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New and emerging infectious diseases

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New and emerging diseases present a constant challenge. Globalization of business, international adoption, immigration, and tourism have contributed to the rapid spread of diseases, such as severe acute respiratory syndrome (SARS). Infectious diseases that emerge in Africa or Asia may arrive on US shores within days. This article reviews the new and emerging pathogens important to dermatologists. (J Am Acad Dermatol 2005;52:1062-8.)

New and emerging diseases present a constant challenge. New pathogens are continually identified, the geographic patterns of disease shift constantly, and known pathogens continually change their patterns of sensitivity and disease manifestations. Tourism and globalization of business have exerted a profound impact on the spread of disease. Tropical and exotic diseases are becoming more common in western countries. The recent outbreak of severe acute respiratory syndrome (SARS) demonstrated the potential for the worldwide spread of virulent diseases in a single season. Travelers often introduce the new pathogens before manifesting serious signs or symptoms, contributing to the global spread of disease.[1] This article reviews the new and emerging pathogens important to dermatologists.

BACTERIAL INFECTIONS

Antibiotic resistance among staphylococcal isolates is a growing problem in many regions. Community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) is increasing in prevalence and is predominantly associated with skin and soft tissue infections.[2,3] Cutaneous abscesses and cellulites are particularly common.[4,5] CA-MRSA appears to be more virulent than methicillin-sensitive *S aureus* (MSSA). In a prospective observational study of 812 US Army soldiers, the baseline prevalence of CA-MRSA colonization was 3%. Soft-tissue infections developed in 9 of the colonized individuals (38%). In contrast, 28% were colonized with MSSA, and only 8 of the latter group (3%) developed clinical infections.[6]

CA-MRSA strains generally share the presence of staphylococcal cassette chromosome mec (SCCmec) type IV in their genomes, but are genetically distinct from hospital acquired strains.[7] Many strains share a common genotype and tend to affect healthy individuals with no known risk factors for nosocomial acquisition. A second group, consisting of two related genotypes, spa types 1 and 7, has been responsible for severe infections in HIV-positive patients in Los Angeles and New York.[8]

It is important to note that abscesses caused by CA-MRSA often respond to incision and drainage alone.[2,3] Antibiotic therapy (trimethoprim/sulfamethoxazole with or without rifampin, tetracycline, vancomycin, or linezolid) is required for patients who do not respond to drainage and for all cases of cellulitis. Unfortunately, sensitivity to tetracycline and sulfa are often not reported by the laboratory. Some of the barriers to reporting are regulatory in nature and must be addressed. The newly formed Institute for Quality in Laboratory Medicine, a partnership representing the governmental and professional organizations involved in the establishment of benchmarks for quality in health care, has the potential to help address some of these issues. The American Academy of Dermatology, a member organization of the Institute for Quality in Laboratory Medicine, should act as a vocal advocate for our patients in seeking regulatory relief that would allow the reporting of all antibiotic sensitivities important to patient care.

Linezolid, an oxazolidinone antibiotic, is useful in skin and soft-tissue infections caused by MRSA.[9] The drug is generally well tolerated; the predominant adverse effect is reversible thrombocytopenia. It may be superior to vancomycin for the treatment of infections caused by MRSA, but some resistance to

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this drug is already developing.[10] Resistance has been noted among *Enterococcus faecalis, Enterococcus faecium, Staphylococcus epidermidis*, and *Streptococcus oralis* and is typically associated with single-nucleotide changes in the genes encoding 23S ribosomal RNA.[11] Because of its cost, and to slow the emergence of resistance to the drug, many clinicians advocate its use only in cases in which no suitable alternative is available.

Severe painful peripheral neuropathy has also been reported with linezolid therapy. Nerve conduction studies have shown mixed sensory-motor neuropathy. As of August 2004, 21 cases of severe peripheral and optic neuropathy had been reported. In most of the cases, the optic neuropathy resolved after linezolid was stopped, but peripheral neuropathy did not. Duration of therapy is the most important risk factor.[12]

Vancomycin-intermediate *S aureus* is now recognized as an important emerging pathogen. Vancomycin-intermediate *S aureus* infection with phenotypic susceptibility to methicillin has been described, reinforcing the importance of culture and sensitivity testing in high-risk patients and any infection unresponsive to initial therapy.[13]

Mupirocin remains a helpful agent for some patients with MRSA, but resistance is emerging. In New Zealand, where mupirocin was available over the counter from 1991 to 2000, mupirocin resistance among *Staphylococcus* spp is markedly higher than in other comparable countries. By 1999, resistance averaged 28%.[14] This observation reinforces the importance of using antibiotics only for appropriate indications.

Virulent toxin-producing strains of group A β-hemolytic streptococci have reemerged as important pathogens.[15] Streptococcal superantigens have been found that contribute to the toxic streptococcal syndrome. The strong resistance of group A streptococcus to phagocytosis appears to be related to factor H and fibrinogen binding by M protein and to disarming of complement component C5a by the C5a peptidase.[16] There has also been a shift in the epidemiology of streptococcal skin infections, with facial erysipelas becoming less common, and leg infections predominating.

Streptococcal resistance has also emerged as an important problem. During the 2001 study year, the SENTRY Antimicrobial Surveillance Program evaluated the resistance rates of β-hemolytic streptococci. Seven hundred eighty-seven isolates were studied, from 25 medical centers in North America. Strains included serogroups A, B, G , C, and F. Resistance to erythromycin and clindamycin was highest among group B isolates. Most of the resistant strains were M-phenotypes, and all of the isolates were susceptible to β-lactams, linezolid, vancomycin, chloramphenicol, quinupristin/dalfopristin, and the fluoroquinolones.[17]

Acinetobacter baumannii has emerged as an important nosocomial pathogen, causing pneumonia, bacteremia, meningitis, urinary tract infections, and skin and soft tissue infections. Multidrug-resistant *Acinetobacter* infections are being reported, and isolates resistant to almost all commercially available antimicrobials have been identified. Older compounds, such as polymyxins, and tetracycline may still be active, and ampicillin/sulbactam is effective in some of these patients.[18]

Bartonella spp cause cat scratch disease and bacillary angiomatosis, as well as culture-negative endocarditis and neuroretinitis. Spread of disease may be through the bite of a flea or body louse. Disease is especially prevalent among the homeless, those with HIV infection, and other immunosuppressed patients. Culture methods have improved, including promising results with liquid culture media, but serologic testing remains the cornerstone of clinical diagnosis. For testing purposes, Vero cell cocultivated antigens appear to provide higher sensitivity and specificity when compared with agar-derived antigens.[19] Molecular techniques, including polymerase chain reaction (PCR), offer high sensitivity and may establish the diagnosis when other tests have failed.

Like *Bartonella quintana*, *B koehlerae* has been reported to be a cause of culture-negative endocarditis. Like *B henselae*, this pathogen is carried by domestic cats. Modifications in the commonly used PCR techniques are needed to distinguish between *B koehlerae* and *B henselae*. Specifically, PCR analysis must target several genes and be coupled with DNA sequencing to avoid species misidentification.[20]

Although *B henselae* infection is strongly associated with cats, a severe protracted illness was recently reported in an otherwise healthy police dog handler.[21] Although the infection may occur in both dogs and cats, in cats, *B henselae* bacteremia often persists for years, whereas in dogs long-term bacteremia is uncommon.[22] This difference probably accounts for the greater epidemiologic association between cats and clinical infection in humans.

Vibrio vulnificus infections typically occur in patients with preexisting liver disease, especially cirrhosis, or in the setting of diabetes mellitus. Patients may present with cellulitis or bullae. Consumption of raw or undercooked shellfish is the most common means of acquiring the infection, but infections have also been reported after cutaneous injuries contaminated with brackish water.

Recently, there has been evidence for prolonged survival of the bacteria on the skin (at least 24 hours), with invasive infection reported after a puncture injury on dry land.[23]

Mycobacterium fortuitum has established itself as an emerging pathogen in patients with AIDS. The infection often occurs late in the course of AIDS, and 9 of 11 patients in a recent series presented with cervical lymphadenitis; two had disseminated infection.[24] Erroneous identification of *M fortuitum* as *Nocardia* spp is a potential pitfall that can lead to a serious delay in appropriate therapy.

There has been a shift in the prevalence of mycobacteria causing cervical lymphadenitis in children, with a shift from *Mycobacterium scrofulaceum* to *Mycobacterium avium*. This shift may be related to widespread chlorination of water selecting more resistant environmental mycobacteria.[25] *Mycobacterium interjectum* has also recently been reported as an important cause of cervical lymphadenitis in otherwise healthy young children.[26]

The re-emergence of tuberculosis has special significance for dermatologists because cutaneous manifestations will first be seen in the outpatient setting. Conditions such as lupus vulgaris and erythema induratum have become rare in the United States, but with the resurgence of tuberculosis worldwide, these conditions will become more common. Factors that have contributed to the re-emergence of tuberculosis include urban crowding, immigration, rural-to-urban migration, and the social disruption caused by war and civil conflicts.[27]

RICKETTSIAL INFECTIONS

The vast majority of cases of tick-borne rickettsiosis in international travelers are African tick bite fever caused by *Rickettsia africae* and Mediterranean spotted fever caused by *Rickettsia conorii*. Most travelers present with a flu-like illness and do not recall a preceding tick bite.[28] The attack rate among travelers is substantial. In a study of 940 travelers to rural sub-Equatorial Africa, African tick bite fever developed in 4.0%. This accounted for 26.6% of those reporting flu-like symptoms. More than 80% had fever, headache, and/or myalgia. Cutaneous signs such as eschars, lymphadenitis, or rash were present in less than 50% of the patients.[29] Both diseases respond to doxycycline.

Human anaplasmosis (HA, formerly called human granulocytic ehrlichiosis) is caused by *Anaplasma phagocytophilum*. Human monocytic ehrlichiosis (HME) is caused by *Ehrlichia chaffeensis*. Both are emerging tick-borne infections caused by obligate intracellular bacteria in the family Anaplasmataceae. The organisms are closely related to the *Rickettsiae* spp. HA is carried by *Ixodes* ticks and HME by *Amblyomma* ticks. Most patients present with fever and variable signs and symptoms, including headache, myalgia, leukopenia, and thrombocytopenia. Meningoencephalitis is common with HME, but not with HA. This appears to be because infected host monocytes cross the central nervous system endothelial cell barriers 6 times more efficiently than neutrophils.[30]

Molecular taxonomic methods have led to the reclassification of many organisms. Recently, *Orientia tsutsugamushi*, the agent responsible for scrub typhus, was removed from the genus *Rickettsia*. There are an estimated 1,000,000 cases of scrub typhus annually, and the disease is re-emerging in Japan, where serious pneumonitis occurs in up to 22% of patients.[31] Any patient with fever and an eschar should be evaluated for rickettsial-type diseases.

VIRAL INFECTIONS

SARS began in rural China, but spread worldwide in a single season, demonstrating the vulnerability of the world population to the spread of new diseases. Overall, the mortality rate was approximately 10%.[32] Recently outbreaks of measles have been reported in Chinese orphanages, and children adopted from Chinese orphanages have brought measles to the United States on commercial airlines.[31] Measles may also be brought back to the United States by tourists and students traveling to areas where the disease is more prevalent. Because of this risk, and to prevent school outbreaks of measles, there was a change in recommendations for measles vaccination in the United States in 1989, with a series of two injections currently recommended. The two-dose strategy has been shown to be effective in reducing the measles risk in the United States.[33] Avian influenza has emerged as a major public health threat in Asia. Like measles and SARS, it may spread rapidly to other continents.[34]

West Nile virus is transmitted by *Culex* mosquitoes. Most infections are asymptomatic, and encephalitis is more likely in older patients. West Nile encephalitis was first identified in New York City in 1999. The initial outbreak included 62 human cases of West Nile virus infection with 7 deaths. In 2002, there were 4156 human cases of infection, with 284 fatalities.[35] The disease can be acquired through organ transplantation, blood transfusion, breast milk, transplacental transmission, and occupational exposure. A variable exanthem is noted in 19% of patients.[36]

The Nipah virus, a virulent paramyxovirus, was first isolated during a large outbreak of viral

encephalitis in Malaysia. It has been identified as a potential bioterrorism agent. Fruit bats are the reservoir for natural infection and probably introduced the virus to pig farms in Malaysia. The virus spreads quickly among pigs and can spread from them to dogs, cats, horses, and humans.[37] Morbidity and mortality are principally related to a systemic vasculitis with widespread thrombotic occlusion and microinfarction in most major organs, including the central nervous system.[38] Although the major symptoms are fever, headache, and giddiness followed by coma, cutaneous vasculitis is also possible.

During the summer of 2003, an outbreak of human monkeypox occurred in the Midwest states. The disease was imported in African animals and transmitted to other animals, including prairie dogs that were sold as pets throughout the Midwest.[39]

Parvovirus B19 is associated with fifth disease, fetal loss, aplastic crisis in those with chronic hemolytic anemia, chronic arthritis, purpuric gloves-and-socks syndrome, and severe illness in immunocompromised patients.[40] Because parvovirus B19 is emerging as an important disease in immunocompromised patients, blood screening has been proposed for donations to high-risk groups.

During the summer of 2002, a large outbreak of acute hemorrhagic conjunctivitis caused by coxsackievirus A24 occurred in South Korea.[41] Given the widespread nature of the infection, it is likely to surface in other locations.

Lassa fever is carried by rodents and rarely reported outside of Africa. The illness is characterized by fever, muscle aches, sore throat, nausea, vomiting, chest pain, and abdominal pain. As with West Nile fever, approximately 80% of human infections with Lassa virus are mild or asymptomatic. The overall death rate is 1%, but 15% to 20% of those sick enough to be hospitalized for Lassa fever die. Widespread cutaneous hemorrhage may occur as the disease progresses. In August 2004, a 38-year-old man in New Jersey died of Lassa fever after returning from travel to West Africa.[42] Delays in accurate diagnosis could result in spread of the disease. Identification and reporting of virulent imported viral illnesses are important to limit spread of the pathogen.

Tanapox is endemic to East Africa, but has recently been reported in a European traveler and an American student who worked with orphaned chimpanzees in Africa.[43] The lesions present as umbilicated nodules with an erythematous halo. The diagnosis can be confirmed by electron microscopy or a tanapox virus–specific PCR assay.[44]

Dengue fever has re-entered the United States; it originally entered across the Mexican border in Texas.[45] *Aedes aegypti* has a widespread distribution in the southern United States, and *Aedes albopictus* mosquito populations have been identified in Florida, Georgia, and Illinois.[46] The transmission patterns are likely to evolve over the coming years. Although the cutaneous manifestations usually consist of nonspecific macular or morbilliform exanthems,[47] infection with a second strain of Dengue can produce Dengue hemorrhagic fever.

Hepatitis C has emerged as a viral disease that often presents with cutaneous manifestations. Porphyria cutanea tarda and mixed cryoglobulinemia are the most common manifestations, but other possible associations include atypical presentations of lichen planus, pruritus, non-Hodgkin's lymphoma, rheumatoid disorders, thrombocytopenia, sialadenitis, thyroid disease, and various neurologic disorders.[48]

FUNGAL INFECTIONS

Recently, there has been evidence that the rising rate of *Candida* bloodstream infections in hospitalized and immunosuppressed patients may be reversing.[49] Invasive aspergillosis and other mold infections, such as fusariosis, have emerged as important pathogens, especially in the transplant population. Non–*Candida albicans* spp are also emerging as important pathogens, in particular *Candida glabrata*.[39] Atypical presentations of *Candida* infections, as well as dermatophytosis and *Malassezia* infection, are common in the setting of transplantation.[50] Cutaneous manifestations are protean and include eschars with scalloped margins, ulcers, cellulitis, and morbilliform rash.

Aspergillus terreus is emerging as an important fungal pathogen.[51] Infections with this pathogen are often lethal, as it is refractory to amphotericin B. Posaconazole and itraconazole have been shown to reduce the residual fungal burden in infected patients and improve survival.[52]

Biofilms are implicated as a mechanism for fungal resistance. Biofilms often form on indwelling catheters and may be a reason why catheter-related sepsis is often refractory to standard therapy. Drug efflux pumps may be up-regulated at the surface of the biofilm. In this setting, lipid formulation of amphotericin and echinocandins perform better than other drugs.[53]

Caspofungin, the first echinocandin available in the United States, has potent candidacidal activity. It also has demonstrated clinical efficacy in aspergillosis refractory to other available therapy. Two other echinocandins, micafungin and anidulafungin, are also available as intravenous formulations. They appear to be well tolerated with few adverse events

and drug interactions. All have potent anticandidal activity. Anidulafungin is also highly active against *Aspergillus*.[54]

Voriconazole, the first second-generation triazole to become available in the United States, is available in intravenous and oral forms. It is effective for the primary therapy of invasive aspergillosis and for salvage therapy for yeasts and other molds. In the setting of invasive aspergillosis, voriconazole has demonstrated a survival benefit over amphotericin B.[55] In high-risk patients whose infections failed to respond to previous antifungal therapy, voriconazole showed efficacy rates of 43.7% for aspergillosis, 57.5% for candidiasis, 38.9% for cryptococcosis, 45.5% for fusariosis, and 30% for scedosporiosis.[56] Side effects include visual adverse events, hepatic enzyme elevation, cutaneous reactions, and drug interactions.

The biologicals represent an important new group of therapeutic agents for inflammatory skin disease. In general, all of these agents are very well tolerated, but the potential for serious infection is a recognized risk. Some alternative immunosuppressive drugs have antifungal properties. Specifically, cyclosporine, tacrolimus, and rapamycin (sirolimus) have potent antifungal effects against a variety of pathogenic fungi. Antifungicidal synergism has been described between the azoles and the calcineurin inhibitors, and animal studies have demonstrated a therapeutic benefit in the setting of fungal infection.[57] It is intriguing to imagine the effects of combination induction therapy for psoriasis using both a biological and a calcineurin inhibitor. The potential for additive toxicity would have to be weighed against any potential antifungal benefits.

Human pythiosis is caused by the fungus-like aquatic organism *Pythium insidiosum*, an aquatic oomycete. Pythiosis can present as localized disease and has systemic and vasculotropic forms. Skin lesions may appear as cellulitis, infarctive, or ulcerative. Arterial pythiosis is usually seen in association with an underlying hematologic disorder, such as thalassemia or aplastic anemia. Arterial pythiosis is characterized by ascending blood vessel involvement and thrombosis of the major arteries of the legs. As the organism is resistant to most antifungal drugs, the death rate is high. Immunotherapy with *P insidiosum* antigen has recently been used successfully in some patients.[58]

PROTOZOAN INFECTIONS

In the past two decades, visceral leishmaniasis has emerged as an opportunistic disease, particularly in HIV-infected patients in southern Europe.[59] Dogs serve as the principal reservoir of disease. Recently, visceral leishmaniasis caused by *Leishmania infantum* has emerged as a widespread zoonotic infection of foxhounds in the United States and parts of Canada.[60] The potential for human disease exists, as sandfly vectors, such as *Lutzomyia vexator*, have recently been identified as far north as upstate New York.[61]

Human cutaneous leishmaniasis, long endemic to South Texas, has recently been reported as far north as Pennsylvania in a patient with no travel history (personal observation and Centers for Disease and Control investigation initiated by William Tyler, MD). *Leishmania mexicana* has recently been identified in white-throated wood rats in Pima County, Arizona.[62] Various forms of leishmaniasis may emerge as important diseases with a widespread distribution in the United States. Cutaneous leishmaniasis will also be seen in many American soldiers returning from Iraq.

CONCLUSION

Emerging infections appear continuously in developed countries and globally. Given the potential for rapid spread of virulent organisms and the potential use of some of these organisms for biological terrorism, surveillance is critical. Early warning systems have been designed that aggregate data from emergency room visits, private-practice billing codes, and veterinary practices with data on absenteeism, nurse hotline calls, and the purchase of medications. Together, the data could provide early warning of the use of a biological weapon or predict the start of an epidemic. The Electronic Surveillance System for the Early Notification of Community-Based Epidemics (ESSENCE) is one such surveillance system that operates in the Washington DC area.[63] The ESSENCE system is an early step in what should ultimately be a global network to track unusual and emerging pathogens.

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