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INSIDE

Financial Disclosure:

Infectious Disease Alert's Physician Editor, Stan Deresinski, MD, FACP, serves on the speaker's bureau of Merck, Pharmacia, GlaxoSmithKline, Pfizer, Bayer, and Wyeth, and does research for Merck. The Peer Reviewer, Connie Price, MD, reports no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company related to this field of study.

Emergence of MRSA USA300 Clone

ABSTRACT & COMMENTARY

By Robert Muder, MD

Hospital Epidemiologist, Pittsburgh VA Medical Center

Dr. Muder does research for Aventis and Pharmacia.

Synopsis: *Active, prospective laboratory-based surveillance of community-onset staphylococcal skin and soft-tissue infections at an Atlanta hospital found that 72% were caused by MRSA. Of these, 90% were due to the MRSA USA300 clone, which is genetically distinct from the predominant hospital associated MRSA clonal types.*

Source: King MD, et al. Emergence of Community-Acquired Methicillin-Resistant *Staphylococcus aureus* USA300 Clone as the Predominant Cause of Skin and Soft-Tissue Infections. *Ann Intern Med*. 2006:144:309-317.

KING AND COLLEAGUES CONDUCTED PROSPECTIVE, LABORATORY-based surveillance of all community-onset staphylococcal skin and soft-tissue infections presenting to Grady Memorial Hospital and its affiliated clinics for a 3.5-month period in 2003. They included all infections with *Staphylococcus aureus* isolated at an outpatient visit or within 72 hours of admission. A community-acquired MRSA isolate was defined as one that demonstrated the USA300 or USA400 pulsed field type or, if the isolate was unavailable for typing, demonstrated resistance only to β-lactam antibiotics and erythromycin. They identified 389 episodes, of which 279 (72%) were caused by MRSA. Two hundred forty-four (87%) isolates causing MRSA infection were community-acquired, using the stated definition. Of the 159 isolates that were identified as community acquired by pulsed-field typing, 157 (99%) were USA300; the remaining 2 were USA400. Multivariate analysis of risk factors for community-acquired MRSA identified black race, female sex, and absence of hospitalization within the previous 6 months as significant.

COMMENTARY

Until the late 1990s, MRSA was primarily identified as a cause of nosocomial infection. However, reports of localized outbreaks of MRSA among persons without exposure to hospital began to appear. These occurred among groups of otherwise healthy people who had close physical contact with one another. These included children in day care, athletes, prisoners, military personnel, and Native Americans living on reservations. These outbreaks were typically caused by a single clonal strain of MRSA belonging to one of 2 clonal types, USA300 or USA400.[1] These strains are phenotypically and genetically distinct from existing hospital associated. Community-acquired strains are usually susceptible to multiple antimicrobials except for β-lactams and erythromycin. Methicillin resistance is caused by a distinct methicillin resistance gene cassette, SCC*mec*IV, previously not found in hospital strains. In addition, many community-acquired strains carry the Panton-Valentine leukocidin (PVL), an exotoxin that is highly toxic to leukocytes and other cells. Its precise pathogenic significance is uncertain, but presence of PVL is associated with severe skin and soft-tissue infections and necrotizing pneumonia in otherwise healthy adults and children. PVL is rarely found in hospital strains of MRSA.

The report that the majority of community-onset staphylococcal infections encountered at a single facility were due to community-acquired strains of MRSA (USA300) is highly disturbing. The significance of this report for the rest of the United States is not yet entirely clear, as it came from a single institution that primarily serves a poor urban population. Although there is no single source of data on the prevalence of community-acquired MRSA in the United States, a review of the literature indicates that it is widespread. A population-based study performed by the CDC in 2001-2002 found that the incidence of community-onset MRSA infections was 25.7/100,000 population in Atlanta and 18.0/100,000 in Baltimore.[2] At a single hospital in Houston, 66% of all community-onset infections leading to hospitalization of children were caused by MRSA.[3] Eighty percent were skin or soft-tissue infections, 11% were pneumonia, and 6% were bone and joint infections. Fourteen isolates were subjected to pulsed field typing, and all were USA300.

How widespread USA300 is in the United States is unclear. In the same issue of the *Annals of Internal Medicine*, Graham and colleagues reported the results of a US population-based study of nasal carriage of *S. aureus* involving nearly 10,000 participants.[3] Only 0.84% of patients were colonized with MRSA, and half of the isolates were SCC*mec*IV strains. This suggests that USA300 MRSA strains are not widespread. That conclusion may be premature, however. The epidemiology of USA300 outbreaks suggests that close contact with an infected person, rather than nasal carriage, is the immediate precursor to infection. Surveys of nasal carriage might dramatically underestimate the contribution of USA300 MRSA to cases of staphylococcal infection.

β-lactam antibiotics have been the drug of choice for community-acquired staphylococcal infections since the discovery of penicillin, but it's clear that this is no longer the case in regions in which community-acquired MRSA has taken hold. For relatively uncomplicated skin and soft-tissue abscesses, incision and drainage alone may be adequate. Purely empiric antimicrobial therapy of suspected staphylococcal soft-tissue infections is not appropriate; therapy should definitely be guided by culture and susceptibility testing. Optimal therapy is uncertain, as there are no randomized trials of therapy. Although most USA300 strains are susceptible to clindamycin by in vitro testing, approximately 10% have inducible clindamycin resistance that is not detected by standard disk diffusion or microtiter assays. Trimethoprim/sulfamethoxazole or minocycline may be reasonable choices as oral therapy for outpatients. Oral linezolid would likely be effective, but it is fairly expensive. Based on a poor track record in treating MRSA infections, quinolones are best avoided regardless of susceptibility testing. ■

Infectious Disease Alert, ISSN 0739-7348, is published monthly by Thomson American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

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EDITORIAL GROUP HEAD: Lee Landenberger.

MARKETING PRODUCT MANAGER: Gerard Gemazian.

MANAGING EDITOR: Robert Kimball.

ASSOCIATE MANAGING EDITOR: Leslie Hamlin.

GST Registration Number: R128870672.
Periodicals postage paid at Atlanta, GA.
POSTMASTER: Send address changes to ***Infectious Disease Alert,*** P.O. Box 740059, Atlanta, GA 30374.

Back issues: $21.
Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

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Questions & Comments

Leslie Hamlin,
Associate Managing Editor, at (404) 262-5416, or e-mail to leslie.hamlin@thomson.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

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CA-MRSA & CAP

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

Synopsis: *Seventeen cases of community acquired pneumonia due to* Staphylococcus aureus *are described. Most were methicillin resistant and caused severe disease with high mortality.*

Source: Hageman JC, et al. Severe Community-Acquired Pneumonia Due to *Staphylococcus aureus*, 2003-04 Influenza Season. *Emerg Infect Dis*. 2006; 12:894-899.

The CDC identified 17 patients with community-acquired pneumonia (CAP) due to *S. aureus* by following up on reports from the Emerging Infections Network of the Infectious Disease Society of America (IDSA) during the 2003-2004 influenza season. The patients ranged in age from 3 months to 62 years (median, 21 years), and 5 (29%) had underlying diseases. All patients had an initial influenza-like illness, and 12 (71%) had laboratory-confirmed acute influenza virus infection. Only one had documented receipt of influenza vaccine during 2003-2004. Twelve (93%) of 13 patients for whom data was available were hypotensive. One-fourth of patients had involvement of multiple lobes of the lung, and one-fourth had radiographic evidence of cavitation or necrosis; 31% had effusions/empyema. ICU admission was required by 81%; 62% required mechanical ventilation, and 46% required chest tube placement. Five (29%) died, a median of 7 days (range, 3 to 73 days) after the onset of symptoms; one was dead on arrival at hospital.

Of the 13 *S. aureus* isolates available, 13 (76%) were methicillin-resistant (MRSA). All contained one or more toxin genes, but 11 of these had only the genes encoding the Panton-Valentine leukocidin. All the isolates were found to be of community-associated pulsed field types; 85% were USA300 (most subtype 0114) and the remainder were USA400.

COMMENTARY

This study is important in bringing 2 epidemiological strands together—the known increased risk of S. aureus as a cause of CAP complicating influenza virus infection and the emergence of novel strains of MRSA in the community. The cases described here were of remarkable severity, indicating a need for early initiation of appropriate antibiotic therapy and, thus, requires awareness of the problem of community-acquired MRSA (CA-MRSA) among clinicians. These cases also demonstrate the importance of procuring specimens, including sputum for microbiological evaluation and examination of Gram stains, something which appears to be increasingly neglected.

Hageman and colleagues point out a warning published in 1959 that during influenza epidemics antibiotic therapy should included coverage of relatively antibiotic-resistant staphylococci.[1] At the time, of course, they were referring to penicillin-resistant organisms, not MRSA which had not yet been described (methicillin became available in 1959-1960). This warning remains valid at a time when virulent CA-MRSA are increasingly prevalent and, at the same time, acquiring resistance to additional antibiotics, including the respiratory fluoroquinolones. ■

Reference

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Classifying MRSA—A Modest Proposal

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

The rapidly evolving epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) colonization and infection has resulted in

Table 1

Centers for Disease Control Definition of CA-MRSA

Persons with MRSA infections that meet all of the following criteria are likely to have CA-MRSA infections (diagnosis of MRSA was made in the outpatient setting or by a culture positive for MRSA within 48 hours after admission to the hospital):

- No medical history of MRSA infection or colonization
- No medical history in the past year of:
  - Hospitalization
  - Admission to a nursing home, skilled nursing facility, or hospice
  - Dialysis
  - Surgery
- No permanent indwelling catheters or medical devices that pass through the skin into the body

ambiguity in the designation of individual instances as either community or health care associated. This essay represents a proposal for a telegraphic system of unambiguous description of isolates. Please note, however, that this proposal was quickly rejected by 2 journals, and should be judged accordingly.

The CDC classification of MRSA as being of community origin (CA-MRSA) depends upon diagnosis of infection or colonization in an outpatient, or on a positive culture obtained in the first 48 hours of hospitalization, in the absence of factors indicating the possibility of acquisition in the healthcare setting (see Table 1).[1] Strains of MRSA have also been classified as being hospital or community acquired based upon their SCC*mec* gene type, with SCC*mec* type IV and SCC*mec* type V considered as indicative of an isolate being CA-MRSA.[2] In the absence of molecular characterization of SCC*mec*, some authors have used antibiotic susceptibility phenotype as a surrogate to suggest community or hospital origin.

Unfortunately, these designations have not kept pace with the evolution of the epidemiology of MRSA. Strains considered of hospital origin may be acquired in the community, and vice versa.[3,4] As a consequence, the use of the terms, HA-MRSA and CA-MRSA, are often ambiguous in their meaning. There is an important need for a more precise and unambiguous method of communicating the nature of the isolate or infection. The following is a suggestion whose purpose is to provide improved clarity in communications regarding MRSA.

Assignment as hospital-acquired MRSA (HA-MRSA) or CA-MRSA is made by the CDC epidemiologic definition ($_{EPI}$), by molecular characterization of SCC*mec* ($_{MOL}$), or both ($_{EPI/MOL}$). The molecular classification may be expanded to make it more precise when further information is available; (eg, CA_{MOL}(SCC*mec*IV)-MRSA or CA_{MOL}(USA300)-MRSA). In cases in which the molecular type is inferred from the phenotypic expression of antibiotic susceptibility, the designation ($_{PHE}$) may substitute for ($_{MOL}$). This system allows for an accurate telegraphic description of isolates whose classification may differ depending upon the means utilized (eg, CA-MRSA by molecular methods and HA-MRSA by the CDC epidemiological definition, yielding the designation $CA_{MOL}HA_{EPI}$-MRSA). Excluding the use of the phenotypic designation by antibiotic susceptibility pattern, the resultant possibilities are as seen in *Table 2*.

Table 2

Proposed Classification of MRSA

Basis of Designation	Classification[a]	
Epidemiologic	CA_{EPI}-MRSA	HA_{EPI}-MRSA
Molecular[b]	CA_{MOL}-MRSA	HA_{EPI}-MRSA
Both	$CA_{EPI/MOL}$-MRSA	$HA_{EPI/MOL}$-MRSA

[a] Some infections or isolates may be classified as community acquired by one method and hospital acquired by the other. There are 2 such possibilities: $CA_{MOL}HA_{EPI}$-MRSA and $CA_{EPI}HA_{MOL}$-MRSA.

[b] HA-$MRSA_{MOL}$: contains SCC*mec* type I, SCC*mec* type II, or SCC*mec* type III. CA-$MRSA_{MOL}$: contains SCC*mec* type IV or SCC*mec* type V.

The dynamic nature of the evolving epidemiology of MRSA, however, may eventually render the distinctions between the settings in which this organism is acquired irrelevant. In the meantime, however, this proposed classification is intended to help remove much of the ambiguity in communications regarding HA-MRSA and CA-MRSA. ■

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An Emerging Extended-Spectrum Triazole Antifungal: Noxafil® (Posaconazole)

SPECIAL FEATURE (PART 2 OF 2)

By Jean Yong Nam, PharmD Candidate, Rehan Noori, PharmD Candidate, and Jessica C. Song, MA, PharmD

Jean Yong Nam and Rehan Noori are PharmD Candidates at the University of the Pacific School of Pharmacy, and Jessica C. Song is Pharmacy Residency Coordinator, Santa Clara Valley Medical Center

Jean Yong Nam, Rehan Noori, and Jessica C. Song report no financial relationship relevant to this field of study.

Comparisons of Antifungals

POSACONAZOLE EXHIBITS NUMEROUS ADVANTAGES over other triazoles in regards to drug-drug interactions, bioavailability issues, and its side-effect profile. As seen in *Table 5*, unlike various triazoles, posaconazole does not inhibit the majority of cytochrome P450 isoenzymes, with only marginal inhibition of CYP 3A4.[3,5,8]

Posaconazole offers an advantage over other triazoles, especially in critically ill patients who require acid suppression for stress-related mucosal damage prevention. A study by Courtney and colleagues showed that unlike ketoconazole and itraconazole, changes in pH have a clinically insignificant effect on posaconazole absorption, resulting in a broad-spectrum antifungal with predictable absorption regardless of gastric pH.[2]

At present, one echinocandin, caspofungin, is FDA-approved for use in the treatment of invasive Aspergillosis refractory to standard therapy.[26] A recent update of a pivotal study demonstrated a success (complete or partial response) rate of 45% with caspofungin therapy.[27] This is nearly the same success rate demonstrated for posaconazole in the salvage setting.[5]

Posaconazole has been reported to be effective in some cases of zygomycosis, as demonstrated by a success (complete or partial response) rate of 60% in one retrospective report. Of note, 20% of the patients included in this report received voriconazole prior to experiencing breakthrough zygomycosis. Survival rates of 61% and 69% have been observed in Zygomycetes-infected patients treated with amphotericin B deoxycholate and lipid-associated formulations of amphotericin B, respectively.[21]

Current guidelines from the Infectious Disease Society of America recommend the use of topical agents (clotrimazole troches, nystatin) or fluconazole for treatment of initial episodes of oropharyngeal candidiasis.[28] Results of a recent trial indicate that posaconazole is equivalent in efficacy to fluconazole for the treatment of oropharyngeal Candidiasis, but is more effective in prolonging mycologic success. Both micafungin and posaconazole have been studied in the prophylaxis of IFIs in HSCT patients. Micafungin was shown to have a superior overall treatment success compared with fluconazole ($P = 0.03$),[26] whereas, success rates trended in favor of posaconazole ($P = 0.074$).[4] See *Table 4*, which outlines the key data regarding the efficacy of posaconazole in patients with oropharyngeal candidiasis and in patients with zygomycosis.

Conclusion

Posaconazole represents a new and exciting drug for the treatment of numerous opportunistic invasive fungal infections caused by pathogens such as *Aspergillus* spp, *Candida* spp, *Fusarium* spp, and *Zygomycetes* spp. Efficacy of posaconazole is comparable to caspofungin (salvage therapy for invasive aspergillosis), fluconazole (oropharyngeal candidiasis) and amphotericin B deoxycholate/lipid formulations (zygomycosis), with the advantage of significantly fewer side effects and drug-drug interactions.

Currently, posaconazole is the only triazole antifungal agent that has demonstrated activity against Zygomycetes, a pathogen that is usually eradicated with amphotericin B. Moreover, unlike the echinocandins (caspofungin, micafungin, anidulafungin), which are only available as parenteral agents, posaconazole is able to be administered orally (ingestion and through nasogastric tube). If FDA approval is granted, posaconazole likely will be prescribed for prophylaxis of IFIs in patients who are at high risk of acquiring these infections, treatment of refractory invasive aspergillosis, treatment of non-albicans oropharyngeal candidiasis, and some zygomycosis. ■

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- References 1-20 can be found in Part I of this article printed in the June 2006 issue of *Infectious Disease Alert*.

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Table 4

Clinical Trials of Posaconazole for the Treatment of Oropharyngeal Candidiasis and Zygomycosis

Study Characteristics	• 350 HIV patients with oropharyngeal candidiasis Posaconazole: No. of pts. 178; Mean age ± SD 36.4 ± 7.8 Fluconazole: No. of pts. 172; Mean age ± SD 37.6 ± 9.1	• 91 subjects with proven or probable Zygomycosis ° Nearly two-thirds of patients had one site of infection ° Approximately half of patients had received antifungal prophylaxis (mostly azoles; 20% received voriconazole) ° Approximately half of patients were enrolled due to refractory Zygomycosis
Design	• Multicenter, randomized, evaluator-blinded study	• Retrospective case series report
Inclusion Criteria	• Male or female HIV patients ≥ 18 years • Oropharyngeal Candidiasis ° ≥ 2 plaques or single plague ≥ 3 cm ° Evidence of Candida species ° Anticipated survival of > 2 months ° Ability to swallow study medication ° Karnofsky performance score ≥ 60	• Questionnaires sent to physicians treating patients infected with Zygomycetes during the period of 8/01-11/04 • Patients with Zygomycosis were enrolled in this compassionate use program if: ° Disease progression was observed despite antifungal Rx ° Failure to improve after 7 day course of standard antifungal ° Patients were intolerant to prior antifungals
Exclusion Criteria	• Use of systemic antifungals 1 week before enrollment • Use of topical antifungals 2 days before enrollment • Received other investigational agents in preceding month • First-time use of protease inhibitors 30 days before enrollment • Use of medications that could interact with azoles • Chemotherapy-related oral mucositis • Platelet count < 75,000/mm^3 • QT_c interval prolonged by > 10% of normal value • History of treatment failure with fluconazole • Evidence of hepatic or renal disease (ALT/AST > 5 x ULN; SCr > 3 x ULN)	• Patients were excluded if they: ° Participated in other posaconazole trials ° Did not have proven or probable case of Zygomycosis
Study Drugs	• Posaconazole 200 mg oral suspension (40 mg/mL) on day 1, followed by 100 mg/d x 13 days • Fluconazole 200 mg oral suspension (40 mg/mL) on day 1, followed by 100 mg/d x 13 days • 2-month follow-up	• Posaconazole oral suspension, 800 mg/d (divided bid or qid) • Duration: ° Ranged from 6-1005 days ° Minimum of 30 days for 80% of subjects
Evaluation	• Primary end point—Percentage of subjects who achieved clinical success after 14 days of treatment ° Clinical success defined as cure (minimal or no symptoms, lack of plaques or ulcers) or improvement (partial resolution of baseline signs/symptoms of candidiasis) • Secondary end points ° Durability of clinical success or clinical relapse on day 42 ° Clinical response after 7 days of therapy ° Mycological success on days 7, 14, and 42	• Treating physician evaluated response to posaconazole on the basis of: ° Signs/symptoms, microbiologic findings ° Histopathologic and radiographic findings • Responses classified as: ° Complete (resolved infection) ° Partial (clinically significant improvement) ° Stable disease (no decline in condition/no improvement) ° Failure (decline in condition) • Clinical success (complete or partial) evaluated at ≤ 12 weeks from starting posaconazole therapy

Table 4 continued on the next page

Table 4

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Results	• Completion of study ° Completion of 14 day therapy: 89% ° Completion of follow-up: 83% • Clinical success after 14 days of treatment (1^0 end point) ° Posaconazole, 91.7%; fluconazole, 92.5% • 95% CI, -6.61% to 5.04% • Criteria for non-inferiority satisfied • Mycological success on day 14 ° Posaconazole, 68% ° Fluconazole, 68% • Mycological success on day 42 ° Posaconazole, 40.6% ° Fluconazole, 26.4% (P = 0.038) • No significant difference in clinical success rates observed on day 7 with posaconazole and fluconazole • Clinical relapse rates on day 42 ° Posaconazole, 31.5% ° Fluconazole, 38.2% (P = 0.24)	• Overall success (complete or partial response) at 12 weeks, 60% ° Primary pathogens included Rhizopus (n = 25; 52% success rate), Mucor (n = 17; 76.5% success); Cunninghamella (n = 8; 75% success), Rhizomucor (n = 7; 28.6% success) ° Success rates of patients with hematologic malignancy (n = 48), receipt of chronic steroids (n = 31), graft-versus-host disease (n = 30), diabetes mellitus (n = 30), neutropenia (n = 29), and receipt of stem cell transplant ranged from 52.6% to 62.1% • Success rates observed in this study were similar to the usual success rates seen with amphotericin B products ° Survival rate with amphotericin B deoxycholate: 61% ° Survival rate of 69% with lipid formulations of amphotericin B • Since 20% of patients received voriconazole: ° Increased frequency of Zygomycosis cases likely associated with the use of antifungals (voriconazole) that do not have activity against Zygomycetes for patients who are receiving intensive immunosuppressive therapy • Success rate Zygomycosis of brain, 72.7%

Table 5

Comparison of Select Triazoles in Their Inhibition of Various Cytochrome P450 Isoenzymes[3]

	1A2	2C9	2C19	2D6	2E1	3A4
Posaconazole	--	--	--	--	--	x
Itraconazole	x	x	n/a	n/a	n/a	x
Voriconazole	n/a	x	x	n/a	n/a	x
Fluconazole	x	x	x	n/a	n/a	x
Ketoconazole	x	x	x	n/a	n/a	x

x indicates inhibition of CYP450 isoenzyme

n/a = information not available

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Discontinuing Non-Nucleoside Reverse Transcriptase Inhibitors

ABSTRACT AND COMMENTARY

By Dean L. Winslow, MD, FACP

Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center, Clinical Professor of Medicine, Stanford University School of Medicine

Dr. Winslow is a consultant for Bayer Diagnostics and Pfizer/Agouron, and is on the speaker's bureau for Pfizer/Agouron.

Synopsis: *The prolonged persistence of nnRTI after their discontinuation increases the risk of HIV resistance..*

Source: Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. May 4, 2006; www.AIDSinfo.nih.gov

DUE TO THE LONG HALF-LIVES OF NEVIRAPINE AND efavirenz, it is now recommended that when non-nucleoside reverse transcriptase inhibitor (nnRTI)-containing antiretroviral regimens are discontinued, backbone nucleoside analogs should be continued for 4-7 days to reduce the likelihood of development of nnRTI resistance.

COMMENTARY

One of the reasons for the excellent clinical efficacy of nnRTI-containing antiretroviral therapy regimens is that, while limited by the potential for development of high-level resistance with a single amino acid substitution, the intrinsic potency of these regimens is higher than the other classes of agents. In addition to generally good tolerability, the prolonged half-lives of both nevirapine and efavirenz may also partially compensate for the occasional missing of doses, which is a fact of life in the real world of clinical medicine. In fact, levels of nnRTIs may be detectable for up to 8 weeks following discontinuation of the agent.[1]

This prolonged half-life (with resulting significant exposure of the virus in vivo to subinhibitory levels of the antiretroviral) has been shown to result in the development of nnRTI-resistant virus in 60% of women who were treated with single dose nevirapine for prevention of mother-to-child transmission of HIV. A recently published study conducted in South Africa shows that giving 4-7 days of zidovudine plus lamivudine, following a single dose of nevirapine, reduced the risk of postnatal resistance development in the mother from 60% to 10%-12%.[2] While not formally studied in the routine clinical setting, based on these data, in order to prevent functional monotherapy with a nnRTI after discontinuing a HAART regimen, it seems prudent to continue the nucleosides for 4-7 days following discontinuation of the nnRTI in order to preserve this class of agents as a future option (hence, the recommendations made in the latest edition of the HHS antiretroviral therapy guidelines).

Another potentially, clinically significant piece of information is the recently developed evidence that certain host genetic polymorphisms (especially in the cytochrome P450 CYP2B6 isoform) may result in even slower rates of clearance. These polymorphisms appear to be more common in Hispanic and African American patients, and may increase both the likelihood and severity of nnRTI-related adverse effects in patients who have these polymorphisms.[3,4] At Santa Clara Valley Medical Center in San Jose (where I currently practice), approximately 60% of our HIV clinic population is Latino. It is certainly my impression (although not yet supported by hard numbers) that the incidence of efavirenz-induced skin rashes is significantly higher in Latino patients than it is in non-Latino Caucasians.

The nnRTIs remain important agents in our armamentarium. Some of this new information has real clinical relevance and will help us use these agents in a more optimal fashion. ■

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Treatment of Rheumatoid Arthritis and Risk of Serious Infection

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

Synopsis: *Anti-TNF antibody therapy of rheumatoid arthritis is associated with significantly increased risks of malignancies and of serious infections.*

Source: Bongartz T, et al. Anti-TNF Antibody Therapy in Rheumatoid Arthritis and the Risk of Serious Infections and Malignancies: Systematic Review and Meta-Analysis of Rare Harmful Effects in Randomized Controlled Trials. *JAMA*. 2006;295:2275-2285. Erratum in: *JAMA*. 2006;295:2482.

While the use of anti-TNF agents for the treatment of diseases such as rheumatoid arthritis (RA) is known to be associated with an increased risk of serious infections and malignancies, the degree of risk has remained undefined. Bongartz and colleagues evaluated 9 randomized, placebo-controlled trials in which one of the 2 US FDA licensed anti-TNF antibodies (infliximab and adalimumab) was administered for at least 12 weeks. The trials involved 3493 patients who received active therapy and 1512 who received placebo.

Anti-TNF therapy was associated with a pooled odds ration for the development of malignancy of 3.3 (95%; CI, 1.2-9.1), and were significantly more common in patients given higher doses of ant-TNF antibody. The number needed to harm (analogous to the number needed to treat, but dealing with adverse outcomes) was 154 for one additional malignancy within a treatment period of 6-12 months. The pooled odds ratio (anti-TNF relative to placebo) for serious infection, defined as one that required antimicrobial therapy and/or hospitalization, was 2.0 (95%; CI, 1.3-3.1). The number needed to harm was 59 within 3 to 12 months of treatment. Only 12 of 126 serious infections were identified as being granulomatous, including 10 cases of tuberculosis and one each of histoplasmosis and coccidioidomycosis.

COMMENTARY

Expression of the risk in terms of patient-years of exposure may have provided a more insightful and reliable result. These results, nonetheless, provide a more quantitative assessment of the risk of these two complications in patients with RA receiving one of 2 anti-TNF antibody therapies. Comparable information regarding the use of anti-TNF treatment of other diseases, such as Crohn's disease, would be welcome. While the development of granulomatous infections has been recognized in patients receiving these therapeutics, these accounted for only 9.5% of the cases of serious infection in this study. Thus, while the overall risk of such infections appears to be low, the relative risk remains poorly quantified.

Examination of a large database has identified a similar risk of serious infections in RA patients treated with anti-TNF therapy. Adjusted relative risks of serious infections in patients with RA in the German biologics register were 2.2 (95% CI, 0.9-5.4) for patients receiving etanercept and 2.1 (95% CI, 0.8-5.5) for patients receiving infliximab, when compared with controls.[1]

In contrast to these findings, assessment of another database has failed to identify a risk of pneumonia severe enough to require hospitalization in RA patients receiving anti-TNF therapy. Evaluation of almost 17,000 RA patients in the National Databank for Rheumatic Diseases who were evaluated semiannually for 3.5 years found no significant risk of hospitalization for pneumonia among infliximab or adalimumab recipients.[2] Methotrexate therapy was also not associated with increased risk of hospitalization for pneumonia, but prednisone use was, with a hazard ration of 1.7 (95% CI, 1.5-2.0). This risk of prednisone therapy was dose-related and, surprisingly, was present even in patients receiving < 5 mg prednisone daily (HR 1.7; 95% CI, 1.5-2.0). Leflunomide was also associated with increased risk. ■

References

1. Listing J, et al. Infections in Patients with Rheumatoid Arthritis Treated with Biologic Agents. *Arthritis Rheum*. 2005;52:3403-3412.

2. Wolfe F, et al. Treatment for Rheumatoid Arthritis and the Risk of Hospitalization for Pneumonia: Associations with Prednisone, Disease-Modifying Antirheumatic Drugs, and Anti-Tumor Necrosis Factor Therapy. *Arthritis Rheum*. 2006;54:628-634.

CME Questions

1. **Which of the follwoing is correct?**
   a. Posaconazole inhibits many cytochrome P450 enzymes, resulting in a large number of pharmacoinetic drug-drug interactions.
   b. Posaconazole absorption is markedly affected by gastric pH.
   c. Posaconazole has been reported to have efficacy in some patients with zygomycoses.
   d. Posaconazole can only be administered intravenously.

2. **Which of the follwoing is correct?**
   a. The HIV-1 non-nucleoside reverse transcriptase inhibitors (nnRTI) all have very short serum elimination half-lives, in the range of 40-60 minutes.
   b. When antireteroviral therapy consisting of a nnRTI-based regimen is discontinued, the nucleoside analogs should be continued for 4-7 days after the nnRTI is discontinued.
   c. Genetic polymorphisms play no role in determing the plasma clearance of nnRTIs.
   d. Resistance to nevirapine rarely occurs after single dose use of this drug alone to prevent mother-to-child HIV transmission.

3. **Which of the following is correnct?**
   a. Classical hospital-acquired MRSA commonly carry the Panton-Valentine leukocidin.
   b. USA300 and USA400 designate *S. aureus* strains considered to be community-acquired.
   c. USA300 strains of *S. aureus* are susceptible to beta-lactam antibiotics.

Answers: 1. (c); 2. (b); 3. (b)

CME Objectives

The objectives of *Infectious Disease Alert* are:

• To discuss diagnosis and treatment of infectious diseases;

• To present current data regarding use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;

• To present the latest information regarding the pros, cons, and cost-effectiveness of new and traditional diagnostic tests;

• To discuss new information regarding how infectious diseases (eg, AIDS) are transmitted and how such information can lead to the development of new therapy. ■

In Future Issues:

A New Rotavirus Vaccine

UPDATES

By Carol A. Kemper, MD, FACP

Updated Recommendations for Tdap in Adults

ACIP Recommendations, March 2, 2006; www.cdc.gov/nip/vaccine/Tdap

In October 2005, the American Committee on Immunization Practices provided provisional recommendations for the acellular pertussis vaccine (Tdap) (ADACELTM, Sanofi Pasteur) as a single booster dose for persons 11-64 years of age. Additional provisional recommendations were drafted in February, which include:

- Health Care Personnel with direct patient contact, especially those with direct contact with infants < 12 months of age, should receive a single booster dose of Tdap as soon as possible. Immediate vaccination should be encouraged by clinics and hospitals if the last dose of Td was at least 2 years previous; otherwise, HCWs should wait 2 years following their last dose of Td to receive a booster dose of Tdap.
- Adults who have or anticipate having contact with an infant < 12 months of age should receive a single booster dose of Tdap. This includes parents, uncles, aunts, grandparents, childcare providers, and tweener and teen sibs. Ideally, Tdap should be administered one month before contact with the infant. An interval of at least 2 years since the last dose of Td was administered is recommended, although a "shorter interval can be used."
- Pregnant and parturient women who received their last dose of Td < 10 years ago should receive Tdap after delivery.
- Pregnant women who received their last dose of Td > 10 years previous who require Td during pregnancy should receive Td in preference to Tdap.
- Pregnancy is not a contraindication to Tdap, but no formal recommendations for its use during pregnancy have been made.
- Adults who have an incomplete or unknown tetanus vaccination history should receive the series of 3 vaccinations: The preferred schedule is an initial dose of Tdap, followed by a dose of Td 4 weeks later, and a second dose of Td 6 to 12 months later; however, the dose of Tdap can be substituted for any one of the doses in the series.

These recommendations will become official following review and publication in the *MMWR*, although physicians, clinics, and hospitals should be prepared to implement them as soon as they are formalized. ■

Avian Influenza—Its Not the Birds

ProMED-mail post; www.promedmail.org; June 6, 2006.

This interesting tidbit, first published in the *Hindustan Times*, contradicts the presumption that recent outbreaks of Avian Influenza around the globe are due to migratory birds heading across western Asia and Europe. Recent molecular studies completed on virus strains from recent outbreaks occurring in India in February and March of this year identified 2 different viruses (with 3.5% divergence). Sequencing of the HA1 and HA2 genes showed that the viruses had likely originated in central and southern China—and not in regional migratory birds. Outbreaks occurred in 2 communities, Navapur and Jalgaon, which are located about 140 km apart in Maharashtra. The outbreak in Navapur was milder, predominately struck backyard poultry, and was relatively easier to control. The outbreak in Jalgaon occurred 12 days later, was more serious, struck larger poultry farms, and took longer to control. The 2 viruses subsequently spread to other areas, but have been controlled, and no new cases have been reported in 2 months.

Everyone assumed that given the regional proximity and timeframe, the outbreaks were due to the same virus from a common source. Recent data from Africa also suggest that migratory birds are not the source of infection in that country. Smuggled birds, poultry parts, and contaminated feed are hot suspects. ■

Plumes of Bacteria Surround Animal Facilities

Green CF, et al. *J Occup Environ Hyg*. 2006;3:9-15.

Bioaerosols have been found surrounding large animal facilities where bacteria routinely slough from the skin and cavities of pigs or cattle, and animals root around in feces and waste. Generally such facilities are open to the outdoors or have

large ventilation systems venting exhaust to the outdoors.

Levels of bacteria were evaluated in the air upwind at 25 meters and downwind 25 m, 50 m, 100 m, and 150 m from a large, confined animal feeding operation housing hogs. The buildings were only 4 years old. Samplers designed to detect colony forming units of bacteria were spaced at various locations from the facility, at various times of the day, on 4 separate dates in the summer of 2003 (somewhere in the Midwest). The samplers were designed with a cascade impactor containing 200 orifices, which allowed for the separation of non-respirable particles or respirable particles (< 8 micrometers in diameter). Wind direction, wind speed, and humidity were recorded. Interestingly, the more humid the environment, the bacteria absorb more water, become denser, and are less susceptible to the bactericidal effects of UV radiation. This being the Midwest in the summer, it was quite humid at 87-93%. (Thus, there are more bacteria floating around in hot, humid summer months.)

Upwind of the facility, the samplers detected an average of 82 CFU/m^3, of which 62% was respirable. Inside the facility, the culturable level of bacteria averaged 18,185 CFU/m^3, of which ~8500 CFU/m^3 was respirable. Downwind, there was an approximate 1-log drop in culturable bacteria at 25 m, and about a 2-log drop by 100 m. However, even at 150 m downwind, there were still 2.5 times more culturable bacteria organisms as found upwind of the facility. Surprisingly, *Staphylococcus aureus* represented about 76% of the bacteria cultured inside the facility, and was the dominant organism found downwind. Total coliforms represented ~7% of the culturable organisms. Not all of the bacteria cultured were identified.

The bacterial plumes downwind of large animal facilities may be a source of infection for humans, and may lead to spread of antibacterial resistance. Since the greatest exposure occurs inside the facility, Green and colleagues recommend the use of particle respirators when entering and working within the facility, and removing all clothing and showering prior to heading home at the end of the day. Ideally, ventilation systems should filter air released to the outdoors.

I am curious what the real risk to workers and populations living downwind of these facilities might be. It is notable that these experiments were conducted at least 5 months after the last application of manure to surrounding farmland, suggesting Green et al were concerned about a sufficient risk of contamination of these results from routine farm work. Outbreaks of infection have rarely occurred in barn dances and at county fairs, other venues for kicking up your heels and throwing shit around. Perhaps the concentration of animals in these larger facilities warrants additional precautions, but for someone who grew up around animals and who still routinely spreads manure around the garden, it's hard to get too worked up. After all, as one of my Infectious Disease attendings was fond of pointing out, you just have to imagine the world as covered by a thin layer of feces. ■

Risk of PML with Natalizumab

Yousry TA, et al. Evaluation of Patients Treated with Natalizumab for Progressive Multifocal Leukoencephalopathy. *N Engl J Med*. 2006;354:924-933.

Following reports of 3 cases of progressive multifocal leukoencephalopathy (PML) associated with the administration of natalizumab (Tysabri, Biogen Idec and Elan Pharmaceuticals), the FDA suspended the use of this agent in February 2005, much to the disappointment of many people with multiple sclerosis. Natalizumab is a recombinant humanized antibody directed tot he alpha-4 integrins, and had been approved for use in relapsing MS. These authors conducted a detailed review of patients receiving natalizumab in clinical trials for multiple sclerosis, Crohn's disease, or rheumatoid arthritis. Of 3417 patients enrolled in clinical trials, 3116 (91%) had more recently received the drug for a mean of 17.9 months, and were included in the evaluation. Of those patients with MS, 97% were evaluated within 3 months after discontinuing drug.

Forty-four patients developed a suspicious triad of progressive neurologic disease, abnormal MRI scan, and high levels of plasma JC DNA, and were examined by an expert panel. JC virus was not detected in the cerebrospinal fluid of 43 of these patients; the final patient developed progressive MS and was classified as indeterminate because follow-up data could not be obtained. After intensive review, only the original 3 cases of PML were confirmed, and no new cases of PML were identified. Based on these data, the risk of PML associated with the administration of natalizumab is estimated to be ~1/1000 (95% confidence interval, 0.2 to 2.8 per 1000). ■

Financial Disclosure:

Dr. Carol A. Kemper, MD, FACP, reports no financial relationship relevant to this field of study.

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Capping Drug Benefits—Will it Help Control Healthcare Costs?

Controlling healthcare costs is tricky business, and sometimes the best intentions have adverse outcomes, as pointed out in a new study in the June 1 *New England Journal of Medicine*. Financial caps on Medicare drug benefits were reviewed in a large group of Medicare + Choice beneficiaries in northern California (over 150,000 individuals) who had $1,000 annual drug benefit cap compared to those who did not have a limit on their drug benefits (41,904 individuals). The cap on pharmacy costs was effective at reducing pharmacy costs by 31% (95% CI, 29 to 33%), but the capped group had total healthcare costs that were only 1% lower overall (95% CI, -4 to 6%). Those with capped benefit were more likely to visit the emergency department (RR, 1.09 [1.04 to 1.14) and were also more likely to be hospitalized for non-elective admissions (RR, 1.13 [1.05 to 1.21]). The death rate was also higher in the capped group (RR, 1.22), with a difference of 0.68 per hundred person-years [0 .30 to 1.07]. Patients on chronic medications for hypertension, hyperlipidemia, or diabetes were more likely to be nonadherent to drug therapy if they had a capped benefit and, for each of those diagnoses, physiologic outcomes were worse for subjects with capped drug benefits, including systolic blood pressure over 140 mm Hg, serum LDL greater than 130, and a HbgA1c over 8 (respective risk ratios 1.05 [1.00 to 1.09], 1.13 [1.03 to 1.25], 1.23 [1.03 to 1.46]).

The authors conclude that a cap on drug benefits was associated with lower drug consumption and unfavorable clinical outcomes. In patients with chronic diseases, the benefit cap was associated with nonadherence to drug therapy and poorer clinical outcomes. Overall, any savings realized by a drug cap was offset by an increase in the rate of hospital admissions and emergency department visits (*N Engl J Med*. 2006;354:2349-2359). An accompanying editorial states, "Effective strategies for reducing the level and growth of spending will need to rely on tools other than high-deductible plans and limits on benefits" such as preventative care and dealing with the obesity epidemic, as well as improved information systems (*N Engl J Med*. 2006;354:2385-2386).

The STAR Trial (Tamoxifen and Raloxifene)

Results from the long awaited STAR trial (the National Surgical Adjuvant Breast and Bowel project Study of Tamoxifen and Raloxifene) have been published as an early release article on the *JAMA* website. This multicenter trial of nearly 20,000 women mean age 58.5 years with an increased 5-year breast cancer risk was designed to compare the incidence of invasive breast cancer, uterine cancer, noninvasive breast cancer, bone fractures, and thromboembolic events in those treated with oral tamoxifen 20 mg per day or raloxifene 60 mg per day over 5 years. Tamoxifen has been used to treat early and advanced breast cancer for more than 30 years, and has also been shown to reduce the risk of invasive and non-invasive breast cancer in women who were at increase risk.

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5416. E-mail: leslie.hamlin@thomson.com.

The STAR was designed to see if the second-generation selective estrogen receptor modulator (SERM) raloxifene would also be effective in this role. Raloxifene is currently approved for the prevention and treatment of postmenopausal osteoporosis. After 5 years, there were 163 cases of invasive breast cancer in the tamoxifen group and 168 in the raloxifene group (incidence, 4.30/1000 vs 4.41/1000; RR, 1.02; 95% CI, 0.82 to 1.28). Noninvasive breast cancers were slightly more common in the raloxifene group (1.52 vs 2.11 cases per 1000; RR, 1.40; 95% CI, 0.98 to 2.00). The rate of uterine cancer was lower in the raloxifene group (RR, 0.62; 95% CI, 0.35 to 1.08). No differences were found for other invasive cancers, ischemic heart disease, stroke, or osteoporotic fractures. Thromboembolic events were more common in the tamoxifen group (RR, 0.70 nickel and 95% CI, 0.54 to 0.91). Cataracts and cataract surgery were also less common in the raloxifene group. The overall death rate and the causes of death were the same in both groups.

The authors conclude that raloxifene is as effective as tamoxifen in reducing the risk of invasive breast cancer, and has a lower risk of thromboembolic events and cataracts but is associated with a nonsignificant higher risk of noninvasive breast cancer (*JAMA* early release, posted online June 5, 2006 jama.ama-assn.org). This study is important because although there was no control group, tamoxifen is proven to reduce breast cancer incidence and is approved for this indication, but with a higher incidence of endometrial cancer, thromboembolic events, DVT, and stroke. Previous studies have shown that raloxifene reduces the risk of estrogen receptor-positive invasive breast cancer by up to 66% over 8 years of treatment compared to placebo (MORE and CORE trials [*JNCI* 2004;96:1751-1761]). Quality-of-life issues have been a concern with SERMs, and was hoped that raloxifene would be the better tolerated than tamoxifen.

An accompanying article also published online focused on patient reported symptoms and quality of life issues in participants in the STAR trial. There was no significant differences between tamoxifen and raloxifene in patient reported outcomes for physical health, mental health, and depression, although the tamoxifen group reported better sexual function (age-adjusted repeated measure odds ratio 1.22%; 95% CI, 1.01 to 1.46). Women in the raloxifene group reported more musculoskeletal problems ($P = .002$), dyspareunia ($P < .001$), and weight gain ($P < .001$). Women in the tamoxifen group reported greater severity of gynecological problems ($P < .001$), vasomotor symptoms ($P < .001$), leg cramps ($P < .001$), and bladder control symptoms ($P < .001$). Overall, mean symptom severity was low among women in both groups (*JAMA*. early release, posted online June 5, 2006 jama.ama-assn.org).

An accompanying editorial points out that tamoxifen is rarely used as an agent for protection against breast cancer in women at risk, and it had been hoped that raloxifene would provide an alternative with equal efficacy for breast cancer and less adverse effects. Unfortunately, the STAR trial does not clearly demonstrate this. Both drugs are effective at preventing breast cancer but both carry increased risk of endometrial cancer and thromboembolic events. Raloxifene has an advantage of being approved for reduction of osteoporotic fractures, but whether this will convince primary care physicians to prescribe the drug for women at risk of breast cancer is unknown (*JAMA*. early release, posted online June 5, 2006 jama.ama-assn.org).

FDA Actions

Merck has received approval to market a vaccine to prevent human papilloma virus (HPV) infections. The vaccine received a priority review, and is seen as a major advance because of the association between HPV and cervical cancer. The vaccine targets HPV types 16 and 18, which are responsible for 70% of cervical cancers and types 6 and 11, which are the most common cause of genital warts. HPV vaccine is given in 3 separate IM injections over 6 months and will cost $120 per dose, $360 for the entire course. It is approved for use in females age 9 to 26. Merck will market the HPV vaccine as Gardisil.

Merck has also received approval to market its live zoster vaccine for the prevention of herpes zoster in individuals aged 60 and older. The vaccine, which is a live attenuated varicella-zoster virus, is given as a single-dose subcutaneous injection. The vaccine has been shown to significantly decrease the rate of varicella-zoster (shingles) in older adults and decrease the rate of postherpetic neuralgia in those who developed shingles despite the vaccine. Merck will market the live zoster vaccine as Zostavax. ■