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Infectious Disease

Editor's Note: *In this feature, brief items, primarily gleaned from abstracts or articles in journals and other resources not commonly perused by most US infectious disease physicians, will be presented, usually without comment. — Stan Deresinki, MD, FACP*

HIV Infection & Complications (Cont. from Nov. 1, 2002 issue)

Chloroquine Inhibits HIV

Chloroquine, at clinically relevant concentrations, inhibits HIV-1 and HIV-2 *in vitro* at a postintegration step affecting the structural integrity of newly produced viral envelope glycoproteins (Savarino A, et al. *AIDS*. 2002;15:2221-2229).

'Simplification' of Antiretroviral Therapy

HIV-infected patients receiving a PI plus nucleoside analogs and who had suppressed viral replication as well as absence of the RT 215 mutation were randomized to continue their regimen or to change to treatment with abacavir/lamivudine/zidovudine. Virologic failure after a median of 84 weeks occurred in 6% of the continuation and 15% of the switch group (P = 0.081); prior zidovudine monotherapy and "archived" RT mutations were significantly associated with failure (Opravil M, et al. *J Infect Dis*. 2002;185:1251-1260).

CD4+ NK Cells and Persistent HIV Infection

A subset of NK cells expressing CD4 serves as a persistent reservoir of HIV-1 in patients receiving HAART (Valentin A, et al. *Proc Natl Acad Sci USA*. 2002;99:7015-7020; Kolte L, et al. *J Infect Dis*. 2002;185:1578-1585).

Cyclophosphamide and HAART

The addition of cyclophosphamide to antiretroviral therapy failed to diminish the cellular reservoir of HIV (Bartlett JA, et al. *AIDS Res Hum Retroviruses*. 2002;18:535-543).

Intermittent HAART is Predictive of Mortality

Multivariate analysis of a large cohort of patients who started

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INSIDE

HAART between 1996 and 1999 found that those who took their drugs intermittently were approximately 3 times more likely to die after 1 year of follow-up than those who took them continuously (Hogg RS, et al. *AIDS*. 2002;16:1051-1058).

Why Does the CD4+/CD8+ Ratio Fail to Normalize in Some Successful HAART Recipients?

A statistically significant inverse correlation was found between the frequency of CD4+ T cells carrying HIV-1 proviral DNA and the CD4+/CD8+ T-cell ratio in individuals with prolonged suppression of plasma HIV RNA during HAART therapy. It is suggested that this evidence of low-level viral replication, while insufficient for the maintenance of HIV-1-specific CTL responses, accounts for the lack of normalization of the CD4+/C8+ ratios in some patients with virological suppression during HAART (Chun TW, et al. *J Infect Dis*. 2002;185:1672-1676).

Apoptosis, Response to IL-2, & Discordant Responses

Failure of CD4 count to rapidly rise despite virological suppression was associated with underexpression of the anti-apoptic molecule Bcl-2 and increased susceptibility to spontaneous apoptosis, together with decreased responsiveness to IL-2 (David D, et al. *AIDS*. 2002; 16:1093-1101).

Drug Resistance Mutations & Discordant Responses

RT mutations, M184V and protease mutations, L24I and V82A were significantly associated with increased CD4 count despite virological failure, while RT Y181C was associated with a reduced probability of immunologic recovery (Antinori A, et al. *AIDS*. 2001;15:2325-2327).

Low-Level Viremia & Virological Treatment Failure

Evaluation of virus from 14 patients on ART who developed persistent low-level viremia (reaching a median of 1450 copies/mL) after an initial decrease to < 500 copies/mL detected the presence of new primary resistance mutations in 93%. Aleman and colleagues conclude that low-level viremia after virological treatment failure can select for virus with several new drug resistance mutations and that this serial accumulation of mutations will limit future treatment options (Aleman S, et al. *AIDS*. 2002;16:1039-1044).

Amprenavir and Lopinavir Cross-Resistance

In vitro exposure to increasing concentrations of amprenavir was associated with progressive accumulations of mutations at protease codons 10, 46, 47, 50, and 84, as well as at Gag codon 449 and at the p1/p6 cleavage site. Phenotypic susceptibility to amprenavir was progressively reduced with increasing numbers of protease mutations and changes in susceptibility to lopinavir-paralleled changes in amprenavir susceptibility. The presence of either 184V or 150V mutations was associated with a reduction in replicative capacity of at least 90% (Prado JG, et al. *AIDS*. 2002;16:1009-1017).

Mitochondrial Function During HAART

Evaluation of 8 HIV-infected patients with lipodystrophy or elevated p-lactate while receiving HAART showed, relative to controls, reduced work capacity and a trend toward reduced maximal oxygen consumption, but a normal increase in blood lactate during exercise and no evidence of serious damage to skeletal muscle mitochondrial function (Roge BT, et al. *AIDS*. 2002;16:973-982).

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Statins & Polyneuropathy

A case control study found a significantly increased risk of idiopathic polyneuropathy (odds ratio, 4.6) in patients who had received statins for 2 or more years (Gaist D, et al. *Neurology*. 2002;58:1333-1337).

Leukoencephalopathy in HAART Recipients

Postmortem examination of the brains of 7 HAART-experienced but severely immunocompromised patients (6 with poor control of HIV replication) with leukoencephalopathy found evidence of intense perivascular infiltration by HIV-gp41 immunoreactive mononuclear cells, together with myelin loss, axonal injury, and gliosis. Langford and associates suggest that the pathology may be the result of HAART-associated immune reconstitution (Langford TD, et al. *AIDS*. 2002;16:1019-1029).

CMV in CSF in AIDS

Cell-associated CMV DNA was detected in the CSF of 8 of 9 AIDS patients independently of the presence of neurological symptoms (Stanojevic M, et al. *Virus Research*. 2002;85:117-122).

Aseptic Meningitis, Optic Neuritis, & Aseptic Meningitis due to VZV in an AIDS Patient

An HIV-infected patient presented with VZV meningitis and retrobulbar optic neuritis that preceded the onset of progressive outer retinal necrosis (FrancoParedes C, et al. *AIDS*. 2002;16:1045-1049).

Recurrent Pneumococcal Disease in HIV-Infected Patients

The recurrence rate of invasive pneumococcal disease was 6.4-fold higher in HIV-infected individuals than in those not HIV-infected and was due to reinfection rather than relapse in most (McEllistrem MC, et al. *J Infect Dis*. 2002;185;1364-1368).

HIV and Syphilis—Treatment Failure

Of 18 HIV-infected patients in Mozambique with latent syphilis treated with 2 M IU IM q.d. of the combination of benzylpenicillin G and the repository form benzylpenicillin G evaluated 1 year later, 9 (44.4%) had serological failure as defined by the continued presence of a positive RPR (Tattevin P, et al. *Scand J Infect Dis*. 2002;34:257-261).

HIV-1, HIV-2, and Tuberculosis Incidence and Mortality

A study in Guinea-Bissau found that, compared to non-HIV infected individuals, HIV-2 infection was associated with an increased incidence of tuberculosis, while HIV-1 infection (with or without concomitant HIV-2 infection) was associated with both an increase in tuberculosis incidence and associated mortality (Seng R, et al. *AIDS*. 2002;16:1059-1066).

Cryptococcal Disease in Uganda

Prospective evaluation of a large cohort of HIV-infected adults in Entebbe, Uganda, found that cryptococcal disease occurred at a rate of 40.4 per 1000 person-years and was associated with 17% of all the deaths in the cohort. The median survival after diagnosis was only 26 days (range, 0-128 days) (French N, et al. *AIDS*. 2002;16:1031-1038).

Immunopathogenesis of Lethal PCP

Studies in a murine model of PCP found that adoptive transfer of CD25-CD4+ T cells was associated with a reduced organism load but led to lethal pneumonia while transfer of the putatively regulatory CD25+CD4+ T cells suppressed this immune response and prevented the development of lethal pneumonia. This is consistent with the notion that PCP in immunocompromised patients results from a deficiency in regulatory T cells in a PC colonized individual (Hori S, et al. *European J Immunol*. 2002;32:1282-1291).

Ritonavir & KS

Ritonavir was shown to have direct *in vitro* antiangiogenic and antitumorigenic effects against Kaposi sarcoma (Pati S, et al. *Blood*. 2002;99:3771-3779).

Phase I Trial of IL-12

IL-12 administration was well tolerated in a Phase I placebo-controlled trial, but did not improve antigen-specific immune responses and did not affect HIV viral load (Jacobson MS, et al. *AIDS*. 2002;16:1147-1154).

Miscellaneous

***Chlamydia pneumoniae* & Temporal Arteritis—Not!**

No evidence of *C pneumoniae* DNA was found by PCR in temporal artery biopsies of 90 patients with temporal arteritis (Regan MJ, et al. *Arthritis Rheum*. 2002;46:1056-1060).

Maternal Antibody to TSST-1 May Protect Infants Against Kawasaki Syndrome

Studies of maternal-infant pairs found evidence that Kawasaki syndrome in infants younger than 6 months of

age is related to exposure to TSST-1 and that maternal antibody against this superantigen may be protective (*J Infect Dis*. 2002;185:1677-1680).

Early IVIG in Kawasaki Syndrome

Administration of IVIG to children with Kawasaki syndrome within 5 days of the onset of fever was associated with a reduced frequency of coronary ectasia at 12 months when compared with administration during days 6 to 9 after fever onset (Tse SML, et al. *J Pediatr*. 2002; 14:450-455).

Cats in Norway Do Not Have Bartonella Bacteremia

None of 100 cats examined in Norway were bacteremic with *B henselae* and only 1 was antibody positive. Human cat scratch disease is rare in Norway (Bergh K, et al. *APMIS*. 2002;110:309-314).

Tula Virus Infection

A 12-year-old Swiss boy developed a paronychium, fever and rash after being bitten by a wild rodent in the first reported human case of infection by Tula virus, a known hantavirus previously believed to be nonpathogenic in humans (Schultze A, et al. *Eur J Clin Microbiol Infect Dis*. 2002;21:304-306). ■

Fluoroquinolones and Tendinopathies

ABSTRACT & COMMENTARY

Synopsis: *The excess risk of Achilles tendon disorders attributable to fluoroquinolone use was estimated to be 3.2 cases per 1000 patient-years, with most of that increase accounted for by patients 60 years of age and older who concomitantly receive corticosteroids.*

Source: van der Linden PD, et al. Fluoroquinolones and risk of Achilles tendon disorders: Case-control study. *BMJ*. 2002; 324:1306-1307.

The IMS database containing information from UK general practices covering 1 million to 2 million inhabitants was queried in order to perform a nested case control study designed to examine risk factors for the development of Achilles tendon disorders (ATD) related to fluoroquinolone use. The cohort included 47,776 adults who had received a fluoroquinolone, of whom 704 (1.4%) had Achilles tendonitis and 38 (.08%) had Achilles tendon rupture. This represented an overall excess risk of 3.2 cases per 1000 patient-years. The adjusted relative risk (RR) of ATD was 1.9 (95% CI, 1.3-2.6) for current fluoroquinolone use; there was no increased risk associated with recent (but not current) or remote past use. While there was no increased risk associated with current use among those younger than 60 years of age, for those 60 years of age or older, the RR was 3.2 (2.1-4.9) and for those in this latter age group who were also receiving corticosteroids, the RR was 6.2 (3.0-12.8). Those with both risk factors, age older than 60 years and corticosteroid use, accounted for 87% of cases of ATD.

■ **COMMENT BY STAN DERESINSKI, MD, FACP**

A large increase in both fluoroquinolone use and nontraumatic tendon ruptures were observed in The Netherlands between 1991 and 1996.[1] It was concluded, however, that less than 7% of the increase in tendon ruptures could be attributed to the increase in fluoroquinolone use. Nonetheless, the epidemiologic and laboratory evidence demonstrates a strong causal relationship.

Fluoroquinolones are known to cause cartilaginous abnormalities in immature animals, such as beagle pups. Histologic changes in tenocytes of experimental animals exposed to fluoroquinolones include vacuolation of tenocytes and decrease in fibril diameter with an increase in the distance between individual collagenous fibrils. In vitro experiments indicate that fluoroquinolones stimulate matrix-degrading protease activity of fibroblasts while inhibiting fibroblast metabolism.

Much evidence supports the hypothesis that tendinopathy is the consequence of chelation of magnesium ions by fluoroquinolones—a class effect and the reason why simultaneous oral administration of magnesium-containing antacids and fluoroquinolones results in markedly impaired gastrointestinal absorption of the latter. Thus, both magnesium deficiency and ciprofloxacin administration can each cause similar biochemical changes in the Achilles tendons of immature dogs.

Fluoroquinolones remain highly effective antibiotics in most regions. The low incidence of tendon disorders should not preclude their use, especially when only a tiny fraction of these complications involve actual tendon rupture. Nonetheless, the recognition that patients older than age 60 years, especially those receiving corticosteroids, comprise those at significant risk should alert the clinician. An evaluation in The Netherlands in 1998 found that the median time from initiation of fluoro-

quinolone use to onset of tendon symptoms was 6 days.[2] It is unfortunate, of course, that these risk factors describe a large number of patients with underlying chronic obstructive lung disease who are at risk of acute bacterial exacerbations and who might benefit, on occasion, from fluoroquinolone therapy. Thus, if a fluoroquinolone is the treatment of choice in such a patient, it might be beneficial, albeit unproven, to correct any magnesium deficiency that might be present, with the hope that this would reduce the potential for development of a tendinopathy. ■

References

1. van der Linden PD, et al. Fluoroquinolone use and the change in incidence of tendon ruptures in The Netherlands. *Pharm World Sci.* 2001;23:89-92.
2. van der Linden PD, et al. Tendon disorders attributed to fluoroquinolones: A study on 42 spontaneous reports in the period 1988 to 1998. *Arthritis Rheum*. 2001;45:235-239.

Gonna Wash Those Bugs Right Off of My Hands

ABSTRACT & COMMENTARY

Synopsis: *The CDC has published a new set of recommendations aimed at preventing health care-associated infections by optimizing hand hygiene in health care personnel. The following is a summary of some of those recommendations, selected because of their strength and/or novelty.*

Source: CDC. Guidelines for hand hygiene in health care settings: Recommendations of the health care infection control practices advisory committee and the HICPAC/SHEA/APIC/IDSA hand hygiene task force. MMWR 2002;51(No. RR-16):1-45.

"What separates two people most profoundly is a different sense and degree of cleanliness." — Nietzsche, in "Beyond Good and Evil" 1886, p. 271, translated by Walter Kaufmann.

ALTHOUGH VISIBLY SOILED HANDS SHOULD BE washed with either a nonantimicrobial soap and water or with an antimicrobial soap, an alcohol-based hand rub should be used for routine hand decontamination. Such hand decontamination is to be performed before direct contact with a patient, as well as after skin or mucous membrane contact, or contact with body fluids, potentially contaminated objects (eg, wound dressings), and after removing gloves. The use of soap is also recommended before eating and after using a restroom, as well as if exposure to *Bacillus anthracis* is suspected or proven (because of the lack of efficacy of other products against spores and the hope that the spores would be dislodged by hand washing with soap).

When soap is used, vigorous hand rubbing should be performed for at least 15 seconds and a disposable towel used for drying should be used to turn off the faucet. Hot water should be avoided because its use may increase the risk of development of dermatitis. Hand rubbing with an alcohol-based product should continue until the hands are dry.

For surgical hand antisepsis, jewelry should first be removed and debris removed from under the fingernails. Soaps or alcohol products with persistent (residual) activity should be used; washing with a nonantimicrobial soap should precede use of the alcohol product. The duration of the scrub, which should include the forearms, should be that recommended by the manufacturer, usually 2 to 6 minutes; drying must be allowed to occur before gloving.

In selecting hand-hygiene products for use in an institution, great importance should be given to choosing ones with a low potential for provoking irritation with repeated use; feedback from staff is invaluable. "The cost of hand-hygiene products should not be the primary factor influencing product selection." Health care workers should be supplied with lotions or creams to minimize the occurrence of contact dermatitis. Do not add soap to partially empty soap dispensers, a practice that may lead to bacterial contamination.

Artificial fingernails or extenders may not be worn during direct contact with patients at high risk of infection and natural nail tips should be kept at a length of less than ¼ inch.

Gloves should be worn whenever contact with blood or other potentially infectious materials, skin that is not intact, or mucous membranes is likely to occur. Gloves should be removed after caring for a patient, should not be washed, and should not be used in care of a second patient.

The adherence of health care workers to recommended hand-hygiene practices should be monitored and feedback on performance provided in the context of a multidisciplinary program to improve adherence. This program should include provision of a readily accessible alcohol-based hand-rub product, including, in high-workload areas, at the entrance to patient rooms or at the

bedside and at other convenient locations, as well as in individual pocket-sized containers to be carried by health care workers.

Adherence to the recommended policies should be made an institutional priority and appropriate administrative support and financial recourses provided. A series of performance indicators should be measured. In addition to periodic monitoring with feedback of adherence to hand hygiene practices, including adherence to policies regarding the wearing of artificial nails, there should be monitoring of the volume of hand washing liquids used per 1000 patient-days. Reassessment of adherence should be performed as part of outbreak investigations.

The guideline along with promotional materials and fact sheets is available at: http://www.cdc.gov/handhygiene. ■

How Humans Assist Cholera

ABSTRACT & COMMENTARY

Synopsis: *Passage through the human gastrointestinal tract enhances the infectiousness of* Vibrio cholerae.

Source: Merrell DS, et al. Host-induced epidemic spread of the cholera bacterium. *Nature*. 2002;417:642-645.

An in vitro passaged strain of Vibro cholerae (DSM-V894) was mixed with *V cholerae* 01 Inaba El Tor recovered from stools of Bangladeshi patients and immediately used to inoculate infant mice by gavage. The mice were subsequently sacrificed, their small intestines homogenized, and quantitative cultures performed to determine the relative infectivity of the passaged strain and of the strains freshly recovered from human stool. The latter proved to have markedly enhanced infectivity, outcompeting the passaged strain by as much as 700-fold. This enhanced infectivity was, however, lost after this strain itself was passaged in vitro.

Epidemic cholera is the consequence of contaminated water supplies. To investigate whether the competitive advantage of *V cholerae* freshly shed from human stool was maintained in circumstances that could account for propagation of the disease in nature, mouse infectivity experiments were repeated after incubation of such strains into pond water; the hyperinfectious state of these strains was, in fact, maintained.

Transcriptional analysis using a spotted DNA microarray found that at least 237 genes were differentially expressed, with 44 genes being induced and 193 suppressed in human-shed *V cholerae*. The transcriptum (ie, the complete collection of transcribed RNAs of these stool-derived isolates) was consistent with that observed with bacterial growth in an environment in which oxygen and iron are limited; Merrell and colleagues point out that these are conditions that have been demonstrated to prevail in the rice-water stools of cholera. Genes encoding a number of known virulence factors, including cholera toxin, were not differentially regulated, while expression of genes involved in chemotaxis was repressed in stool-derived *V cholerae*, an effect that could possibly lead to increased shedding from the gastrointestinal tract.

COMMENT BY STAN DERESINSKI, MD, FACP

This remarkable set of experiments paints a fascinating picture of the genetic machinations of *V cholerae* that optimize its survival in very different environments. Merrell et al suggest that ingested *V cholerae* that escape the acid environment of the stomach and find their way to the small intestine and then into the colon alter their gene expression so that the organism becomes "hyperinfectious." Furthermore, the organism maintains this state after shedding of these isolates in diarrheal stools into a nutrient-poor aquatic environment. In contrast, this state is lost upon exposure of the organism in nutrient-rich culture media.

Passage through the gastrointestinal tract of the human host increases the infectiousness of *V cholerae* and this infectiousness is maintained in environments such as pond water. Thus, as pointed out by Merrell et al, human infection enhances subsequent water-borne spread of *V cholerae* by lowering the dose required to establish infection in subsequent victims. The human host thus plays a key role in conditioning these organisms to ensure continued epidemic spread of cholera. In the words of Pogo: "We have met the enemy and it is us!" ■

CME Questions

Which of the following is correct?

a. The presence of a I84V mutation in the HIV-1 protease gene is associated with enhanced viral replicative capacity.
b. The presence of a I50V mutation in the HIV-1 protease gene is associated with enhanced viral replicative capacity.
c. Maximum resistance to amprenavir is commonly associated with the presence of just a single mutation in the protease gene.
d. ***Phenotypic reduction in susceptibility of HIV-1 to amprenavir are paralleled by reduction in susceptibility to lopinavir.

24. Which of the following is associated with an increased risk of Achilles tendinopathy related to fluoroquinolone use?

a. Age younger than 60 years
b. **Corticosteroid use
c. Female gender
d. Past, but not current use of fluoroquinolones

Readers are Invited

Readers are invited to submit questions or comments on material seen in or relevant to *Infectious Disease Alert*. Send your questions to: Rob Kimball—Reader Questions, *Infectious Disease Alert*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374, or via the Internet by sending e-mail to robert.kimball@ahcpub.com. We look forward to hearing from you. ■

In Future Issues:

Yellow Fever

UPDATES

By Carol A. Kemper, MD, FACP

Longer-Lasting Immunity to Smallpox?

Source: ProMED-mail post. August 30, 2002; www.promedmail.org.; Frelinger JA, Garba ML. *N Engl J Med*. 2002;347:689-690.

SCIENTISTS AT THE UNIVERSITY OF North Carolina have provided new evidence that smallpox vaccination may provide at least partial protection for up to 35 years or longer. CD8+ T-lymphocyte cell responses to vaccinia virus were evaluated in persons who had received smallpox vaccine anywhere from 1 to 35 years ago. Four were laboratory workers who received smallpox vaccine for occupational exposure within the previous 5 years, 5 had received vaccine from 6 to 35 years earlier, and 4 had received vaccine more than 35 years ago. In those who were recently vaccinated, an average of ~6.5% of CD8+ lymphocytes were activated in vitro, as determined by overnight cell culture, compared with about 6% of cells from subjects vaccinated 5 to 35 years earlier and 4% of those from persons vaccinated more than 35 years ago. This is considered a fairly vigorous immune system response, with little loss of reactivity for a period of more than 35 years.

Public health officials are cautioning that this data not be overly enthusiastically interpreted, pointing to contradictory data derived in the past. Many experts believe that the benefits of vaccine are probably limited to a 10-year period. However, outbreaks of smallpox occurring in the early 1900s suggested that vaccination provided protection from serious illness and death for up to 50 years. The above laboratory data appear consistant with those historical reports. ■

Is There a Rabid Bat in Your Belfry?

Source: Messenger SL, et al. *Clin Infect Dis*. 2002;35:738-747.

FOR THOSE OF YOU WHO RECENTly attended the HIVMA meeting in Chicago on October 25 you had the opportunity to hear Stan Deresinski's description of being sprayed by fruit bat urine as he entered his flat in Kampala last spring—raising concerns of possible rabies exposure. Cryptogenic exposure to bats is believed to be the leading cause of human rabies—at least in the United States. Various rabies virus variants have been isolated from nearly all of the 41 bat species found in the United States. While the number of cases of human rabies has steadily decreased in the United States over the past 40 years, at least 1 to 2 cases continue to occur annually. Of the 28 indigenous cases diagnosed in the United States since 1980, an animal bite could not be documented in 89%.

Molecular studies suggest that most of these cryptogenic cases are due to virus variants infecting insectivore bats. Two bat species, the silver-haired bat (*Lasionycteris noctivagans*) and the eastern pipistrelle (*Pipistrelle subflavus*), appear to be more frequently associated with human rabies infection, although these bats are seldom found in association with humans or human habitats. Interesting, only a minority of cases of human rabies in this survey was from rabies virus commonly associated with house bats.

Another interesting tidbit: Most cases of human rabies in the United States occur in the fall. Assuming an incubation period of 4-8 weeks, this is consistent with the period of greatest risk of exposure to bats occurring during the late summer months. Although rare, clinicians should be prepared to consider rabies as a cause of acute encephalitis, especially in the late summer and fall. ■

Nosocomial *C difficile*: Way Common

Source: Wanahita A, et al. *Clin Infect Dis*. 2002;34:1585-1592.

A SIGNIFICANT PROPORTION OF hospital patients with leukocytosis, with or without fever, may have unrecognized *Clostridium difficile* infection. In a prospective observational study of 400 inpatients with leukocytosis > 15,000 cells/mm^3, infection was the leading factor contributing to the elevated white blood count in 52% of cases, followed by physiologic stress (38%), medication or drugs (11%), hematologic malignancy (6%), or necrosis or inflammation (6%). Overall, 8.5% with white blood cell counts > 15,000 cells/mm^{3}were diagnosed with *C difficile* infection.

In those subjects with leukocytosis > 30,000 cells/mm^3, pneumonia was still the leading explanation, but *C difficile* infection was next most frequent, occurring in 25% of patients who did not have hematologic malignancy. Even in those without obvious diarrhea, *C difficile* should be strongly considered in any hospital patient with leukocytosis. ■