affected following multiple dosing of topiramate (100 mg every 12 hr) in 13 healthy adults (6 M, 7 F). Amitriptyline: There was a 12% increase in AUC and C_{max} for amitriptyline (25 mg per day) in 18 normal subjects (9 male; 9 female) receiving 200 mg/day of topiramate. Some subjects may experience a large increase in amitriptyline concentration in the presence of topiramate and any adjustments in amitriptyline dose should be made according to the patient's clinical response and not on the basis of plasma levels. Sumatriptan: Multiple dosing of topiramate (100 mg every 12 hr) in 24 healthy volunteers (14 M, 10 F) did not affect the pharmacokinetics of single dose sumatriptan either orally (100 mg) or subcutaneously (6 mg). Risperidone: There was a 25% decrease in exposure to risperidone (2 mg single dose) in 12 healthy volunteers (6 M, 6 F) receiving 200 mg/day of topiramate. Therefore, patients receiving risperidone in combination with topiramate should be closely monitored for clinical response. Propranolol: Multiple dosing of topiramate (200 mg/day) in 34 healthy volunteers (17 M, 17 F) did not affect the pharmacokinetics of propranolol following daily 160 mg doses. Propranolol doses of 160 mg/day in 39 volunteers (27M, 12F) had no affect on the exposure to topiramate at a dose of 200 mg/day of topiramate. Dihydroergotamine: Multiple dosing of topiramate (200 mg/day) in 24 healthy volunteers (12 M, 12 F) did not affect the pharmacokinetics of a 1 mg subcutaneous dose of dihydroergotamine. Similarly, a 1 mg subcutaneous dose of dihydroergotamine did not affect the pharmacokinetics of a 200 mg/day dose of topiramate in the same study. Others: Concomitant use of TOPAMAX®, a carbonic anhydrase inhibitor, with other carbonic anhydrase inhibitors, e.g., acetazolamide or dichlorphenamide, may create a physiological environment that increases the risk of renal stone formation, and should therefore be avoided. Drug/Laboratory Tests Interactions: There are no known interactions of topiramate with commonly used laboratory tests. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** An increase in urinary bladder tumors was observed in mice given topiramate (20, 75, and 300 mg/kg) in the diet for 21 months. The elevated bladder tumor incidence, which was statistically significant in males and females receiving 300 mg/kg, was primarily due to the increased occurrence of a smooth muscle tumor considered histomorphologically unique to mice. Plasma exposures in mice receiving 300 mg/kg were approximately 0.5 to 1 times steady-state exposures measured in patients receiving topiramate monotherapy at the recommended human dose (RHD) of 400 mg, and 1.5 to 2 times steady-state topiramate exposures in patients receiving 400 mg of topiramate plus phenytoin. The relevance of this finding to human carcinogenic risk is uncertain. No evidence of carcinogenicity was seen in rats following oral administration of topiramate for 2 years at doses up to 120 mg/kg (approximately 3 times the RHD on a mg/m^2 basis). Topiramate did not demonstrate genotoxic potential when tested in a battery of *in vitro* and *in vivo* assays. Topiramate was not mutagenic in the Ames test or the *in vitro* mouse lymphoma assay; it did not increase unscheduled DNA synthesis in rat hepatocytes *in vitro;* and it did not increase chromosomal aberrations in human lymphocytes *in vitro* or in rat bone marrow *in vivo*. No adverse effects on male or female fertility were observed in rats at doses up to 100 mg/kg (2.5 times the RHD on a mg/m^2 basis). **Pregnancy: Pregnancy Category C:** Topiramate has demonstrated selective developmental toxicity, including teratogenicity, in experimental animal studies. When oral doses of 20, 100, or 500 mg/kg were administered to pregnant mice during the period of organogenesis, the incidence of fetal malformations (primarily craniofacial defects) was increased at all doses. The low dose is approximately 0.2 times the recommended human dose (RHD=400 mg/day) on a mg/m^2 basis. Fetal body weights and skeletal ossification were reduced at 500 mg/kg in conjunction with decreased maternal body weight gain. In rat studies (oral doses of 20, 100, and 500 mg/kg or 0.2, 2.5, 30, and 400 mg/kg), the frequency of limb malformations (ectrodactyly, micromelia, and amelia) was increased among the offspring of dams treated with 400 mg/kg (10 times the RHD on a mg/m^2 basis) or greater during the organogenesis period of pregnancy. Embryotoxicity (reduced fetal body weights, increased incidence of structural variations) was observed at doses as low as 20 mg/kg (0.5 times the RHD on a mg/m^2 basis). Clinical signs of maternal toxicity were seen at 400 mg/kg and above, and maternal body weight gain was reduced during treatment with 100 mg/kg or greater. In rabbit studies (20, 60, and 180 mg/kg or 10, 35, and 120 mg/kg orally during organogenesis), embryo/fetal mortality was increased at 35 mg/kg (2 times the RHD on a mg/m^2 basis) or greater, and teratogenic effects (primarily rib and vertebral malformations) were observed at 120 mg/kg (6 times the RHD on a mg/m^2 basis). Evidence of maternal toxicity (decreased body weight gain, clinical signs, and/or mortality) was seen at 35 mg/kg and above. When female rats were treated during the latter part of gestation and throughout lactation (0.2, 4, 20, and 100 mg/kg or 2, 20, and 200 mg/kg), offspring exhibited decreased viability and delayed physical development at 200 mg/kg (5 times the RHD on a mg/m^2 basis) and reductions in pre- and/or postweaning body weight gain at 2 mg/kg (0.05 times the RHD on a mg/m^2 basis) and above. Maternal toxicity (decreased body weight gain, clinical signs) was evident at 100 mg/kg or greater. In a rat embryo/fetal development study with a postnatal component (0.2, 2.5, 30, or 400 mg/kg during organogenesis; noted above), pups exhibited delayed physical development at 400 mg/kg (10 times the RHD on a mg/m^2 basis) and persistent reductions in body weight gain at 30 mg/kg (1 times the RHD on a mg/m^2 basis) and higher. There are no studies using TOPAMAX® in pregnant women. TOPAMAX® should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. In post-marketing experience, cases of hypospadias have been reported in male infants exposed in utero to topiramate, with or without other anticonvulsants; however, a causal relationship with topiramate has not been established. **Labor and Delivery:** In studies of rats where dams were allowed to deliver pups naturally, no drug-related effects on gestation length or parturition were observed at dosage levels up to 200 mg/kg/day. The effect of TOPAMAX® on labor and delivery in humans is unknown. **Nursing Mothers:** Topiramate is excreted in the milk of lactating rats. The excretion of topiramate in human milk has not been evaluated in controlled studies. Limited observations in patients suggest an extensive secretion of topiramate into breast milk. Since many drugs are excreted in human milk, and because the potential for serious adverse reactions in nursing infants to TOPAMAX® is unknown, the potential benefit to the mother should be weighed against the potential risk to the infant when considering recommendations regarding nursing. **Pediatric Use:** Safety and effectiveness in patients below the age of 2 years have not been established for the adjunctive therapy treatment of partial onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome. Topiramate is associated with metabolic acidosis. Chronic untreated metabolic acidosis in pediatric patients may cause osteomalacia/rickets and may reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated (see **WARNINGS**). Safety and effectiveness in pediatric patients have not been established for the prophylaxis treatment of migraine headache. **Geriatric Use:** In clinical trials, 3% of patients were over 60. No age related difference in effectiveness or adverse effects were evident. However, clinical studies of topiramate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Dosage adjustment may be necessary for elderly with impaired renal function (creatinine clearance rate ≤70 mL/min/1.73 m^2) due to reduced clearance of topiramate (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION** in full Prescribing Information). **Race and Gender Effects:** Evaluation of effectiveness and safety in clinical trials has shown no race or gender related effects.

ADVERSE REACTIONS: The data described in the following section were obtained using TOPAMAX® (topiramate) Tablets.

Migraine: In the four multicenter, randomized, double-blind, placebo-controlled, parallel group migraine prophylaxis clinical trials, most of the adverse events with topiramate were mild or moderate in severity. Most adverse events occurred more frequently during the titration period than during the maintenance period. Table 2 includes those adverse events reported for patients in the placebo-controlled trials where the incidence rate in any topiramate treatment group was at least 2 % and was greater than that for placebo patients. **Table 2:** Incidence of Treatment-Emergent Adverse Events in Placebo-Controlled, Migraine Trials Where Rate Was ≥2 % in Any Topiramate Group and Greater than the Rate in Placebo-Treated Patients[a].
Body System/Adverse Event followed by Placebo (N=445) first, TOPAMAX® Dosage (mg/day) 50 (N=235) second, 100 (N=386) third, 200 (N=514) fourth: Body as a Whole – General Disorders: Fatigue 11, 14, 15, 19; Injury 7, 9, 6, 6; Asthenia 1, <1, 2, 2; Fever 1, 1, 1, 2; Influenza-Like Symptoms <1, <1, <1, 2; Allergy <1, 2, <1, <1; Central & Peripheral Nervous System Disorders: Paresthesia 6, 35, 51, 49; Dizziness 10, 8, 9, 12; Hypoaesthesia 2, 6, 7, 8; Language Problems 2, 7, 6, 7; Involuntary Muscle Contractions 1, 2, 2, 4; Ataxia <1, 1, 2, 1; Speech Disorders/Related Speech Problems <1, 1, <1, 2; Gastro-Intestinal System Disorders: Nausea 8, 9, 13, 14; Diarrhea 4, 9, 11, 11; Abdominal Pain 5, 6, 6, 7; Dyspepsia 3, 4, 5, 3; Dry Mouth 2, 2, 3, 5; Vomiting 2, 1, 2, 3; Gastroenteritis 1, 3, 3, 2; Hearing and Vestibular Disorders: Tinnitus 1, <1, 1, 2; Metabolic and Nutritional Disorders: Weight Decrease 1, 6, 9, 11; Thirst <1, 2, 2, 1; Musculoskeletal System Disorders: Arthralgia 2, 7, 3, 1; Neoplasms: Neoplasm NOS <1, 2, <1, <1; Psychiatric Disorders: Anorexia 6, 9, 15, 14; Somnolence 5, 8, 7, 10; Difficulty with Memory NOS 2, 7, 7, 11; Difficulty with Concentration/Attention 2, 3, 6, 10; Insomnia 5, 6, 7, 6; Anxiety 3, 4, 5, 6; Mood Problems 2, 3, 6, 5; Depression 4, 3, 4, 6; Nervousness 2, 4, 4, 4; Confusion 2, 2, 3, 4; Psychomotor Slowing 1, 3, 2, 4; Libido Decreased 1, 1, 1, 2; Aggravated Depression 1, 1, 2, 2; Agitation 1, 2, 2, 1; Cognitive Problems NOS 1, <1, 2, 2; Reproductive Disorders, Female: Menstrual Disorder 2, 3, 2, 2; Reproductive Disorders, Male: Ejaculation Premature 0, 3, 0, 0; Resistance Mechanism Disorders: Viral Infection 3, 4, 4, 3; Otitis Media <1, 2, 1, 1; Respiratory System Disorders: Upper Respiratory Tract Infection 12, 13, 14, 12; Sinusitis 6, 10, 6, 8; Pharyngitis 4, 5, 6, 2; Coughing 2, 2, 4, 3; Bronchitis 2, 3, 3, 3; Dyspnea 2, 1, 3, 2; Rhinitis 1, 1, 2, 2; Skin and Appendages Disorders: Pruritis 2, 4, 2, 2; Special Sense Other Disorders: Taste Perversion 1, 15, 8, 12; Taste Loss <1, 1, 1, 2; Urinary System Disorders: Urinary Tract Infection 2, 4, 2, 4; Renal Calculus 0, 0, 1, 2; Vision Disorders: Vision Abnormal <1, 1, 2, 3; Blurred Vision[b] 2, 4, 2, 4; Conjunctivitis 1, 1, 2, 1. [a]Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category. [b]Blurred vision was the most common term considered as vision abnormal. Blurred vision was an included term that accounted for >50% of events coded as vision abnormal, a preferred term. Of the 1,135 patients exposed to topiramate in the placebo-controlled studies, 25% discontinued due to adverse events, compared to 10% of the 445 placebo patients. The adverse events associated with discontinuing therapy in the topiramate-treated patients included paresthesia (7%), fatigue (4%), nausea (4%), difficulty with concentration/attention (3%), insomnia (3%), anorexia (2%), and dizziness (2%). Patients treated with topiramate experienced mean percent reductions in body weight that were dose-dependent. This change was not seen in the placebo group. Mean changes of 0%, -2%, -3%, and -4% were seen for the placebo group, topiramate 50, 100, and 200 mg groups, respectively. Table 3 shows adverse events that were dose-dependent. Several central nervous system adverse events, including some that represented cognitive dysfunction, were dose-related. The most common dose-related adverse events were paresthesia, fatigue, nausea, anorexia, dizziness, difficulty with memory, diarrhea, weight decrease, difficulty with concentration/attention, and somnolence. **Table 3**: Incidence (%) of Dose-Related Adverse Events From Placebo-Controlled, Migraine Trials[a]. Adverse Event followed by Placebo (N=445) first, TOPAMAX® Dosage (mg/day) 50 (N=235) second, 100 (N=386) third, 200 (N=514) fourth: Paresthesia 6, 35, 51, 49; Fatigue 11, 14, 15, 19; Nausea 8, 9, 13, 14; Anorexia 6, 9, 15, 14; Dizziness 10, 8, 9, 12; Weight decrease 1, 6, 9, 11; Difficulty with Memory NOS 2, 7, 7, 11; Diarrhea 4, 9, 11, 11; Difficulty with Concentration/Attention 2, 3, 6, 10; Somnolence 5, 8, 7, 10; Hypoaesthesia 2, 6, 7, 8; Anxiety 3, 4, 5, 6; Depression 4, 3, 4, 6; Mood Problems 2, 3, 6, 5; Dry Mouth 2, 2, 3, 5; Confusion 2, 2, 3, 4; Involuntary Muscle Contractions 1, 2, 2, 4; Abnormal Vision <1, 1, 2, 3; Renal Calculus 0, 0, 1, 2. [a]The incidence rate of the adverse event in the 200 mg/day group was ≥2% than the rate in both the placebo group and the 50 mg/day group. **Other Adverse Events Observed During Migraine Clinical Trials** Topiramate, for the treatment of prophylaxis of migraine headache, has been administered to 1,367 patients in all clinical studies (includes double-blind and open-label extension). During these studies, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified WHOART dictionary terminology. The following additional adverse events that were not described earlier were reported by greater than 1% of the 1,367 topiramate-treated patients in the controlled clinical trials: **Body as a Whole:** Pain, chest pain, allergic reaction. **Central & Peripheral Nervous System Disorders:** Headache, vertigo, tremor, sensory disturbance, migraine aggravated. **Gastrointestinal System Disorders:** Constipation, gastroesophageal reflux, tooth disorder. **Musculoskeletal System Disorders:** Myalgia. **Platelet, Bleeding, and Clotting Disorders:** Epistaxis. **Reproductive Disorders, Female:** Intermenstrual bleeding. **Resistance Mechanism Disorders:** Infection, genital moniliasis. **Respiratory System Disorders:** Pneumonia, asthma. **Skin and Appendages Disorders:** Rash, alopecia. **Vision Disorders:** Abnormal accommodation, eye pain.

Additional adverse events observed with the use of topiramate for epilepsy included abdomen enlarged, abnormal dreaming, abnormal hair texture, acidosis, acne, aggravated convulsions, aggressive reaction, albuminuria, alcohol intolerance, alkaline phosphatase increased, amenorrhea, anemia, angina pectoris, apathy, appetite increased, apraxia, arthralgia, arthrosis, AV block, back pain, body odor, bradycardia, breast discharge, breast pain, cerebellar syndrome tongue paralysis, chloasma, convulsions grand mal, coordination abnormal, creatinine increased, cystitis, deep vein thrombosis, dehydration, delirium, delusion, depersonalization, dermatitis, diabetes mellitus, diplopia, dyskinesia, dystonia, dysuria, eczema, edema, EEG abnormal, ejaculation disorder, emotional lability, encephalopathy, eosinophilia, esophagitis, euphoria, eye abnormality, face edema, fecal incontinence, flatulence, flushing, gait abnormal, gamma-GT increased, gastritis, GI disorder, gingival bleeding, gingivitis, glossitis, granulocytopenia, gum hyperplasia, hallucination, hearing decreased, hematoma, hematuria, hemorrhoids, hot flushes, hyperaesthesia, hyperchloremia, hyperglycemia, hyperkinesia, hyperlipemia, hypernatremia, hypertension, hypertonia, hypertrichosis, hypocalcemia, hypocholesterolemia, hypoglycemia, hypokalemia, hyponatremia, hypophosphatemia, hyporeflexia, impotence, infection viral, iritis, lacrimation abnormal, leg cramps, leg pain, leukopenia, leukorrhoea, libido increased, lymphadenopathy, lymphocytosis, lymphopenia, manic reaction, marrow depression, melena, menorrhagia, micturition frequency, muscle contractions involuntary, muscle weakness, mydriasis, myopia, neuropathy, neurosis, nocturia, nystagmus, oliguria, pallor, pancytopenia, paranoia, paranoid reaction, parosmia, personality disorder, phlebitis, photophobia, photosensitivity reaction, polycythemia, polyuria, postural hypotension, prostatic disorder, prothrombin increased, psychiatric disorders, psychosis, ptosis, pulmonary embolism, purpura, rash erythematous, renal pain, rigors, saliva increased, scotoma, seborrhoea, SGOT increased, SGPT increased, skeletal pain, skin discoloration, skin disorder, stomatitis, strabismus, stupor, suicide attempt, sweating increased, syncope, sysphonia, thrombocythemia, thrombocytopenia, tongue edema, upper motor neuron lesion, urinary incontinence, urinary retention, urine abnormal, urticaria, vasodilation, vasospasm, visual field defect, and xerophthalmia.

Postmarketing and Other Experience: In addition to the adverse experiences reported during clinical testing of TOPAMAX®, the following adverse experiences have been reported worldwide in patients receiving topiramate post-approval. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: bullous skin reactions (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis), hepatic failure (including fatalities), hepatitis, pancreatitis, pemphigus, and renal tubular acidosis.

Other serious as well as minor adverse events have been reported with the use of TOPAMAX® in other indications or at different dosages. Please see full prescribing information.

DRUG ABUSE AND DEPENDENCE: The abuse and dependence potential of TOPAMAX® has not been evaluated in human studies.

OVERDOSAGE: Overdoses of TOPAMAX® have been reported. Signs and symptoms included convulsions, drowsiness, speech disturbance, blurred vision, diplopia, mentation impaired, lethargy, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness and depression. The clinical consequences were not severe in most cases, but deaths have been reported after poly-drug overdoses involving TOPAMAX®. Topiramate overdose has resulted in severe metabolic acidosis (see **WARNINGS**). A patient who ingested a dose between 96 and 110 g topiramate was admitted to hospital with coma lasting 20-24 hours followed by full recovery after 3 to 4 days. In acute TOPAMAX® overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has been shown to adsorb topiramate *in vitro*. Treatment should be appropriately supportive. Hemodialysis is an effective means of removing topiramate from the body.

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OMP DIVISION
ORTHO-McNEIL PHARMACEUTICAL, INC.
Raritan, NJ 08869

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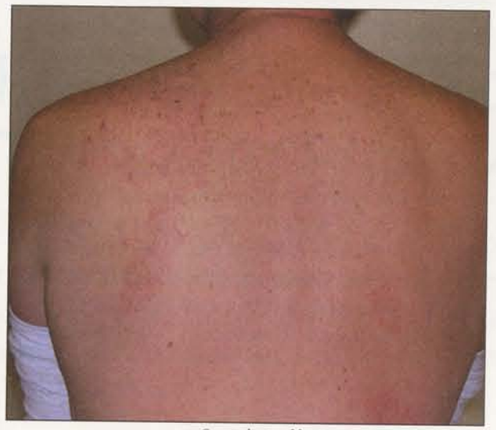
DIAGNOSIS AT A GLANCE

By Robert S. Levine, DO, Stephen M. Schleicher, MD, and Brian R. Irwin, DO



Case submitted by Drs. Levine and Schleicher

CASE 1

A 49-year-old man presents with a rash on his back that has been present for three months. Intermittently during this period, he has received treatment with topical steroids, which has produced transient improvement followed by flares. Lately, he has noted increased pruritus and extension of the eruption. Examination of the affected area reveals erythematous, scaling patches with well-defined borders and scattered papules. All toenails manifest thickening and discoloration.

What is your diagnosis?

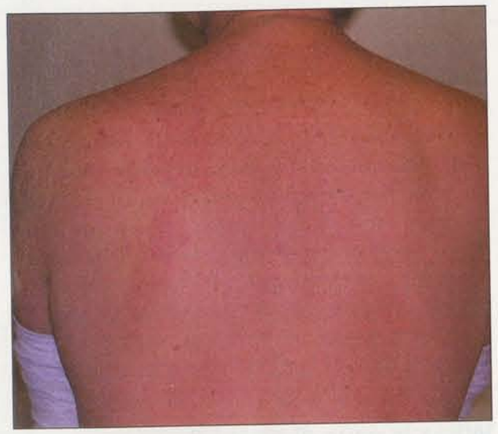
Case submitted by Dr. Irwin

CASE 2

A four-month-old girl presents to your practice for evaluation of new-onset seizures. She has no known medical problems, nor any recent history of fever or other possible symptoms of illness, and is up to date with immunizations. She was born to a healthy mother who drank no alcohol and experienced no perinatal complications, and she has met all developmental milestones to date. Her family history is noncontributory. Physical exam reveals a sizable facial hemangioma. The neurologic exam is normal, as are her heart, abdomen, and oral mucosa. A computed tomography (CT) scan of the head and X-rays of the skull are unremarkable.

What is your diagnosis?

Turn page for answers



CASE 1

This patient has developed tinea incognito, a dermatophyte infection altered by the use of steroids. Tinea corporis classically presents as an oval or circular scaling patch with sharply defined, raised borders and central clearing. Use of topical steroids leads to worsening of this condition and may induce papules and pustules. Skin scraping will reveal hyphae and spores, and the diagnosis can be confirmed by culture. Treatment entails discontinuation of topical steroids and implementation of antifungal therapy. Extensive cases are best treated with oral medication (griseofulvin, itraconazole, or terbinafine).

CASE 2

This patient has Sturge-Weber syndrome. She has the classic "port wine stain" (although it does look much like a hemangioma), which is usually located over the distribution of the first branch of the trigeminal nerve. She underwent an extensive workup for her seizures, which continued for many months. A repeat CT scan revealed intracranial calcifications. These calcifications, which line the skull lumen along the cerebral gyri, appear in a "train track" pattern and may not be present until a child's second or third year. Seizures occur in most patients; mental retardation is seen in roughly 60%. Patients who are refractory to anticonvulsant medication may benefit somewhat from surgical removal of skull calcifications. Other common manifestations of Sturge-Weber, which were absent in this patient, include infantile glaucoma, mucosal telangectasias, and aortic abnormalities.

Dr. Levine is a family practice resident at the Long Beach Medical Center in Long Beach, New York. Dr. Schleicher is director of the DermDx Centers for Dermatology of Northeastern Pennsylvania as well as Schleicher Dermatology Associates in Bonita Springs, Florida. He is a clinical instructor of dermatology at the Philadelphia College of Osteopathic Medicine, at Kings College in Wilkes-Barre, Pennsylvania, and at Arcadia University in Glenside, Pennsylvania. He is also a member of the EMERGENCY MEDICINE *editorial board. Dr. Irwin is a physician in private practice at Saco River Medical Group in Conway, New Hampshire.*

RECOGNIZING AND MANAGING THORACIC EMPYEMA

How does empyema develop and who is most at risk for it? When should a pleural effusion be considered an empyema? When is thoracentesis safe? How do treatment considerations differ in the exudative and fibropurulent stages of the condition? The author reviews what clinicians should know.

By Michael J. Bono, MD, FACEP

Thoracic empyema, the accumulation of pus in the pleural cavity, has long been recognized as a significant disease entity. Hippocrates described empyema 2400 years ago, and his technique of open drainage with rib resection was practiced until 1918, when the Empyema Commission Report questioned the procedure. Before antibiotics, empyema was a complication in 10% of patients who survived a bout of pneumonia. The antibiotic era brought about a drastic reduction in the incidence of fulminant pneumonia, and consequently the occurrence of pneumonia complicated by empyema plummeted. Penetrating thoracic trauma and complications of thoracic surgery have since emerged as the most common etiologies of empyema.

CONTIGUOUS SPREAD OF ORGANISMS

The most common cause of empyema is the direct contiguous spread of organisms from a focus of infection. As in the pre-antibiotic era, bacterial pneumonia remains the most likely source of infection. Empyema secondary to underlying bacterial pneumonia is called postpneumonic or parapneumonic empyema. Subdiaphragmatic abscess, lung abscess, esophageal perforation, vertebral osteomyelitis, and retropharyngeal abscess may all cause empyema from the direct contiguous spread of organisms.

Up to 20% of empyemas are associated with instrumentation of the pleural space, such as in thoracentesis, tube thoracostomy, or violation of the thoracic cavity during placement of a subclavian central line. In rare instances, empyema will result from lymphatic or hematogenous spread from a distant infection that does not involve the lung. This is more common in children than adults and probably represents a subclinical pneumonic process.

In 1962, the American Thoracic Society categorized parapneumonic empyema into three stages according to the natural progression of the disease. The first stage is the exudative stage, which is very similar to the formation of a parapneumonic effusion. A focus of infection near the pleura causes a small sterile pleural effusion. In this stage, the fluid is characterized by a low cell content of predominately polymorphonuclear leukocytes and normal pH and glucose levels. The lung remains fully expandable in this stage.

The fibropurulent or transitional stage is the beginning of the true infection. Bacteria invade the previously

Dr. Bono is professor of emergency medicine and associate program director of the emergency medicine residency program at the Eastern Virginia School of Medicine in Norfolk.