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Infectious Disease Vexations—Recurrent Furunculosis and Cellulitis

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Vexation: n. a vexing or being vexed // something which annoys one.

Editor's Note—*Recurrent bacterial skin infections produce significant morbidity among adults in both developed and developing countries. Most commonly manifested by the syndromes of recurrent furunculosis and recurrent cellulitis, these diseases attack patients with ostensibly normal immunity. As such they are "unexpected" by the patient and physician alike, particularly in their virulence and high recurrence rate. Furunculosis may also occur in families, leading to devastating psychological consequences.*

Despite the relatively frequent and probably increasing prevalence of these "vexations," there are few established evidence-based guidelines for their therapy and prevention. This review provides a pathophysiological approach to diagnosis, therapy, and prevention of these infections for the practicing physician and his or her patients.

Patients with furunculosis or cellulitis should be rapidly assessed and triaged to outpatient, inpatient, or intensive care depending on the severity of the infection and systemic manifestations. Therapy must include appropriate antibiotics as well as meticulous supportive care and surgical intervention. Because of the likelihood of recurrence of disease, risk factors for infection should be assessed and corrected if possible, starting at the time of initial presentation. Elimination of patient organism reservoirs may be difficult but should be considered for high-risk patients and those prone to relapse. Long-term antibiotic prophylaxis has limited efficacy but might be considered in desperate cases.

It is possible that in the near future, new forms of prevention will become available. Most promising are new vaccines and drugs to prevent colonization of staphylococci and streptococci or to augment innate immunity against these organisms. Until then, clinicians will be challenged to expeditiously diagnose, efficiently treat, and efficaciously prevent recurrence of these infections.

Vexing Skin Infections

It is an understatement that recurrent cutaneous infections are vexing to both patient and physician. Frustrating, costly, and not infrequently dangerous, such illness constitutes a significant proportion of acute care. This report will present management strategies for 2 well-defined syndromes, recurrent furunculosis, usually caused by *Staphylococcus aureus*, and recurrent cellulitis, usually caused by various Streptococci. The approach in both instances is to define the risk factors for recurrent disease, and if possible ameliorate them. With early and effective intervention, a vexation may be lessened, even if not often cured.

Recurrent Furunculosis

Definition

This pesky illness manifests itself by recurrent folliculitis, furuncles, and other skin infections occurring in various locations on the body over months to years. The lesions sometimes

erupt within families and may be seemingly spread from person to person.[1] The prevalence and incidence are unknown but appear higher in warm, humid, and tropical environments. Even so, cases in US cities may account for up to 2% of emergency room visits.[2] The painful and noxious lesions often necessitate incision and drainage, prolonged and repeated courses of antibiotics, and may leave disfiguring scars.

Etiology and Epidemiology

The cause of these infections, of course, is *S aureus*, and the most important risk factor (*see Table 1*) for first-episode and recurrent disease is carriage of a virulent strain[3,4] This organism is persistently found in the anterior nose or skin in 20% of the population, transiently found in 60% of people, and never found in a fortunate 20%.[5] Children become carriers early in life and tend to be persistently colonized until age 10, when most carriage becomes transitory.[6] Under conditions of intense exposure, such as in hospitals and nursing homes, transient carriers will persist in their colonization.

From the reservoir sites, organisms are spread by hand or by clothing to inoculate susceptible skin lesions such as abrasions and cuts, as shown through molecular strain analysis.[4] Familial and community epidemics may be facilitated by close contact and sharing of soap and towels, as seen in an epidemic associated with a steam bath.[7] Infection in abraded or injured skin may be facilitated by foreign material such as dirt or even blood.

Episodes of recurrent disease often follow closely upon initial infection, but the risk of recurrence in any given patient is multifactorial. In the absence of nasal carriage, the risk of recurrent furunculosis in any individual patient is low to nonexistent. Over a period of 3-4 years, patients with recurrent furunculosis may clear their nasal colonization and subsequently have disappearance of their boils.[8]

Pathophysiology

Because of its importance as a reservoir for infection and subsequent transmission of furunculosis, the nose has received intense scrutiny. Propensity of nasal carriage is not related to either leukocyte or immunoglobulin deficiency, but it may be peculiar to characteristics of host glycoproteins or antibacterial characteristics of nasal fluid. Studies performed in human volunteers indicate the specific niche for *S aureus* is the moist squamous epithelium of the anterior septum and vestibule.[9] This area is anterior to nasal hairs and ciliated epithelium sweep bacteria to the throat. Nasal secretions bathing this location appear defective in killing homologous strains carried by subjects despite high levels of neutrophil peptides 1 and 3 and Beta-defensin 2, components of the innate immune system. Interestingly, heterologous carrier strains were also impervious to killing by carrier nasal secretions, but such fluid could inhibit a laboratory strain of *S aureus*. The nasal fluid from noncarriers did inhibit the growth of strains from carriers.[9]

Locations other than the nose can be sites of chronic carriage.[10] These include the vagina, particularly during menses, rectum, perineum, groin, and damaged skin.[11] Some patients with persistent nasal colonization are colonized at multiple sites. While it is suggested that elimination of nasal carriage may allow disappearance of the organism from other areas of the body,[5] it appears as likely that the nose may become re-colonized from peripheral sites.[12]

While human nasal and skin carriage is the major reservoir for family infection, there have been reports of both methicillin-sensitive and methicillin-resistant *S aureus* (MRSA) in noses of pet dogs.[13] Additionally, small colony variant *S aureus*[14] and high toxin or clumping factor strains[15] seem to have advantage in persistence over other bacteria.

Host risk factors for progression from nasal colonization to furuncle seem to cluster around defects of skin integrity and leukocyte function. Patients with frequent injuries, injections, atopic dermatitis and other dermatitides are prone to infection. Once infected, such skin may itself be colonized and promote chronic nasal carriage. Patients with illness requiring frequent skin breech such as insulin-dependent diabetes or renal patients requiring dialysis are infected often.

Occasionally, congenital leukocyte dysfunction such as in chronic granulomatous disease, Chediak-Higashi, and other more ill-defined syndromes may present in adolescence or adulthood.[16] Hyper IgE[17] and common variable immunodeficiency[18] syndromes may manifest themselves as recurrent skin infection in adults, probably through defects in chemotaxis or opsonization. Both diabetes and rheumatoid arthritis[19] are associated with leukocyte defects, as is chronic nifedipine administration,[20,21] low serum iron,[22] and vitamin A deficiency.[23,24]

Infections usually recur in locations specific to individual patients. This is probably related to the proximate site of colonization and means of transfer and inoculation. Habitual nose picking or nail chewing could thus transfer bacteria to face, neck, and back by scratching or soiling shirt collars. Similarly,

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Table 1. Risk Factors for Recurrent Furunculosis

Host Factors
Nasal carriage of *Staphylococcus aureus*
Chronic or recurrent skin disease
Atopic dermatitis
Recurrent infections or infusions
Occupational injuries
Comorbid disease
Diabetes mellitus, especially insulin requiring
Rheumatoid arthritis
Hemodialysis
Leukocyte defects (acquired and congenital)
Immunodeficiency diseases
Hyper IgE (Job) syndromes
HIV
Common variable immunodeficiency
Drugs
Nifedipine
Corticosteroids
Behaviors
Nose picking
Scratching
Intravenous drug abuse
Organism Factors
Adherence factors
Virulence toxins
Small colony variants
Environmental factors
Tropical climates
Dusty conditions
Sharing towels, soap
Athletic teams

shaving or application of antiperspirants might induce axillary disease. Lesions on the buttocks, waist, or perineum probably arise from contiguous colonization and are abetted by sweating and infrequent change of clothing. Finally, contaminated fingers or fomites could be responsible for spread of infection among households.

Clinical Features

Most patients present themselves acutely to the emergency room or their physician with a painful boil. Usually the diagnosis is obvious, but sometimes systemic illness is severe. Vomiting and diarrhea may provoke hypotension and should prompt aggressive management for possible toxic shock syndrome.[25]

Typically the skin is inflamed and may be exquisitely tender. Lesions in thick-skinned areas of the body, such as the upper back and neck, may be undermined with sinus tracts. Called carbuncles, these usually need surgical intervention for control.

Evaluation and Management (*see Table 2*)

History

Important historical aspects include predisposition to *S aureus* in general and MRSA in particular. Preexisting conditions such as diabetes, renal disease, drug abuse, wounds, skin disorders, and atherosclerosis all increase risk of staphylococcal disease.[26] Of increasing concern is community-acquired MRSA. There have been focal MRSA outbreaks in some closed communities (Native Americans in the Midwest,[27] high school wrestling and football teams,[28] and drug addicts.[29]) It remains rare, however, that community-acquired MRSA is not traced back to a health care facility such as a nursing home, dialysis center, or previous hospitalization.[30]

Physical Examination

Key physical findings include evidence of toxic shock syn-

Table 2. Diagnostic Principles for an Episode of Furunculosis

History
How long has patient been ill?
Establish risk factors for staphylococcal disease
Establish risk factors for MRSA
Known previous MRSA infection or carriage?
Potential health care exposure?
Potential community exposure?
Is this a recurrence?
Does patient have gastrointestinal symptoms suggestive of toxic shock?
Physical examination
Document number, size, location, fluctuance and spread of primary lesions
Does patient have suppurative regional lymphadenopathy?
Does patient have evidence of systemic toxicity?
Evidence of toxic shock syndrome?
Evidence of endocarditis?
Laboratory tests
Blood cultures
Complete blood count, differential and peripheral smear
Screening chemistries

Table 3. Therapeutic Principles for an Episode of Furunculosis

Triage

Systemically ill patients

- Toxic shock syndrome—intensive care unit
- Signs of sepsis—hospitalize
- High risk for MRSA—hospitalize

Limited infection—outpatient therapy

Is Lesion Amenable to Drainage?

Aspirate for culture and sensitivity

Simple incision and drainage

Surgical consultation

Empiric Antibiotics

Outpatient therapy: Cloxicillin, dicloxicillin, cephalexin, or cephradine

Clindamycin if beta-lactam allergic

Inpatient therapy:

- Intravenous oxacillin or nafcillin
- If beta-lactam allergic: Vancomycin
- If bacteremia suspected: Add gentamicin for 3 days
- If MRSA suspected: Add vancomycin

Antibiotic switch and duration

Change to best single agent after receipt of culture and sensitivity

Bacteremia: 2 weeks parenteral drug, with transesophageal echocardiogram

Non-bacteremia: switch to oral dicloxacillin when symptoms abate

Duration: Total 2 weeks therapy unless endocarditis established

drome, bacteremia, endocarditis, or metastatic spread of infection. Particular attention should be made for evidence of hypotension, cardiac murmur, conjunctival and digital petechiae, and evidence of diffuse or exfoliative rash. Examine regional and distant lymph nodes for adenitis and suppurative lymphadenopathy that might benefit from aspiration.

Laboratory Tests

Patients who are systemically ill should have blood cultures prior to antibiotics, as well as complete blood count and screening metabolic profile, particularly looking for evidence of hyperglycemia or renal insufficiency. A peripheral smear may demonstrate leukocyte abnormalities such as toxic granulations, Dohle bodies, leukopenia, or abnormal morphology of leukocyte granules.

Table 4. Prevention of Recurrent Furunculosis

Ameliorate risk factors

- Diabetic control
- Treat/prevent skin disease and injury
- Remove or replace at risky drugs: nifedipine, steroids, immunosuppresives
- Correct leukocytic defects: GM-CSF for neutropenia?
- Infection control
- Behavioral modification

Nasal de-colonization (Especially recommended for recurrent disease, MRSA, or toxic-shock syndrome associated disease)

- Intranasal mupirocin 5-day course with chlorhexidine washing
- Repeated (monthly to quarterly) mupirocin courses
- Family and pet therapy
- Rifampin

Experimental and anecdotal therapies

- Vitamin C
- Iron sulfate
- Bacterial interference with less pathogenic strains
- Pentoxifylline
- Staphylococcal vaccines

Therapeutic Management (*see Table 3*)

Emergency therapy should be stratified as to the severity of systemic signs. Patients with toxic shock syndrome need intensive supportive management and adjunctive therapy, preferably in an intensive care unit.[25] Less systemically ill patients should be hospitalized and treated with intravenous antibiotics, with correction of underlying predisposing conditions. All patients, unless allergic, should get intravenous nafcillin or oxacillin in high dose. If there is suspicion of endocarditis, gentamicin should be added. Depending upon risk of MRSA exposure as noted, vancomycin might be considered in initial empiric therapy. Systemic antibiotics should be adjusted based on results of blood and other cultures. Linezolid for MRSA has the advantage of both parenteral and oral dosing but is very expensive. Gentamicin should be discontinued after 3 days even if blood cultures were positive. If blood cultures are negative, most patients may be switched to oral therapy after fever and tachycardia improve.

Lesions amenable to incision and drainage should be aspirated for culture and sensitivity, particularly because of the rise of MRSA. Adequate drainage often requires surgical intervention, which may remarkably improve pain and systemic signs. If the patient is not to be admitted, cloxacillin, dicloxacillin, cephalexin, or cephradine is usually given in oral doses of 30-

40 mg/kg/d in 4 divided doses. Duration of therapy should be no more than 7-10 days.[11] Comparison of 10-14 days vs 2 months of therapy showed no benefit of longer therapy in prevention of recurrence.[8]

Prevention (*see Table 4*)

How to prevent recurrent staphylococcal infections is less well defined. As noted above, almost all patients who have significant disease are colonized in the nose and possibly other locations. Besides correcting underlying illness, such as uncontrolled diabetes, the most common approach has been to attempt decolonization of the patient with 2% mupirocin nasal ointment applied to each nostril twice daily for 5 days. This drug is the latest in a line of nasally applied or secreted drugs that have shown some promise in lessening nasal carriage.[8] The Cochrane Review cites only 1 article supporting use of mupirocin nasal ointment.[31] In this study, patients applied 7 days of mupirocin and also washed with chlorhexidine soap and used chlorhexidine powder to other possible carriage sites. Prior to treatment, colonization rates were nose 67%, axillae 22%, groin 23%, and perianal 19%. At 91 days after treatment, only 43% of those receiving mupirocin had positive nasal cultures compared to 89% of those receiving chlorhexidine/neomycin cream. A subsequent trial did show that monthly treatment with 5 days of mupirocin nasal ointment among patients with an average of 4 episodes of furunculosis per year significantly lowered the rate of recurrent infection.[32] In this small Israeli investigation, the mean patient age was 25 years. Compared to placebo, the number of infections in the treatment group decreased by 50%, with 8 of 17 treated patients completely free of relapse over 1 year. There was good correlation between negative nasal culture and freedom from relapse, and a linear relationship between the number of monthly pretreatment cultures that were positive and subsequent number of infections.

Mupirocin trials performed among health care workers have also been encouraging, with 71% nasal eradication rates at 3 months after a single 5-day course.[33] Unfortunately, the all-site eradication rate in hospitalized Swiss patients with MRSA was only 25% despite chlorhexidine washing, and there was only 44% nasal eradication at day 26.[12] In a similar study, after 5 days of intranasal mupirocin AIDS patients had 63% nasal eradication at 2 weeks, but only 29% at 10 weeks.[34] Still another group successfully decolonized 87% of liver transplant recipients, but 37% relapsed and 23% of patients developed staphylococcal infection.[35] Even so, a much more vigorous thrice-daily nose and skin mupirocin/chlorhexidine wash protocol combined with quarantine successfully eradicated MRSA from a Finnish health center and nursing home but would be impractical in most other settings.[36]

Mupirocin appears well tolerated, with headache (9%), rhinitis (8%), and nasal congestion (5%) the side effects most reported. Unfortunately, rapid development of resistance can be a problem, particularly when used among large numbers of people or on the skin.[37] Additionally, the drug is not inexpensive—a single 5-day course costing $39.52 in 1997.[38]

Five-day courses of rifampin every 3 months decreased unspecified staphylococcal infections by 50% in dialysis patients,[39] but at the risk of development of rifampin resistance and potential drug-drug interactions. Other published, but uncontrolled, prophylactic treatments have included pentoxifylline,[40] vitamin C,[41] and iron.[22,42]

Probiotic therapy was attempted by nasal instillation of nonpathogenic *S aureus* strain 502A in the 1960s and 1970s in an effort to produce "bacterial interference" of virulent strains. A 50% decrease in recurrent infections was observed over a 6-month period compared to controls.[1] These studies were later abandoned after reports of metastatic abscess associated with this organism.[43,44]

Finally, staphylococcal vaccines are beginning to reach clinical trials aimed first at dialysis patients.[45-47] To be effective, these vaccines will have to target multiple virulence factors but could be of significant benefit.

Summary

A first episode of staphylococcal skin disease does not warrant subsequent mupirocin preventive therapy unless the infection has been with MRSA or has caused toxic shock syndrome. Any underlying predisposing condition such as diabetes, vitamin deficiency, or dermatitis should be addressed first. Families should also be taught infection control practices. Patients, however, with MRSA or toxic shock

Table 5. Risk Factors for Recurrent Cellulitis

Host Factors
Carriage of beta-hemolytic streptococci
Toe web carriage
Anal carriage
Pharyngeal carriage?
Chronic skin disease
Lymphedema
Tinea pedis
Venous insufficiency
Previous cellulitis
Comorbid diseases
Obesity
Diabetes mellitus
Alcoholism
Drug abuse
Postsurgical: saphenous venectomy, breast surgery
Environmental Factors
Homelessness
Insufficient hygiene
Exposure to children?

Table 6. Eron Classification System for Patients with Skin and Soft-Tissue Infections

Class	Patient Criteria	Triage Decision
I	Healthy, non-systemically ill	Outpatient
II	Toxic or febrile, stable comordid diseases	Observation
III	Toxic or febrile, unstable comordid diseases Limb-threatening infection	Admit to Hospital
IV	Deep seated infection, critical location, sepsis	ICU, Surgery consult

associated organisms should be de-colonized[48] with combined nasal mupirocin and chlorhexidine washing beginning at the time of acute therapy. They should then undergo periodic surveillance for recolonization.[8] Patient recolonization should prompt investigation of possible carriage by family members and probably even pets. On the other hand, because they are constantly re-exposed, chronically ill patients living in nursing homes or frequenting health care facilities will not benefit from eradication attempts.

A healthy patient who suffers recurrent disease should initiate a trial of nasal mupirocin and chlorhexidine washing, particularly if the disease is on the upper body, since it is probably coming from his nose. A 5-day course of mupirocin with nasal swab confirmation of eradication 2 weeks later appears to be a reasonable investment. Later nasal surveillance for recolonization may be justified in some cases.

Recurrent Cellulitis

Definition

Cellulitis may be defined as a spreading infection of the dermis or epidermis. It is thereby distinguished from the more localized folliculitis and furunculosis. The most prevalent organisms associated with cellulitis are beta hemolytic streptococci. Impetigo is caused by either streptococci or staphylococci but may be distinguished by its appearance—either honey-crusts or small pustules.

Epidemiology

Cellulitis is common. Along with abscess, its evaluation accounted for 158 visits per 10,000 patient risk-years in 1991 British medical practice.[49] Starting in the 1970s, there was a shift in the disease from its classical appearance on the face to the lower extremities, now the location of more than 80% of cases.[50] Remarkably, cellulitis recurs among 15-29% of patients within 3 years[51,52] and 50% of patients sometime later in life.[53] Recurrent disease is associated with specific host risk factors (*see Table 5*), among which are diabetes, alcoholism, trauma, dermatophyte infections (athlete's foot), and lymphedema.[53] Case control studies show highest risk exists with lymphedema, skin breaks such as tinea infection and wounds, venous insufficiency, leg edema, and being overweight.[54] The current epidemic of obesity certainly seems to be facilitating cellulitis incidence.

A special form of recurrent cellulitis is that due to "skin popping" of narcotics and clandestine drugs by addicts.[55] Organisms may consist of various oral and skin bacteria that contaminate materials or devices used in this practice.

Two common surgical predispositions for recurrent streptococcal cellulitis are saphenous venectomy and breast cancer surgery. Infections tend to occur months to years after surgery, suggesting that these are not simple surgical site infections. Tinea pedis is a common predisposing condition for leg cellulitis. Risk factors for breast cellulitis include hematoma drainage, presence of lymphedema, the amount of breast tissue resected, previous number of biopsies, and number of breast seroma aspirations.[53]

Pathophysiology

Surprisingly little is known of the mechanisms by which cellulitis recurs. This stems from the difficulty in culturing bacteria from skin aspirates of cellulitis and the rarity of positive blood cultures.[56] Presumably, lymphedema promotes growth of bacteria at the same time it inhibits phagocytosis, thereby allowing spread of infection. Nevertheless, using punch biopsy has been difficult to demonstrate either histological or immunological differences in infection-prone and resistant limbs.[57] Poor hygiene, dermatophyte infection, and trauma presumably allow inoculation of skin colonizing streptococci or staphylococci into very fertile ground. In support of this concept, a study of postvenectomy patients showed strong correlation between toe web colonization with beta hemolytic streptococci and recurrent cellulitis.[58] The perineum or anal canal may be another reservoir for Group B (59) and Group G beta hemolytic streptococci infecting the leg.[60] Similar mechanisms may account for recurrent cellulitis in the breast arising from local trauma or migrating from hand infections.

Once infection has occurred, lymphatics are damaged in most patients as evidenced by lymphoscintigraphy.[61] Many patients are left with clinically evident residual edema.[62] This makes a second episode of cellulitis more likely than the first.

Group A and G streptococci, the most common organisms associated with cellulitis, resist complement-associated opsonization via their M proteins.[63,64] Once infected, animals would be expected to develop antibodies against their specific colonizing M-type strain to protect against recurrent infection. Such antibodies, however, do not appear to protect,[63] possibly due to subtle changes in bacterial M-protein structure.[65] If so, this immune-evading mechanism is similar to that used by *Bor-*

Table 7. Diagnostic Principles for an Episode of Cellulitis

History

- How long has patient been ill?
- Exposure to injury, bite, water?
- Prior skin or bone infection?
- Comorbid disease?
- Prior surgery?

Physical Examination

- Signs of sepsis or systemic illness
- Location of cellulitis: critical location?
- Disproportionate pain
- Measure and demarcate extent of cellulitis
- Presence of discoloration, bullae, crepitus, flucuance, necrosis

Laboratory Tests

- Complete blood count
- Screening chemistries
- Blood cultures if signs of sepsis
- Imaging in suspected stage IV infection
- Gram stain if unusual organism or anthrax suspected
- Quantitative skin biopsy and culture for suspected stage III or IV infection

relia recurrentis, the agent of relapsing fever.

Finally, immunosuppressive and anti-inflammatory drugs, including nonsteroidal anti-inflammatory agents (NSAIDs) delay patient recognition of infection. Patients taking such medicines may have greater risk of severe illness.[66,67]

Clinical Features

The clinical features of recurrent cellulitis differ little from the first episode except that the limb or breast may show scarring or other residue. The first symptom is usually pain, followed soon by redness and warmth in the affected skin. The inoculation site may be occult or obvious and is usually somewhat distal to the center of the spreading erythema or pain. Most patients seek medical attention quicker for recurrent disease than for a first episode. They therefore tend to have less defined erysipelas, lymphangitis, lymphadenopathy and systemic manifestations. Often the patient has initiated self-therapy with antibiotics. The relatively benign course of such patients and difficulty of recovering putative pathogens from skin aspiration or blood culture have prompted some to suggest allergic sensitization as the cause of recurrent disease. Differential diagnosis is usually limited to deep vein thrombosis, insect venom, trauma, and overuse.

Management

Presently, no formal practice guidelines or consensus statements exist for management of first or subsequent episodes of cellulitis, nor is there good evidence on prognosis.[68] A pharma-sponsored expert panel, however, has recently published its deliberations.[69]

History

Pain and failure of self-therapy frequently brings the patient to the emergency room or clinic. At this time, the clinician should make a rapid assessment and clinically stage the patient according to the Eron Classification System[70] (*see Table 6*). Key components of the history (*see Table 7*) are duration and intensity of both local and systemic symptoms, history of injury or exposure to bites or contaminated water, and previous attempted therapy. It is crucial to ascertain history of skin or bone infection and comorbid disease such as diabetes, cardiac, pulmonary, hepatic, hematologic, or renal impairment. As noted above, lymphedema and prior surgery are key risk factors.

Physical examination and triage. Prime components of the physical examination include signs of sepsis, extent and severity of local inflammation, and stability of comorbid diseases. Early streptococcal toxic shock syndrome can result from proliferation of bacteria in bruised as well as punctured dermis and, unless the skin is closely examined, illness may be mistaken as gastroenteritis.[67] Particularly worrisome are disproportionate pain, bullae, hemorrhage or violet discoloration, patchy anesthesia of the skin, crepitus, and fluctuance. These signs represent deep infections of the dermis, fascia, or even fat and muscle, with possible necrosis and gangrene. If so, the infection is Stage IV. Infections of the hands, genitalia, perineum, thighs, face, and head, as well as grossly contaminated wounds such as human bites are particularly dangerous. All such patients should rapidly

Table 8. Therapeutic Principles for an Episode of Cellulitis

Classify severity of infection

Triage patient

Empiric Antibiotics

***Stage I*:** cloxacillin, dicloxacillin, cephalexin or cephardine
Clindamycin if allergic to beta lactam drugs
***Stage II-IV*:** Intravenous clindamycin until stable
Bites: (human and animal): Ampicillin/Sulbactam plus clindamycin
"Water bugs:" Intravenous ciprofloxacin
Diabetes: Penicillin G or clindamycin plus gentamicin
Anthrax: Intravenous ciprofloxacin plus rifampin

Surgical debridement for suspected fasciitis, myonecrosis

Switch to oral therapy when stable, able to take oral drug

Finish 14-day total course with oral therapy

Table 9. Initial Antibiotic Doses for an Adult with an Episode of Furunculosis or Cellulitis

(See text for indications and duration)

Cloxicillin	500 mg po q 6 hr
Dicloxicillin	500 mg po q 6 hr
Cephalexin	500 mg po q 6 hr
Cephardine	500 mg po q 6 hr
Nafcillin	2 gm iv q 4 hr
Oxacillin	2 gm iv q 4 hr
Clindamycin	750 mg iv q 8 hr or 450 mg po q 6 hr
Ampicllin/Sulbactam	3.1 gm iv q 8 hr
Ciprofloxacin	400 mg iv q 12 or 500 mg po q 12 hr
Vancomycin	1 gm iv q 12 hr
Rifampin	600 mg po q day
Gentamicin	2 mg/kg load, followed by 1.5 mg/kg iv q 8 hr
Linezolid	600 mg iv or po q 12 hr

be started on intravenous antibiotic therapy and admitted to the hospital with prompt surgical consultation.

Simple erysipelas or streaky lymphangitis of the lower leg is less worrisome, and might be considered Stage I infection in a healthy patient or patient with stable comorbidity. Most Stage I patients might be treated using closely observed outpatient oral antibiotic therapy and rest.

Unfortunately, up to 42% of patients present with fever, tachycardia, tachypnea, leukocytosis and other signs of sepsis.[71] These Stage II and III patients should be admitted for observation and parenteral antibiotics. Once the systemic signs are improved, the patient might be discharged on oral or parenteral antibiotics to complete the course of therapy.

Laboratory Tests

Routine laboratory tests have not been shown to be useful for prognosis or management.[68] Complete blood count and screening chemistry profile might be helpful to identify diabetes, renal failure, or thrombocytopenia and urinalysis to exclude glomerulonephritis. Stage IV patients warrant imaging studies to look for gas, osteomyelitis, venous thrombosis, or foreign bodies. Blood cultures should be performed in patients with sepsis, while wound biopsy, Gram stain and culture are indicated for severe stage III and stage IV disease. During periods of high bioterror alert status, bullous lesions should be examined for the possibility of anthrax. Anaerobic cultures should be performed on foul-smelling, necrotic, or gas-associated wounds.

Therapeutic Management (*see Tables 8 and 9*)

Streptococci and staphylococci susceptible to beta lactam antibiotics cause most episodes of cellulitis without unusual historical features. An appropriate choice for early Class I infection might be cephalexin or dicloxacillin. These oral beta lactam drugs should be given in generous doses even for Stage I disease, at least 500 mg every 6 hours for adults. It is paramount that the affected limb or tissue be elevated and put at rest.

Otherwise Stage I infections associated with bites, feces, or water are likely due to polymicrobial oral, enteric, or environmental flora and need broader coverage, preferably in the inpatient setting. A parenteral third-generation antipseudomonal penicillin or cephalosporin plus a fluoroquinolone would be appropriate until the organism is identified. These drugs are particularly important for such "water bugs" as *Vibrio vulnificus* and *Aeromonas hydrophila*. Most episodes of recurrent cellulitis fortunately do not require such broad spectrum antibiotics.

Besides beta lactams, adjunctive intravenous clindamycin appears warranted for severe, well-established cellulitis with or without toxic shock syndrome.[67] Clindamycin, as a protein-synthesis inhibiting antibiotic, has been demonstrated to enhance phagocytosis through alteration of the bacterial cell wall structure, inhibition bacterial toxin formation, and modulation of host cytokine release.[72] Furthermore, clindamycin is not subject to high bacterial inoculum effect, the so-called Eagle phenomenon.[72] This refers to the lack of bacterial proliferation and down regulation of penicillin-binding proteins when organisms have reached the maximum growth capacity of the infected tissue. Once the infection is under control, the patient may be switched to combined oral therapy for 3-5 days. The remainder of the 10-14 day antibiotic course is completed with the beta lactam. By limiting the duration of oral clindamycin, one hopes to reduce the risk of *Clostridium difficile* diarrhea.

Diabetic patients occasionally have positive blood cultures, often for Group B streptococcus. In such patients, synergistic combination penicillin and gentamicin is preferred. Again, once the infection is controlled, usually within 2-3 days, switch to an oral cephalosporin to complete the 14-day course of therapy.

All patients are instructed to elevate the affected limb or part, use compression stockings or bandage when up, and expect some pain for a few days to weeks. Nonsteroidal pain medications are usually sufficient. The patient should normally be seen in the follow-up clinic within a few weeks to ensure healing, to exclude abscess or venous thrombosis, and to initiate preventive therapy.

Prevention (*see Table 10*)

Prevention involves reducing risk factors such as edema and tinea pedis and educating the patient on pathogenesis. Patients might benefit from instruction to quickly self-treat minor skin trauma in edematous areas with antiseptics or topical bacitracin. Prophylactic long-term or cyclical antibiotic use has been attempted, but to date no clinical trials support such intervention.[73] Well-fitting support hose extending above the level of lymphedema are helpful but can be very expensive. Moder-

Table 10. Prevention of Recurrent Cellulitis

Ameliorate Risk Factors
Control lymphedema by physical measures
Support hose
Pressure bandages
Elevation of limb
Control tinea pedis
Prevent or avoid skin trauma
Weight loss
Control diabetes
Plausible but untested
Chlorhexidine washing
Treatment of minor skin trauma with mupirocin or bacitracin ointment
Antibiotic Prophylaxis-reserve for after second episode
Penicillin VK 250 mg twice daily or
Clindamycin 150 mg once daily

ate exercise with latter leg elevation may be useful in promoting lymphatic, venous and muscular function. Sequential pneumatic compression devices have facilitated impressive improvement of recurrence rate when used with cyclical 10-day courses of penicillin G in a recent report from Germany.[74]

Support for vigorous therapy of tinea pedis comes from a trial among patients with filariasis.[75] Therapy of tinea pedis is best initiated with topical therapy such as tolnaftate or ketoconazole cream. Suppression of dermatophyte recurrence can usually be accomplished with foot powder and periodic foot inspection by the patient without resorting to systemic drugs such as itraconazole and terbinafine. These latter drugs may be necessary to eradicate toenail disease, but often pose more toxicity and cost than desired.[76] Since the web space is the most implicated streptococcal entry point in recurrent cellulitis, this tissue rather than the nail should be the primary focus of attention.

Finally, low-dose antibiotic suppression such as twice-daily penicillin VK 250 mg or clindamycin 150 mg once daily has been useful for some patients,[77] but monthly injectable penicillin was ineffective for high-risk patients in one study.[78] Chronic antibiotic therapy should be reserved for patients after their second episode of cellulitis.

Summary

Recurrent cellulitis is common, with a lifetime risk of 50% after a first episode. Key management concerns are early recognition of surgical or life threatening disease and prompt administration of antiproliferative and antitoxin antibiotics, usually in the form of parenteral beta lactam and clindamycin therapy for stage III or IV disease. History is critical for identification of unusual organisms that may require broader antibiotic coverage. After therapy of the acute infection, patients should undergo vigorous therapy to limit lymphedema, and prevent tinea and other skin infections or trauma. Chronic suppressive antibiotic therapy may offer some benefit, but only after other prophylactic measures are instituted.

References

1. Steele RW. Recurrent staphylococcal infection in families. *Arch Dermatol*. 1980;116:189-190.
2. Meislin HW, et al. Cutaneous abscesses: Anaerobic and aerobic bacteriology and out-patient management. *Ann Intern Med*. 1977; 87:145-149.
3. Weems JJ, Beck LB. Nasal Carriage of *Staphylococcus aureus* as a risk factor for skin and soft tissue infections. *Curr Infect Dis Rep*. 2002;4:420-425.
4. Toshkova K, et al. The significance of nasal carriage of *Staphylococcus aureus* as risk factor for human skin infection. *FEMS Microbiology Letters*. 2001;202:17-24.
5. Kluytmans J, et al. Nasal carriage of *Staphylococcus aureus*: Epidemiology, underlying mechanisms, and associated risks. *Clin Microbiol Rev*. 1997;10:505-520.
6. Armstrong-Esther CA. Carriage patterns of *Staphylococcus aureus* in a healthy non-hospital population of adults and children. *Ann Hum Biol*. 1976;3:221-227.
7. Landen MG, et al. Outbreak of boils in an Alaskan village: A case-control study. *West J Med*. 2000;172:235-239.
8. Hedstrom SA. Treatment and prevention of recurrent staphylococcal furunculosis: clinical and bacterological follow-up. *Scand J Infect Dis*. 1985;17:55-58.
9. Cole AM, et al. Determinants of *Staphylococcus aureus* nasal carriage. *Clin Diagn Lab Immunol*. 2001;8:1064-1069.
10. Lowy FD. *Staphylococcus aureus* infections. *N Engl J Med*. 1998;339:520-532.
11. Waldvogel FA. *Staphylococcus aureus* (Including Staphylococcal Toxic Shock). In: Mandell GL, et al, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 5th ed. Philadelphia, Penn: Churchill Livingstone; 2001:2069-2083.
12. Harbarth S, et al. Randomized, placebo-controlled, double-blind trial to evaluate the efficacy of mupirocin for eradicating carriage of methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 1999;43:1412-1416.
13. Manian FA. Asymptomatic nasal carriage of mupirocin-resistant, meticillin resistant Staphylococcus aureus (MRSA) in a pet dog associated with MRSA infection in household contacts. *Clin Infect Dis*. 2003;36:326-328.
14. Von Eiff C, et al. Small colony variants of Staphylococci: A link to persistent infections. *Berl Munch Tierarztl Wochenschr*. 2000; 113:321-325.
15. Slobodnikova L, et al. *Staphylococcus aureus* in chronic and recurrent infections. *Folia Microbiol (Praha)*. 1995;40:655-668.
16. Forte WC, et al. Repeated furunculosis in adult male with abnormal neutrophil activity. *Allergol Immunopathol (Madr)*. 2000; 28:328-331.
17. Shemer A, et al. The hyper-IgE syndrome. Two cases and review of the literature. *Int J Dermatol*. 2001;40:622-628.
18. Sidwell RU, et al. A case of common variable immunodeficiency presenting with furunculosis. *Br J Dermatol*. 2002;147:364-367.
19. Nada R, et al. Neutrophil functions in rheumatoid arthritis. *Indian J Pathol Microbiol*. 1999;42:283-289.

20. Kaul N, et al. Effect of neifedipine administration the functional capacity of neutrophils. *Mol Cell Biochem*. 1993;120:81-85.
21. Levy R, et al. Inhibited neutrophil functions in patients treated with nifedipine but not with verapamil or diltiazem. *Eur J Clinic Invest*. 1996;26:376-381.
22. Demircay Z, et al. Phagocytosis and oxidative burst by neutrophils in patients with recurrent furunculosis. *Brit J Dermatol*. 1998;138:1036-1038.
23. Twining SS, et al. Vitamin A deficiency alters rat neutrophil function. *J Nutr*. 1997;127:558-565.
24. Aukrust P, et al. Decreased vitamin A levels in common variable immunodeficiency; vitamin A supplementation in vivo enhances immunoglobulin production and down regulates inflammatory responses. *Eur J Clin Invest*. 2000;30:252-259.
25. Issa NC. Thompson RL. Staphylococcal toxic shock syndrome. Suspicion and prevention are keys to control. *Postgrad Med*. 2001;110:55-56, 59-62.
26. Trilla A, Miro JM. Identifying high-risk patients for *Staphylococcus aureus* infections: Skin and soft tissue infections. *J Chemother*. 1995;7 Suppl 3:37-43.
27. Groom AV, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* in a rural American Indian community. *JAMA*. 2001;286:1201-1205.
28. Lindenmayer JM, et al. Methicillin-resistant *Staphylococcus aureus* in a high school wrestling team and the surrounding community. *Arch Intern Med*. 1998;158:895-899.
29. Charlebois ED, et al. Population-based community prevalence of methicillin-resistant *Staphylococcus aureus* in the urban poor of San Francisco. *Clin Infect Dis*. 2002;34:425-433.
30. Salgado CD, et al. Community-acquired methicillin-resistant *Staphylococcus aureus*: A meta-analysis of prevalence and risk factors. *Clin Infect Dis*. 2003;36:131-139.
31. Leigh DA, Joy G. Treatment of familial staphylococcal infection-comparison of mupirocin nasal ointment and chlorhexidine/neomycin (Naseptin) cream in eradication of nasal carriage. *J Antimicrobial Chemother*. 1993;31:909-917.
32. Raz R, et al. A 1-year trial of nasal mupirocin in the prevention of recurrent staphylococcal nasal colonization and skin infection. *Arch Intern Med*. 1996;156:1109-1112.
33. Doebbeling BN, et al. Long-term efficacy of intranasal mupirocin ointment. A prospective cohort study of *Staphylococcus aureus* carriage. *Arch Intern Med*. 1994;154:1505-1508.
34. Martin JN, et al. A randomized clinical trial of mupirocin in the eradication of *Staphylococcus aureus* nasal carriage in human immunodeficiency virus disease. *J Infect Dis*. 1999;180:896-899.
35. Paterson DL, et al. Lack of efficacy of mupirocin in the prevention of infections with *Staphylococcus aureus* in liver transplant recipients and candidates. *Transplantation*. 2003;75:194-198.
36. Kotilainen P, et al. Eradication of methicillin-resistant *Staphylococcus aureus* from a health center ward and associated nursing home. *Arch Intern Med*. 2001;161:859-863.
37. Farr BM. Mupirocin to prevent *S aureus* infections. *N Engl J Med*. 2002;346:1905-1906.
38. SmithKline Beecham Pharmaceuticals advertising brochure. January 1997.
39. Yu VL, et al. *Staphylococcus aureus* nasal carriage and infection in patients on hemodialysis: Efficacy of antibiotic prophylaxis. *N Engl J Med*. 1986;315:91-96.
40. Wahba-YahavAV. Intractable chronic furunculosis: Prevention of recurrences with pentoxifylline. *Acta Derm Venereol*. 1992; 72:464-462.
41. Levy R, et al. Vitamin C for the treatment of recurrent furunculosis in patients with impaired neutrophil functions. *J Infect Dis*. 1996;173:1502-1505.
42. Weijmer MC, et al. Preliminary report: Furunculosis and hypoferremia. *Lancet*. 1990;336:464-466.
43. Drutz DJ, et al. Bacterial interference in the therapy of recurrent staphylococcal infections: Multiple abscesses due to the implantation of the 502A strain of Staphylococcus. *N Engl J Med*. 1966;275:1161-1165.
44. Houck PW, et al. Fatal septicemia due to *S aureus* 502A. Report of a case and review of the infectious complications of bacterial interference programs. *Am J Dis Child*. 1972;123:45-48.
45. Shinefield H, et al. Use of a *Staphylococcus aureus* conjugate vaccine in patients receiving hemodialysis. *N Engl J Med*. 2002; 346:491-496.
46. Michie CA. Staphylococcal vaccines. *Trends Immunol*. 2002; 23:461-463.
47. Lee JC. Development of antistaphylococcal vaccines. *Curr Infect Dis Rep*. 2001;3:517-524.
48. Andrews M-M, et al. Recurrent nonmenstrual toxic shock syndrome: clinical manifestations, diagnosis, and treatment. *Clin Infect Dis*. 2001;32:1470-1479.
49. Office of Population Censuses and Survey. Morbidity statistics from general practice. Fourth National Study. *Her Majesty's Stationery Office*. 1992 (Series MB5): 272.
50. Ronnen M, et al. Erysipelas. Changing faces. *Int J Dermatol*. 1985;24:169-172.
51. Jorup-Ronstrom C, Britton S. Recurrent erysipelas: Predisposing factors and costs of prophylaxis. *Infection*. 1987;15:105-106.
52. Crickx B. Erysipelas: Evolution under treatment, complications. *Annales de Dermatologie et de Venereologie*. 2001;128:358-362.
53. Baddour LM. Cellulitis syndromes: An update. *International Journal of Antimicrobial Agents*. 2000;14:113-116.
54. Baddour LM. Recent considerations in recurrent cellulitis. *Curr Infect Dis Reports*. 2001;3:461-465.
55. Binswanger IA, et al. High prevalence of abscesses and cellulitis among community-recruited injection drug users in San Francisco. *Clin Infect Dis*. 2000;30:579-581.
56. Perl B, et al. Cost-effectiveness of blood cultures for adult patients with cellulitis. *Clin Infect Dis*. 1999;29:1483-1488.
57. Baddour LM, et al. Biopsy specimen findings in patients with previous lower extremity cellulitis after saphenous venectomy for coronary artery bypass graft surgery. *J Am Acad Dermatol*. 1997;37:246-249.
58. Semel JD, Goldin H. Association of athlete's foot with bacterial cultures of ipsilateral space samples. *Clin Infect Dis*. 1996; 23: 1162-1164.
59. Binnick AN, et al. Recurrent erysipelas caused by grup B streptococcus organisms. *Arch Dermatol*. 1980;116:798-799.
60. Eriksson BKG. Anal colonization of group G beta-hemolytic streptococci in relapsing erysipelas of the lower extremity. *Clin Infect Dis*. 1999;29:1319-1320.
61. de Godoy JM, et al. Lymphoscintigraphic evaluation in patients after erysipelas. *Lymphology*. 2000;33:177-180.
62. Cox NH, et al. Management and morbidity of cellulitis of the leg. *J Roy Soc Med*. 1998;91:634-637.
63. Bisno AL, Gaviria JM. Murine model of recurrent group G strep-

tococcal cellulitis: No evidence of protective immunity. *Infect Immun*. 1997;65:4926-4930.
64. Bisno AL, et al. Molecular basis of group A streptococcal virulence. *Lancet Infect Dis*. 2003;3:191-200.
65. Villasenor SA, et al. Variable susceptibility to opsonophagocytosis of group A streptococcus M-1 strains by human immune sera. *J Infect Dis*. 1999;180:1921-1928.
66. Stevens DL. Could nonsteroidal anti-inflammatory drugs (NSAIDS) enhance the progression of bacterial infections to toxic shock syndrome? *Clin Infect Dis*. 1995;21:977-980.
67. Stevens DL. Streptococcal toxic shock syndrome. *Clin Microbiol Infect*. 2002;8:133-136.
68. Morris A. Cellulitis and erysipelas. *Clinical Evidence*. 2001; 6:1280-1283.
69. Eron LJ, et al. Key Decision Points in Evaluating and Treating Cellulitis: Expert panel recommendations on managing cellulitis from hospital to home. *Supplement to Clinical Geriatrics*. 2002.
70. Eron LJ. Infections of skin and soft tissue infection. Outcomes of a classification scheme. *Clin Infect Dis*. 2003;31:287-
71. Aly AA, et al. Case survey of management of cellulitis in a tertiary teaching hospital. *Med J Australia*. 1996;165:553-556.
72. Russell NE, Pachorek RE. Clindamycin in the treatment of streptococcal and staphylococcal toxic shock syndromes. *Ann Pharmacother*. 2000;34:936-939.
73. Morris A. Cellulitis and erysipelas. *Clinical Evidence*. 2002;8: 323-329.
74. Allard P, et al. Cyclical intravenous antibiosis as an effective therapy concept in chronic recurrent erysipelas. *Hautarzt*. 1999; 50:34-38.
75. Santos I, et al. Predisposing and triggering factors in erysipelas. *Med Cutan Ibero Lat Am*. 1984;12:399-402.
76. Del Rosso JQ. Current management of onychomycosis and dermatomycoses. *Curr Infect Dis Rep*. 2000;2:438-445.
77. Sjoblom AC, et al. Antibiotic prophylaxis in recurrent erysipelas. *Infection*. 1993;21:390-393.
78. Wang JH, et al. Role of benzathine penicillin G in prophylaxis of the lower legs. *Clin Infect Dis*. 1997;25:685-689.

Physician CME Questions

25. Which of the following is the most important risk factor for *Staphylococcus aureus* infection?
    a. Exposure to pathogenic or antibiotic resistant strains
    b. Host nasal colonization with *S aureus*
    c. Defects in number or competence of host leukocytes
    d. Diabetes mellitus

26. A patient with a staphylococcal furuncle on his arm presents with nausea, vomiting, fever, and a diffuse erythematous rash in addition to his primary lesion. What is the most likely diagnosis?
    a. Underlying lymphoproliferative disease
    b. Drug reaction
    c. Toxic shock associated *S aureus*
    d. Food poisoning

27. A 20-year-old previously health college student presents with a 1 cm furuncle on the nape of his neck. He has never had staphylococcal infections before. He has no systemic signs or evidence of bacteremia. Which of the following is the most appropriate acute management of this patient?
    a. Hospitalize and treat with intravenous nafcillin
    b. Incise and drain the lesion, pack and treat without antibiotics as outpatient.
    c. Aspirate and culture the lesion, then treat as outpatient with 10-14 day course of dicloxicillin
    d. Hospitalize and treat with intravenous nafcillin and gentamicin

28. Which of the following patients would be most appropriate for a single course of 5 days intranasal mupirocin as an attempt to eradicate nasal carriage and prevent further infections?
    a. A 46-year-old dialysis patient with recurrent access site infection with MRSA
    b. A 50-year-old man about to undergo a coronary artery bypass surgery.
    c. A 20-year-old previously health college student with his second episode of furunculosis
    d. An 80-year-old nursing home resident with recurrent infected pressure ulcers.

29. What is the lifetime risk of recurrent cellulitis of a lower extremity after a first episode?
    a. 5%
    b. 10%
    c. 25%
    d. 50%

30. Suspicion of cellulitis due to *Aeromonas hydrophila* or *Vibrio vulnificus* because of exposure to contaminated water warrants therapy with which of the following antibiotics?
    a. Rifampin
    b. Linezolid
    c. Ciprofloxacin
    d. Gentamicin

31. What should be done with a 50 year old obese diabetic woman who presents to the emergency department with first episode of lower extremity cellulitis that is associated with fever, tachycardia, leukocytosis, and hyperglycemia? The leg shows no bullae or dark discoloration, but lymphangitis is present.
    a. Treat with outpatient dicloxacillin and bed rest
    b. Admit for brief observation and initiation of intravenous nafcillin
    c. Admit to medical ward and initiation of intravenous nafcillin and gentamicin
    d. Send to Radiology for MRI, then admit to ward or ICU depending on what is found

32. Which of the following measures should be undertaken to prevent recurrent cellulitis after the first episode?
    a. Start daily prophylactic penicillin
    b. Start monthly prophylactic penicillin
    c. Start daily itraconzole to eradicate toenail fungus
    d. Suppress lymphedema with well fitted support hose

Answers: 25. (b); 26. (c); 27. (c); 28. (c); 29. (d); 30. (c); 31. (c); 32. (d)

In Future Issues:

West Nile Virus—
Stan Deresinski, MD

PHARMACOLOGY WATCH

Counterfeit Procrit Uncovered by FDA Surveillance

In one of the more bizarre stories of the year, the FDA has uncovered files of counterfeit Procrit (epoetin alfa—Johnson & Johnson) in routine surveillance. To make matters worse, the fake vials have been contaminated with bacteria and many contain no active ingredient. Johnson & Johnson is sending out a "Dear Doctor" letter to warn health care professionals about the counterfeit vials including the lot numbers of the suspected counterfeits. Fake Procrit was also discovered last summer in United States. At that time, counterfeiters apparently purchased 2000 U/mL vials and labeled them as the higher priced 40,000 U/mL vials. More information is available at the Johnson & Johnson/Ortho Biotech web site including pictures of the counterfeit vials.

Pharmaceutical Marketing Campaigns in Full Swing

Love 'em or hate 'em, direct-to-consumer (DTC) advertisements of pharmaceuticals are big business. The Kaiser Family foundation reports that spending on DTC ads increased nearly 10-fold in 10 years, from $260 million to $2.5 billion in 2000. More than 80% of respondents report seeing or hearing a drug ad in the last 3 months according to an FDA survey, and the Kaiser study reports that one third of patients have asked their doctor about an ad they saw on TV or in print. Unfortunately, drug ads are increasingly unregulated. The FDA is tasked with reviewing DTC ads for false or misleading statements, but according to a recent review in *Consumer Reports*, the agency has only 30 reviewers to handle 30,000 submissions each year. By the time false or misleading ads are pulled from the airways, they have often run their lifespan, with new ads appearing in their place. But are the pharmaceutical companies getting $2.5 billion of value from these ads? Apparently. A recent FDA survey of physicians revealed that when patients initiate a discussion about a prescription drug they've seen advertised, they asked for a prescription more than 50% of the time. Some 66% of physicians said they were not pressured to prescribe a drug in that situation. However, when a specific brand name drug was requested, physicians felt pressured to prescribe it more than 50% of the time. Despite this, physicians are split on the effect of DTC ads on their patients and practice, with 32% feeling negative about the ads, 40% feeling positive, and 28% feeling that DTC advertising has no effect on the practice (www.fda.gov/cder/ddmac/presentations.htm).

Ambulatory Antibiotic Reduction: Take the Good with the Bad

The national campaign to reduce antibiotic use in ambulatory practice seems to be working, but there is good news and bad news. Researchers from UCSF and Harvard reviewed the rates of overall antibiotic use in the National Ambulatory Medical Care Survey between 1991-1992, and compared those rates to usage between 1998-1999. The use of antibiotics decreased in the latter time period especially for the treatment of respiratory tract infections such as the common cold and pharyngitis (visits with a

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prescription decreased from 13% to 10% in adults, and from 33% to 22% among children). The use of broad-spectrum antibiotics increased over the same time span; however, including the macrolides azithromycin and clarithromycin, quinolones, amoxicillin-clavulanate, and second- and third-generation cephalosporins. The use of these antibiotics increased from 24% to 48% of all antibiotic prescriptions among adults and from 23% to 40% among children. An accompanying editorial reiterates the CDC's Campaign for Appropriate Antibiotic Use in the Community, which encourages prescribing antimicrobials only when they are likely to be beneficial to the patient, selecting agents that will target the likely pathogen, and using these agents in the correct dose and for the proper duration. The editorial suggests that we have been effective at decreasing the overall use of antibiotics, but less successful at promoting targeted therapy, ie, using narrow spectrum antibiotics whenever appropriate to reduce the likelihood of resistance in a population (*Ann Intern Med*. 2003;138:525-533,605-606).

Nefazodone Under Attack Once Again

Public Citizen, the national nonprofit watchdog organization, has petitioned the FDA to remove the antidepressant nefazodone (Serzone—Bristol-Myers Squibb) from the US market. The petition is based on evidence of liver toxicity associated with the drug including liver failure and death. Nefazodone was recently pulled from the European market after reports of a worldwide total of 28 cases of liver failure of which 18 patients died. The move in Europe was voluntary on the part of Bristol-Myers Squibb because of the call for increased liver enzyme monitoring requirements in several European countries. In this country, the FDA has required a black box warning on nefazodone since January 2002. Despite these concerns, nefazodone, which is a SSRI antidepressant, continues to be relatively popular, with more than 4 million prescriptions written last year. Bristol-Myers Squibb has no plans to withdraw the drug in this country at present.

Lindane Receives Black Box Warning

The FDA has issued a Public Health Advisory concerning the use of lindane for the treatment of scabies and lice. The boxed warning is the result of concern of potential neurotoxicity especially in children. The new advisory states that lindane is a second-line treatment and updates information about its potential risk in children and adults who weigh less than 110 pounds. The advisory also states that reapplication of lindane lotion or shampoo is not appropriate even if itching continues after the single treatment. The FDA is also requiring package sizes to be limited to 1 and 2 oz in order to minimize the potential for product access in a single treatment. Lindane, also known as gamma benzene hexachloride, is an industrial pesticide, has been in use for decades, and has been banned in several countries. Neurologic side effects include dizziness, seizures, and even death. The drug is currently approved for the treatment of lice and scabies in patients who have failed or are intolerant of other therapies. First-line agents for scabies include permethrin cream (Nix, Elimite, Acticin) and malathion lotion (Ovide) and for lice pyrethrum with piperonyl butoxide shampoo and cream rinse permethrin cream rinse (Nix and Rid).

Aspirin Could Help Reduce Colorectal Adenomas

Two different studies in the same issue of the *New England Journal of Medicine* suggest that daily doses of aspirin reduce the risk of colorectal adenomas. In the first study, 635 patients with previous colorectal cancer were randomized to receive either 325 mg of aspirin per day or placebo. The study was terminated early when a significant reduction in colorectal adenomas was shown during the planned interim analysis. After an average of 12.8 months of follow-up, 1 or more adenomas were found in 17% of patients in the aspirin group and 27% patients in the placebo group ($P = 0.004$). The mean number of adenomas was lower in the aspirin group ($P = 0.003$) and the time to detection of the first adenoma was longer in the aspirin group than in the placebo group ($P = 0.022$). In the second study, 1121 patients with a recent history of adenomas were randomized to placebo (372 patients), 81 mg of aspirin (377 patients), or 325 mg of aspirin (372 patients). Follow-up colonoscopy was done approximately 3 years after randomization. The incidence of 1 or more adenomas was 47% placebo group, 38% in the 81 mg aspirin group, and 45% in the 325 mg aspirin group (global $P = 0.04$). The risk of larger polyps including adenomas measuring > 1 cm or with tubulovillous or villous, or severe dysplasia was also lowest in the 81 mg aspirin group. An accompanying editorial suggests that inhibition of COX-2 may prevent inflammation, increased cell proliferation and angiogenesis. The author also cautions that prophylactic aspirin is not a substitute for colorectal cancer screening (*N Engl J Med*. 2003; 348:883-890, 891-899,879-880). ■

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Use of Hip Protectors in Nursing Homes

Source: Meyer G, et al. *BMJ*. 2003; 326:76-78.

Despite the fact that use of hip protectors (HIP) has demonstrated excellent outcomes reduction when used among elderly persons ie, as much as a 50% reduced incidence of hip fractures, actual use among at-risk populations is markedly suboptimal. For clinicians who have not seen hip protectors before, they are disk-shaped cushions that can be worn under clothing to act as a mechanical defense if a patient falls.

One of the reasons for tepid responsiveness of senior citizens to use of HIP may be inadequate education of healthcare providers and nursing home staff. To that end, Meyer and associates studied a 2-part intervention in 86 German nursing homes. The initial intervention included a 60-90 minute education session for nursing home staff about risk factors for hip fracture, consequences of hip fracture, and effectiveness of hip protectors. Staff was also instructed in steps to address potential obstacles to successful HIP implementation. HIP-educated staff members were assigned to provide a similar information base to resident patients in their nursing homes. Nursing staff also used a documentation sheet on resident falls and their outcomes. HIP were provided for residents free of charge in the intervention group. The control group ("usual care") received a brief informative demonstration of HIP, and 2 HIP for demonstration purposes. The primary end point of the trial was hip fracture. The secondary end point was frequency of HIP use.

The relative risk of hip fracture was 0.57 in HIP users (NNT = 29). Frequency of HIP use was significantly higher in the intervention group (68% vs 15%). Use of HIP, especially when accompanied by an intensive staff education, can reduce hip fractures by more than 40%. ■

Disclosing Unanticipated Outcomes and Medical Errors

Source: O'Connell D, et al. *J Clin Outcomes Man*. 2003;10(1):25-29.

According to the 1999 Institute of Medicine report, medical errors are an important cause of loss of life, resulting in as many as 98,000 deaths annually in the United States. The Lexington, Kentucky VA has followed a policy of full disclosure about medical errors for more than 15 years. They rank in the lowest quartile of VA centers for liability costs, which appears to have resulted not from a reduction in the frequency of malpractice claims—indeed, the absolute number of claims actually has increased—but rather from willingness of injured persons and their families to negotiate fair settlements, after complete and open disclosure.

Steps in adequate disclosure after unanticipated adverse outcome *without* medical error should include: 1) Without defensiveness, be aware of and respond to the needs of the patient and their family; 2) Keep family members apprised of continued clinical care progress; 3) Clarify how the unanticipated outcome may have occurred; 4) Communicate your understanding, empathically, of the concerns of the family; 5) Acknowledge the areas of uncertainty, with an offer to clarify these areas as soon as possible.

When medical error has led to injury, additional steps should include 1) apology and acceptance of responsibility—reluctance to provide a full accountability may actually drive patients to seek legal counsel; 2) determine who best should be included in future disclosure conversations and identify an individual to respond to the family's nonclinical (eg, financial compensation) inquiries; and 3) be proactive in addressing the patient's financial needs, such as costs of family members needing to stay in hotels for a prolonged hospital stay. ■

Non-Invasive Positive Pressure Ventilation to Treat Respiratory Failure Resulting from Exacerbations of COPD

Source: Lightowler JV, et al. *BMJ*. 2003;326:185-187.

When the traditional interventions (eg, bronchodilators, steroids, antibiotics, oxygen) for COPD exacerbation are insufficient to reverse clinical deterioration, clinicians typically rely upon invasive ventilation, with its attendant morbidity, and occasional difficulty in weaning. Noninvasive positive pressure ventilation (NPPV) provides an air/oxygen mixture from a flow generator through a full facial or nasal mask. The subsequent unloading of flagging respiratory musculature enhances respiratory efficiency. Failure rates of this technique have been reported between 9-50%. Lightowler and colleagues performed a Cochrane review and meta-analysis to ascertain effectiveness of

NPPV in patients with respiratory failure secondary to COPD exacerbations.

NPPV, when coupled with usual medical care of COPD exacerbations, was shown to significantly reduce mortality (59%), need for intubation (58%), treatment failure (49%), complications (68%), and length of hospital stay. These data should encourage clinicians to use NPPV earlier in the therapeutic course, before serious acidosis ensues. ■

Effect of Ibuprofen on Cardioprotective Effect of Aspirin

Source: MacDonald TM, Wei L. *Lancet*. 2003;361:573-574.

A substantial amount of literature supports the efficacy of aspirin (ASA) for primary and secondary prevention of cardiovascular disease. The benefits of aspirin for reduction of cardiovascular risk are generally attributed to effects on platelets, mediated by ASA-induced cyclooxygenase-1 inhibition. Earlier in vitro data have indicated that ibuprofen (IBU), but not rofecoxib or diclofenac, competes with the effects of ASA upon platelets, and might hence reduce or abolish the cardioprotective effects. Whether this is reflected clinically has not yet received sufficient scrutiny.

MacDonald and Wei studied more than 7000 persons in the United Kingdom who carried a hospital discharge diagnosis of MI, angina, stroke, PAD, or TIA, were on low-dose ASA (£ 325 mg/d), and survived for at least 1 month post-hospital discharge. This population was further subdivided into persons who concomitantly received IBU (n = 187), diclofenac (n = 206), any other NSAID (n = 429), or no other NSAID (ie, ASA alone n = 6285). The outcomes of the study were all-cause mortality or cardiovascular mortality.

All-cause mortality in the ASA + IBU group was significantly higher than in the ASA alone group (P = 0.0011), but persons who used ASA in combination with other NSAIDs did not show an increased risk. Data on cardiovascular mortality were similar to that demonstrated for all-cause mortality.

MacDonald and Wei conclude that these data support the possibility that the combination of IBU with ASA may be deleterious toward cardiovascular and total mortality risk, when compared with persons taking ASA alone. The NSAID comparators, other than IBU, did not display a similar detraction to the cardiovascular benefits of ASA. ■

Antidepressant Drug Treatment in Depressive Disorders

Source: Geddes JR, et al. *Lancet*. 2003;361:653-661.

Pharmacotherapy for depression is generally recognized to be effective to produce remission in the majority of sufferers. The recommended duration of treatment of depression has undergone evolution, subsequent to the observation that brief treatments (4-6 months, or less), subject the patient to an increased risk of relapse and recurrence.

Geddes and colleagues studied the efficacy of antidepressant treatment to prevent recurrence when continued into long-term (ie, > 6 months) treatment. Pooling data from 31 randomized trials (n = 4410), they evaluated the likelihood of relapse when a patient continued whatever pharmacotherapy had effected a remission, compared with the relapse rate for persons on placebo. The antidepressants included in the meta-analysis include tricyclics, SSRIs, and heterocyclic agents.

The results were consistent across all antidepressants evaluated: continuing therapy reduced the risk of relapse by approximately one half. Only 6 trials reported very long-term data (> 2 years), but even in this patient population, continued antidepressant therapy reduced risk of relapse by more than 50%.

Geddes et al conclude that in persons who respond to antidepressant therapy, continuation of medication produces substantial reduction in likelihood of relapse, which does not appear to diminish even in long-term maintenance trials. ■

Adverse Drug Events Among the Elderly in the Ambulatory Setting

Source: Gurwitz JH, et al. *JAMA*. 2003;289:1107-1116.

When one considers that more than 90% of persons older than age 65 use at least 1 medication per week, and that more than 40% of these individuals use 5 or more medications per week, it should come as no surprise that adverse events, even in the ambulatory setting, may occur. Although more attention has been given recently to hospital and nursing home medication misadventures, less scrutiny of ambulatory adverse events, and their potential for prevention, is available.

The population studied (n = 27,617) comprised predominantly persons enrolled in a Medicare + Choice Plan. Adverse events were tabulated for a 12-month period. When adverse events related to medications were identified (n = 1523), a physician panel adjudicated whether the event was preventable.

Cardiovascular drugs were the class most often represented by adverse effects (26%), followed by antimicrobials (14.7%), diuretics (13.3%), non-opioid analgesics (11.8%), and anticoagulants (7.9%). More than one fourth of the adverse medication related events were judged preventable by the clinician review. Among the serious, life threatening, or fatal adverse events, a substantially greater portion was judged to be preventable: 42.4%.

Medication-related adverse events are commonplace and not infrequently serious. Since a substantial number of such events are judged to be preventable, enhanced strategies for risk reduction are needed. ■

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