, Reed JC. Image-guided catheter drainage of the infected pleural space. *J Thorac Imaging* 1991; 6:65-73
29. Naidich DP, Zerhouni EA, Siegelman SS. *Computed tomography and magnetic resonance of the thorax*. 2d ed. New York: Raven Press 1991; 418-32
30. Himmelman RB, Callen PW. The prognostic value of loculations in parapneumonic pleural effusions. *Chest* 1986; 90:852-56
31. Waite RJ, Carbonneau RJ, Balikian JP, et al. Parietal pleural changes in empyema: appearances at CT. *Radiology* 1990; 175:145-50
32. Neff CC, van Sonnenberg E, Lawson EX, et al. CT follow-up of empyemas: pleural peels resolve after percutaneous catheter drainage. *Radiology* 1990; 176:196-97
33. LeMense GP, Strange C, Sahn SA. Empyema thoracis. Therapeutic management and outcome. *Chest* 1995; 107:1532-37
34. Bergh NP, Ekroth R, Larsson S, et al. Intrapleural streptokinase in the treatment of haemothorax and empyema. *Scand J Cardiovasc Surg* 1977; 11:265-68
35. Henke CA, Leatherman JW. Intrapleurally administered streptokinase in the treatment of acute loculated non-purulent parapneumonic effusions. *Am Rev Respir Dis* 1992; 145:680-84
36. Moulton JS, Benkert RE, Weisiger KH, et al. Treatment of complicated pleural fluid collections with image-guided drainage and intracavitary urokinase. *Chest* 1995; 108:1252-59
37. Park CS, Chung WM, Lim MK, et al. Transcatheter instillation of urokinase into loculated pleural effusion: analysis of treatment effect. *AJR* 1996; 167:649-52
38. Bouros D, Schiza S, Patsourakis G, et al. Intrapleural streptokinase versus urokinase in the treatment of complicated parapneumonic effusions. A prospective, double-blind study. *Am J Respir Crit Care Med* 1997; 155:291-95
39. Ridley PD, Brainbridge MV. Thoracoscopic debridement and pleural irrigation in the management of empyema thoracis. *Ann Thorac Surg* 1991; 51:461-64
40. Landreneau RJ, Keenan RJ, Hazelrigg SR, et al. Thoracoscopy for empyema and hemothorax. *Chest* 1996; 109:18-24
41. Wait MA, Sharma S, Hohn J, et al. A randomized trial of empyema therapy. *Chest* 1997; 111:1548-51
42. Ashbaugh DG. Empyema thoracis. Factors influencing morbidity and mortality. *Chest* 1991; 99:1162-65

