

REVIEW ARTICLE

Julie R. Ingelfinger, M.D., *Editor*

Fire-Related Inhalation Injury

Robert L. Sheridan, M.D.

From the Burn Service, Shriners Hospital for Children, the Division of Burns, Massachusetts General Hospital, and the Department of Surgery, Harvard Medical School—all in Boston. Address reprint requests to: Dr. Sheridan at the Burn Service, Shriners Hospital for Children, 51 Blossom St., Boston, MA 02114, or at rsheridan@mgh.harvard.edu.

N Engl J Med 2016;375:464-9.

DOI: 10.1056/NEJMra1601128

Copyright © 2016 Massachusetts Medical Society.

INHALATION INJURY HAS BEEN RECOGNIZED AS AN IMPORTANT CLINICAL problem among fire victims since the disastrous 1942 Cocoanut Grove nightclub fire.¹ Despite the fact that we have had many years' experience with treating injuries related to fires, the complex physiological process of inhalation injury remains poorly understood, diagnostic criteria remain unclear, specific therapeutic interventions remain ineffective, the individual risk of death remains difficult to quantify, and the long-term implications for survivors remain ill defined. Central to these uncertainties is the complex nature of the injuries, which include a varying combination of thermal injury to the upper airway, bronchial and alveolar mucosal irritation and inflammation from topical chemical exposure, systemic effects of absorbed toxins, loss of ciliated epithelium, accrual of endobronchial debris, secondary systemic inflammatory effects on the lung, and subsequent pulmonary and systemic infection.

INCIDENCE, PREVENTION, AND IMPLICATIONS OF INHALATION INJURY

Data from the National Inpatient Sample and the National Burn Repository suggest that there are roughly 40,000 inpatient admissions for burns in the United States annually; at a conservative estimate, 2000 of these admissions (5%) involve concomitant inhalation injury.² Structural fires are most common in developed environments, especially in impoverished communities. During the past decade, a strong emphasis has been placed on the installation of smoke detectors in residential buildings, which seems to have slightly reduced the incidence of burn and inhalation injury resulting from fires in buildings.

In virtually all epidemiologic studies of burns, inhalation injury is an independent predictor of death, particularly in patients with cutaneous burns over 20% or more of the body-surface area.³ In a classic study that described a large clinical experience at the U.S. Army Institute of Surgical Research, the predicted mortality among patients with burns was 20% higher when inhalation injury was present than when it was not; if secondary pneumonia developed, mortality was 60% higher.⁴

PATHOPHYSIOLOGICAL PROCESS

Inhalation injury can result from direct local thermal and chemical exposures, immune responses to these factors, systemic effects of inhaled toxins, accrual of endobronchial debris, and secondary infection. Structural fires generate smoke that contains a large variety of chemicals, products of incomplete combustion, and aerosolized debris of widely varying particle sizes. Air temperature during fires

varies enormously; typically low at floor level, air temperature can be hundreds of degrees Fahrenheit just a few feet above the floor. The effect on individual patients is complex and unpredictable (Fig. 1).

DIRECT LOCAL INJURY

Direct thermal damage is generally confined to the supraglottic airway, except in rare cases of steam inhalation, such as those that involve the inhalation of pressurized steam in engineering spaces. Most injuries that occur below the glottis are caused by aerosolized chemicals and incomplete products of combustion. The type and severity of these injuries are highly unpredictable, depending on the agents released and the particle sizes inhaled; smaller particles travel to a more distal location in the airway before deposition. The local effects include irritation, mucosal slough, bronchospasm, increased bronchial blood flow, surfactant depletion, and inflammation.

SECONDARY INFLAMMATION

Protean, intense inflammatory responses to inhalation injury may occur, which can generate local reactive oxygen species, attract inflammatory cells, and trigger the release of numerous pro-inflammatory molecules and cytokines.⁵ The local pulmonary effects of the inflammatory responses include bronchospasm and vasospasm, bronchorrhea and alveolar flooding, bronchial exudate and cast formation, and ventilation-perfusion mismatching. The systemic effects lead to a clinically significant increase in the volume of resuscitation fluid required in patients with cutaneous burns who have coincident inhalation injury.⁶

ANOXIA

Oxidation of combustibles rapidly consumes available oxygen. Inhalation of oxygen-deficient gas can cause hypoxic brain injury, which is treated like any anoxic brain injury; the neurologic outcome of treatment is variable.

CARBON MONOXIDE EXPOSURE

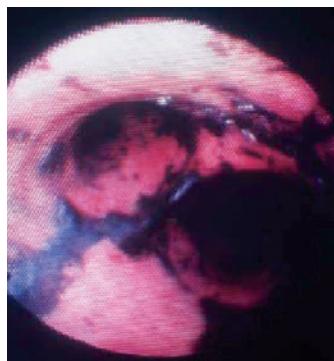
Carbon monoxide, which is released during combustion, is a colorless and odorless gas that is rapidly absorbed after inhalation. Carbon monoxide avidly binds to heme-containing moieties, notably hemoglobin and enzymes of the intra-



Initial Physical Findings: Direct thermal injury is generally confined to the face and upper airway. Physical findings include facial burns, burned nasal hairs, and soot in the nares and mouth.



Bronchial Cast: Accrued endobronchial debris and exudate can cause obstruction of distal airways contributing to ventilation-perfusion mismatching and secondary infection.



Bronchoscopic View: Aerosolized chemicals and incomplete products of combustion can deposit throughout the subglottic airway and lungs. Severity of injury depends on both the agents and particle sizes inhaled; smaller particles travel more distally. Bronchoscopic findings include mucosal irritation, pallor, ulceration, and carbonaceous debris.



Facial Burn: Anoxia, carbon monoxide effects, cyanide effects, local and systemic inflammation, airway obstruction, and infection contribute to morbidity and mortality in patients with inhalation injury. The effects are more marked in those with large cutaneous burns.

Figure 1. The Pathogenesis of Inhalation Injury.

The physiological process of inhalation injury is complex and involves a variable and often unpredictable degree of direct local thermal and chemical exposure, reactive immune responses, systemic effects of inhaled toxins, accrual of endobronchial debris, and secondary infection. Shown are airway soot observed on physical examination, a positive diagnostic bronchoscopic view, a sloughed endobronchial cast, and a patient with inhalation injury.

mitochondrial cytochrome system; the binding results in reduced oxygen delivery (through the formation of carboxyhemoglobin) and reduced oxygen utilization (through impaired function of the cytochrome cascade). Carboxyhemoglobin levels of 10 to 20% are associated with headache and nausea; levels of 20 to 30%, with muscle weakness and impaired cognition; and levels of 30 to 50%, with cardiac ischemia and unconsciousness. Higher levels are often lethal. Treatment with oxygen during prehospital care may

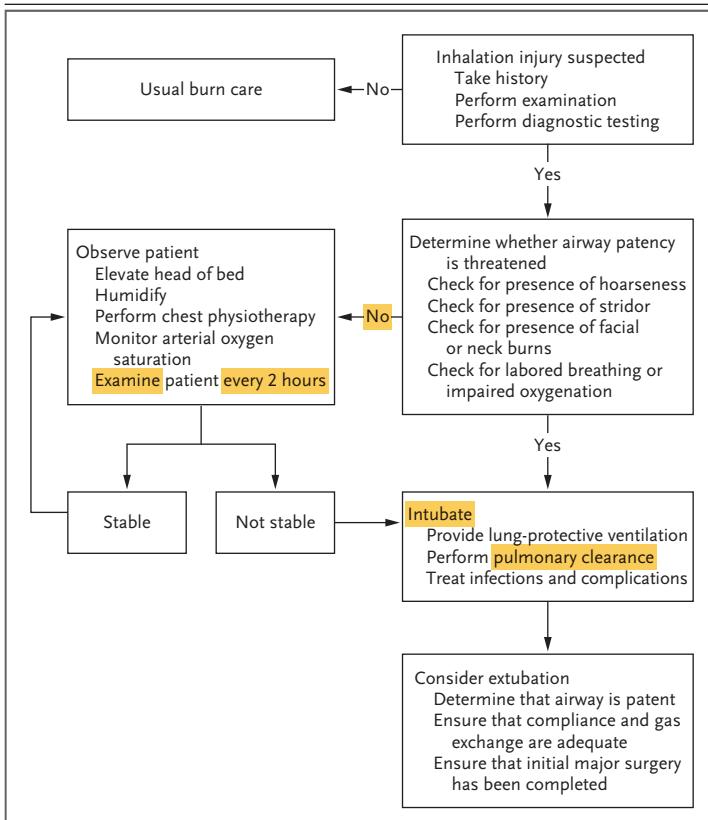


Figure 2. An Algorithm for Early Management of Fire-Related Inhalation Injury.

Compromise of airway patency or gas exchange with fluid resuscitation may develop in patients with large surface burns, particularly those at the extremes of age or with underlying medical conditions. If initial intubation is not required, the patient should be watched particularly closely to determine whether subsequent intubation is needed.

obscure the degree of initial exposure, because carboxyhemoglobin levels normalize quickly when the patient breathes 100% oxygen; cytochrome clearance probably takes longer. Delayed development of neurologic sequelae after carbon monoxide exposure has been reported in a small percentage of patients.⁷

CYANIDE EXPOSURE

Hydrogen cyanide gas is released with the combustion of a number of synthetic polymers and is readily absorbed by inhalation. Similar to carboxyhemoglobin, hydrogen cyanide interferes with oxygen utilization at the cytochrome level and is thought to be a minor contributor, along with anoxia and carbon monoxide poisoning, to early deaths from an acute inhalation injury.⁸ Cyanide poisoning is associated with a persis-

tent acidosis despite an otherwise successful resuscitation.

SECONDARY INFECTION AND RESPIRATORY FAILURE

Injury to endobronchial and alveolar epithelium results in mucosal slough, which increases the amount of debris within the airways and reduces the amount and efficacy of ciliary clearance. These problems contribute to the progressive small-airway occlusion, atelectasis, ventilation-perfusion mismatching, and infection that complicate the management of inhalation injury in the days after a burn injury. Indeed, most in-hospital deaths related to inhalation injury are caused by these secondary developments, rather than by the initial insult.

DIAGNOSIS

Although various grading schemes have been proposed,⁹ diagnosis and severity grading of inhalation injury have never been reliably predictive of outcome.¹⁰ The principal tools for assessment are clinical evaluation, bronchoscopy, and radiography.

CLINICAL EVALUATION

Assessing the clinical presentation is the most reliable method of diagnosis and approximate grading of severity.⁹ A history of burns from a fire in a closed space, cutaneous burns around the nose and mouth, singed nasal hair, soot in the airway, carbonaceous sputum, hoarseness, wheezing, and stridor all suggest inhalation injury (Fig. 2). Indexes of oxygenation at the completion of fluid resuscitation have been shown to correlate loosely with the severity of inhalation injury but can be greatly influenced by the fluid volume required for resuscitation and ventilation mode.¹⁰

BRONCHOSCOPIC EXAMINATION

Flexible bronchoscopy of the upper airways may reveal carbonaceous debris, ulceration, pallor, and mucosal slough (Fig. 1). Bronchoscopic grading schemes have been shown to correlate loosely with subsequent clinical course.¹¹ Although bronchoscopy for pulmonary clearance may have value later in the hospital course, the value of immediate removal of debris visible on bronchoscopic examination has not been shown.

Table 1. Brief Summary of Options or Indications in the Management of Fire-Related Inhalation Injury.

Issue	Current Standard of Care*	Additional Available Options or Indications†
Diagnosis	Clinical history and examination	Bronchoscopy, radionuclide scanning, computed tomographic scanning
Associated carbon monoxide exposure	100% Normobaric oxygen for 6 hours	Hyperbaric oxygen treatment
Associated cyanide exposure	Fluid resuscitation; hydroxycobalamin, if acidosis is unexplained	Empirical hydroxycobalamin; sodium nitrite and sodium thiosulfate as adjunctive therapy
Indication for intubation	Overt signs of upper-airway obstruction, failure of gas exchange, obtunded neurologic status	Evolving upper-airway obstruction, worsening gas exchange, or deteriorating neurologic status
Mechanical ventilation strategy	Pressure-controlled, lung-protective ventilation	Percussive ventilation; high-tidal-volume ventilation
Pulmonary clearance technique	Spontaneous cough; blind endobronchial suctioning, if intubated	Repeated bronchoscopies, as needed
Pharmacologic adjuncts	None	Nebulized heparin and N-acetylcysteine together
Empirical agents	None	Glucocorticoids with or without antibiotics

* The current standard of care refers to the most common approach to diagnosis or therapy.

† The additional available options or indications listed are used by some clinicians; high-level proof of efficacy with respect to these options or indications has not been established, and therapies have not been universally adopted.

IMAGING

Plain chest radiographs that are obtained immediately after admission are usually normal and are therefore not useful for diagnosis or severity stratification.¹² Radionuclide ventilation scanning has been advocated; inhomogeneous clearing of tracer associated with small-airway obstruction signifies inhalation injury.¹³ However, because the radionuclide ventilation technique is cumbersome and has not been found to be universally reliable, clinical use of this technique is currently rare. Computed tomographic scanning has shown promise for stratification of severity and for predicting clinical course.¹⁴ However, the information from such scans is unlikely to change the management of inhalation injury in a patient and comes at a logistic and fiscal cost that is likely to preclude routine application.

CLINICAL COURSE AND PRACTICAL MANAGEMENT

The spectrum of severity of inhalation injury is enormous — from minor injury in a healthy firefighter who has no cutaneous burn but is coughing up soot to life-threatening injury in a young child who has a large, deep surface burn and is unconscious from hypoxia and carbon monoxide exposure. However, each case of inhalation injury includes some component of upper-

airway thermal injury, lower-airway chemical injury, systemic toxic effects, endobronchial debris, reactive inflammation, and secondary infection.

Despite many controversies, certain clinical consequences are predictable and have an important effect on practical clinical care. The current standard of care and other options are shown in Table 1.

MANAGEMENT EARLY AFTER EXPOSURE (0 TO 72 HOURS)

The presence of inhalation injury does not mandate intubation. If airway patency is not threatened, particularly if cutaneous burns involve less than 20% of the body-surface area, elevation of the head of the bed, humidification of the air, and close observation are appropriate. Endotracheal intubation is advised in patients who have facial edema, hoarseness, or stridor or in patients with large cutaneous burns in whom facial edema is likely to develop with resuscitation. It is crucial to maintain endotracheal tube security, because upper-airway edema makes reintubation difficult. Immediate tracheostomy is rarely necessary. In some patients, bronchospasm caused by aerosolized irritants can be an acute problem, though it usually responds to nebulized beta-agonists. Neither prophylactic antibiotics nor empirical glucocorticoids are advised. Profound early hypoxia is unusual but generally responds to standard measures of critical care that are based on pressure-

controlled ventilation and positive end-expiratory pressure.

Carbon monoxide exposure is common with inhalation injuries and may be obscured by a rapid reduction in carboxyhemoglobin levels owing to the administration of oxygen before hospital admission. Controversy swirls around the role of hyperbaric oxygen treatment in patients with burns who have had clinically significant carbon monoxide exposure. Our understanding of the neurophysiological processes involved is incomplete and does not unequivocally support purely oxygen-based therapies.¹⁵ From a practical perspective, wheezing and airway debris are relative contraindications to hyperbaric oxygen treatment because they increase the risk of gas embolism and pneumothorax at decompression.¹⁶ If a high carboxyhemoglobin level is documented, or if substantial carbon monoxide exposure is suspected, the standard treatment is 100% normobaric oxygen for 6 hours.¹⁷ Resuscitation monitoring is also compromised during transport to and time within the hyperbaric chamber. If hyperbaric oxygen treatment can be performed safely, such as in patients who do not have cutaneous burns, wheezing, or clinically important airway debris, the treatment may be considered; 100% normobaric oxygen is the safer and more practical alternative in other circumstances.

Hydrogen cyanide gas is formed during the combustion of many synthetic polymers and is readily absorbed by inhalation and quickly metabolized. High-level exposure compromises cellular oxygen utilization. Controversy exists with respect to the usefulness of testing and treating cyanide exposure in patients with inhalation injury. Currently in North American burn centers, most patients with inhalation injury are neither tested nor treated for cyanide exposure.¹⁸ Cyanide poisoning manifests as persistent acidosis despite hemodynamic normalization. Simple treatment with hydroxycobalamin is available and can be administered empirically in patients with cyanide poisoning.¹⁹

MANAGEMENT AT INTERMEDIATE TIME AFTER EXPOSURE (3 TO 21 DAYS)

Standard pressure-controlled, lung-protective ventilation strategies suffice for most patients who require ventilator assistance.²⁰ High-frequency percussive ventilation has been championed by some clinicians because of its ability to enhance pulmonary clearance and oxygenation; however,

meaningful differences in outcome are difficult to discern, and delivery of the therapy can be logistically challenging.²¹ Some investigators have reported improved outcomes — possibly related to improved pulmonary clearance — when higher volumes are used to inflate the lungs in persons with inhalation injury, although such use must be balanced against the risk of ventilator-induced lung injury.²² Because of mucosal slough and loss of ciliary clearance, pulmonary clearance is a major priority in the care of patients with inhalation injury. In most patients, chest physiotherapy and suctioning suffice. For particularly tenacious secretions that are occasionally seen in patients, bronchoscopy for pulmonary clearance may be useful.²³ Pulmonary infection is a common complication and is treated with targeted antibiotics and pulmonary clearance.

Nebulized heparin and N-acetylcysteine have been advocated to enhance the clearance of debris and improve the outcome in patients with inhalation injury.²⁴ Clinical studies have shown conflicting results, and frequent nebulization may increase the risk of pneumonia.²⁵ Although nebulization is used in many centers, this therapy has not been universally adopted.

Decisions about weaning and extubation are made according to the usual criteria for critical care. Resolution of airway edema should be documented before extubation, particularly in small children. Tracheostomy is reserved for patients who are expected to require more than 3 weeks of intubation — generally those with large cutaneous burns. Pulmonary clearance is enhanced by tracheostomy, but this is rarely the primary indication. As is the case with pulmonary care for conditions not related to burns, salvage therapy for patients in whom standard therapies are failing includes extracorporeal support, which is only rarely required by patients with fire-related inhalation injury.

LONG-TERM ISSUES

Patients with severe injuries may not survive, but the few studies that have examined the long-term outcomes of pulmonary function after inhalation injury have shown that the majority of survivors have few late complications.^{26,27} However, not enough research has been performed in this area to determine whether subclinical long-term complications are common.²⁸

Complications from direct thermal damage that involve the upper airway, endotracheal access injury, or both, occur in a small minority of cases but can be severe. Patients with such complications may present with symptoms of upper-airway obstruction during the weeks to months after extubation. Therapy is difficult and may require complex reconstructive airway operations.²⁹

portive, with a focus on the prevention of therapy-induced lung and airway injury, the facilitation of pulmonary clearance, and the management of secondary respiratory failure and pulmonary infection. Despite these difficulties, most survivors will ultimately have a good outcome, with few overt long-term sequelae from the inhalation component of their burn injury.

CONCLUSION

Inhalation injury remains difficult to diagnose and accurately grade. Therapy remains sup-

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

REFERENCES

- Aub JC, Pittman H, Brues AM. The pulmonary complications: a clinical description. *Ann Surg* 1943;117:834-40.
- Veeravagu A, Yoon BC, Jiang B, et al. National trends in burn and inhalation injury in burn patients: results of analysis of the Nationwide Inpatient Sample database. *J Burn Care Res* 2015;36:258-65.
- Ryan CM, Schoenfeld DA, Thorpe WP, Sheridan RL, Cassem EH, Tompkins RG. Objective estimates of the probability of death from burn injuries. *N Engl J Med* 1998;338:362-6.
- Shirani KZ, Pruitt BA Jr, Mason AD Jr. The influence of inhalation injury and pneumonia on burn mortality. *Ann Surg* 1987;205:82-7.
- Albright JM, Davis CS, Bird MD, et al. The acute pulmonary inflammatory response to the graded severity of smoke inhalation injury. *Crit Care Med* 2012;40:1113-21.
- Endorf FW, Gamelli RL. Inhalation injury, pulmonary perturbations, and fluid resuscitation. *J Burn Care Res* 2007;28:80-3.
- Guzman JA. Carbon monoxide poisoning. *Crit Care Clin* 2012;28:537-48.
- Barillo DJ, Goode R, Esch V. Cyanide poisoning in victims of fire: analysis of 364 cases and review of the literature. *J Burn Care Rehabil* 1994;15:46-57.
- Ryan CM, Fagan SP, Goverman J, Sheridan RL. Grading inhalation injury by admission bronchoscopy. *Crit Care Med* 2012;40:1345-6.
- Hassan Z, Wong JK, Bush J, Bayat A, Dunn KW. Assessing the severity of inhalation injuries in adults. *Burns* 2010;36:212-6.
- Spano S, Hanna S, Li Z, Wood D, Cartotto R. Does bronchoscopic evaluation of inhalation injury severity predict outcome? *J Burn Care Res* 2016;37:1-11.
- Putman CE, Loke J, Matthey RA, Ravin CE. Radiographic manifestations of acute smoke inhalation. *AJR Am J Roentgenol* 1977;129:865-70.
- Shiau YC, Liu FY, Tsai JJ, Wang JJ, Ho ST, Kao A. Usefulness of technetium-99m hexamethylpropylene amine oxime lung scan to detect inhalation lung injury of patients with pulmonary symptoms/signs but negative chest radiograph and pulmonary function test findings after a fire accident — a preliminary report. *Ann Nucl Med* 2003;17:435-8.
- Yamamura H, Morioka T, Hagawa N, Yamamoto T, Mizobata Y. Computed tomographic assessment of airflow obstruction in smoke inhalation injury: relationship with the development of pneumonia and injury severity. *Burns* 2015;41:1428-34.
- Roderique JD, Josef CS, Feldman MJ, Spiess BD. A modern literature review of carbon monoxide poisoning theories, therapies, and potential targets for therapy advancement. *Toxicology* 2015;334:45-58.
- Sheridan RL, Shank ES. Hyperbaric oxygen treatment: a brief overview of a controversial topic. *J Trauma* 1999;47:426-35.
- Buckley NA, Juurlink DN, Isbister G, Bennett MH, Lavonas EJ. Hyperbaric oxygen for carbon monoxide poisoning. *Cochrane Database Syst Rev* 2011;4:CD002041.
- Dumestre D, Nickerson D. Use of cyanide antidotes in burn patients with suspected inhalation injuries in North America: a cross-sectional survey. *J Burn Care Res* 2014;35(2):e112-7.
- Anseeuw K, Delvau N, Burillo-Putze G, et al. Cyanide poisoning by fire smoke inhalation: a European expert consensus. *Eur J Emerg Med* 2013;20:2-9.
- Peck MD, Koppelman T. Low-tidal-volume ventilation as a strategy to reduce ventilator-associated injury in ALI and ARDS. *J Burn Care Res* 2009;30:172-5.
- Al Ashry HS, Mansour G, Kalil AC, Walters RW, Vivekanandan R. Incidence of ventilator associated pneumonia in burn patients with inhalation injury treated with high frequency percussive ventilation versus volume control ventilation: a systematic review. *Burns* 2016 March 26 (Epub ahead of print).
- Sousse LE, Herndon DN, Andersen CR, et al. High tidal volume decreases adult respiratory distress syndrome, atelectasis, and ventilator days compared with low tidal volume in pediatric burned patients with inhalation injury. *J Am Coll Surg* 2015;220:570-8.
- Carr JA, Crowley N. Prophylactic sequential bronchoscopy after inhalation injury: results from a three-year prospective randomized trial. *Eur J Trauma Emerg Surg* 2013;39:177-83.
- Miller AC, Elamin EM, Suffredini AF. Inhaled anticoagulation regimens for the treatment of smoke inhalation-associated acute lung injury: a systematic review. *Crit Care Med* 2014;42:413-9.
- Kashefi NS, Nathan JJ, Dissanaik S. Does a nebulized heparin/N-acetylcysteine protocol improve outcomes in adult smoke inhalation? *Plast Reconstr Surg Glob Open* 2014;2(6):e165.
- Rosenberg M, Ramirez M, Epperson K, et al. Comparison of long-term quality of life of pediatric burn survivors with and without inhalation injury. *Burns* 2015;41:721-6.
- Bourbeau J, Lacasse Y, Rouleau MY, Boucher S. Combined smoke inhalation and body surface burns injury does not necessarily imply long-term respiratory health consequences. *Eur Respir J* 1996;9:1470-4.
- Palmieri TL. Long term outcomes after inhalation injury. *J Burn Care Res* 2009;30:201-3.
- Gaissert HA, Lofgren RH, Grillo HC. Upper airway compromise after inhalation injury: complex strictures of the larynx and trachea and their management. *Ann Surg* 1993;218:672-8.

Copyright © 2016 Massachusetts Medical Society.