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## INSIDE



# Global HIV Perspective Suggests a Long Way to Go

SPECIAL REPORT

*The challenge facing the global community is to immediately marshall sufficient resources to ensure rapid scale-up of life-saving prevention strategies.* ***— Global HIV Prevention Working Group 2003***

NOT LONG AGO AT ONE OF THE BIANNUAL WORLD AIDS CONFERences in Geneva, the topic of global HIV perspective was a colorful Bridging the Gap. Now 5 years later, the time has come to close that gap. To do that, a Global HIV Working Group has provided a region-by-region analysis to specify the gaps and recommend recovery measures. The major finding is that spending from all sources in 2002 was $3.8 billion short of what will be needed in 2005.

The findings of the working group are very, very sobering. But they believe the worst-case scenario is avoidable. The approach to make it avoidable consists of substrategies that are targeted at 5 global regions: sub-Saharan Africa, Asia and the Pacific, Eastern Europe and Central Asia, the Caribbean and Latin America, and North Africa and the Middle East.

It is beyond my scope to summarize all the regional strategies but here are some high points.

- More than 40 million people are infected with HIV worldwide. Epidemiologists grossly underestimated a decade ago how broadly the epidemic would spread.
- China and India lean on the brink of widespread pandemonium.
- In the former Soviet Union, many risk factors will threaten millions in those risk groups.
- In sub-Saharan Africa, only 6% of people have access to voluntary counseling and testing.
- In Asia and the Pacific, only 10% of drug infectors benefit from harm reduction.
- In Eastern Europe and Central Asia, drug infection is a widespread risk factor.
- In North Africa and the Middle East, there are extremely limited

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harm-reduction programs; only about 5% of sex workers have programs to help them and their clients avoid HIV.

The funding gap is huge and the discussion of the billions needed to curb the epidemic worldwide is a focus of the working group. In 2002, $1.9 billion was spent worldwide. A total of $5.7 billion is needed in 2005, so the gap is $3.8 million. More deplorable, in 2002 in Eastern Europe and Central Asia, only $23 million was spent. By 2005, $1.2 billion is needed. These figures are now confidence inspiring.

The concept of combination prevention pervades the strategies of the working group: volunteer counseling and testing (VCT), programs for injecting drug users, application of effective antiretroviral therapy, STD control, prevention of mother-to-child transmission, guaranteeing a safe blood supply, applying standard infection control practices, and policy reforms including legalization of the sale of syringes without a prescription and mandating condoms in brothels.

There are models of success in these measures to quell spread and minimize morbidity. In South Africa, condom distribution increased from 6 million in 1994 to 358 million in 2002. In Zimbabwe after peer-based HIV/AIDS education entered factories, there was a 34 percent reduction in new infections. In the Ivory Coast, the government has asked all businesses with more than 50 employees to establish committees for HIV/AIDS.

The Ugandan experience is unique in its success. President Yoweri Museveni since 1986 has led an unprecedented battle to curb HIV, and he did it by enlisting national stakeholders, including faith-based groups, to fight the disease. Who says that sexual mores cannot be altered in such countries? Look at the rates of sexually active 15 year olds—nearly 50% in 1991 in Uganda but less than 25% by 2001. Indeed, the result has been that prenatal rates have fallen in Kampala from 30% to 11.3% since 1992. Clearly, the empowerment of women and girls is a centerpiece in changing the HIV scenario in sub-Saharan Africa. Easier said than done in regions where women often cannot own or inherit their own land and where 80% contract the virus from their partners.

When we consider Asia and the Pacific we see success models: the 100% condom policy in Thailand, a multisectoral strategy in Cambodia, empowerment of sex workers in Bangladesh, and STD control in India. These successes are hardly sufficient. For starters, $1.48 billion additional annual spending will be needed in 2005. In this region also there is—a strange term evolves—a condom gap. There is a condom access gap, a condom promotion gap, a condom resource gap, and a condom effectiveness gap. Clearly, the world needs to help these countries emerge with much better condom policies.

In Latin America, Brazil is the only real success story. In Brazil, prevention as well as treatment initiatives have enabled the country to have a marked reduction in HIV. In another arena, Brazil has made it possible for up to 60% of intravenous drug users who participated in government harm-reduction programs to have their own injection equipment.

North Africa and the Middle East may be the most challenging region in terms of social acceptance of HIV programs. Witness that only $23 million in 2002 was spent on HIV/AIDS. Middle Eastern government would benefit from modeling programs in North African countries like Morocco, where there are 30 community-based projects. Morocco found how to use funds from the Global Fund to Fight AIDS, Tuberculosis and Malaria to scale up these programs.

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It was reassuring to see that the working group did not leave the need for research out of their analysis. Target areas will require "substantial new resources . . . for new prevention tools" to expand the work in vaccines, microbicides, antiretroviral therapies, female barrier methods, circumcision, and STD control.

The working group studied the source of funds to fight HIV. From where are all these billions to come? The developing countries themselves actually account for over 30%. Bilateral donors account for another 30%. The rest come from foundations, the United Nations, and the World Bank. It is interesting to look at select donor countries. Who does the most? Among developed countries and based on giving as a share of national revenues, the UK, Norway, Holland, and Canada outrank the United States. France is last. The working group met as the current Bush Administration in the United States declared that the United States would spend $10 billion to $15 billion over the next 5 years, a seemingly huge number compared to the $514 million it produced in 2002. Yet, even though the figure for prevention needs is $5.7 billion in 2005, the figure for care and support is $5.5—figures that rise to $6.6 billion and $8.7 billion, respectively, by 2007. Clearly billions of currency will be needed beyond the US commitment.

The final recommendations of the working group run the lines that have been summarized above and include:

- increased global spending;
- prevention scale up;
- immediate scale up of tactics already proven effective;
- emphasis on new initiatives to reflect a continuum of services;
- dedication by donor countries to partner with multilateral agencies to build "human capacity and infrastructure;"
- policy reforms to address social and economic conditions that produce vulnerability to HIV/AIDS;
- research into new prevention strategies; and
- efforts to understand spending in low- and middle-income countries.

Ironically, just as the HIV Global Workshop findings were being published in a journal for political analysis, the HIV Medicine Association of the Infectious Diseases Society of America published a group of 3 papers to address this other important issue.[1] Vermund, on behalf of the Infectious Disease Society of America (IDSA) and the HIV Medicine Association, has written a Consensus Statement. A group of scientists led by a Tufts-New England Medical Center group with academic connections in South Africa wrote a second article of how to set the research agenda. A third group from the Macfarlane Burnet Institute in Melbourne wrote the last article on monitoring HIV infection in resource-constrained countries.

In the last article from Australia, the Macfarlane Burnet researchers present several low-cost methods to monitor CD4+ lymphocytes and viral loads. As much money as is needed for treatment of HIV-infected patients in poor countries, very little has been discussed about evaluation of therapies. For example, a test called a Cavidi assay is a simple way to measure viral load. One mL of plasma is needed but can be diluted for testing.

Several bead methods (the Coulter Manual CD4 Count kit and the Dynabead T4-T8 systems) approximate flow cytometry for helper-cell quantitation. Other low-cost options are being studied for CD4+ lymphocyte determination. These systems go by names like the Capcelia CD4/CD8 whole blood assay and the TRAx CD4 Test Kit, both of which work with an EIA format. What the Macfarlane Burnet study doesn't tell us is what the savings need to be with less expensive methods to make them feasible.

The Tufts group, led by David M. Kent, came up with an agenda that sounds much like that in the developed world: development of guidelines, monitoring for toxicity and treatment failure, and determination of drug failure and viral resistance. Factors that affect adherence are important in poor countries too. Kent lists the classic issues like pill burden, poor doctor/health-care provider relationship, youth and substance abuse—all clearly important for the standard Western patient as well as a poor African. What Kent doesn't discuss are the factors like the number of miles patients have to walk to get medication, cost of treating comorbid conditions, and STD management and prevention.

The Consensus Statement refers to 87 articles. What emerges are 8 concepts that could be applied to trial designs. Concept 11, in particular, seemed exciting to me. It asks the question of whether the use of ART alters how the community used counseling and testing centers or alters the prevalence of unsafe sex. The consensus advises the development of low-cost methods that the Australian paper discussed. Another concept, No. 10, was imaginative. In this proposed study, clinical signs would be used instead of routine surrogates for quality care. And who said physical diagnosis was dead? It would just be too ironic if truly careful history and physical diagnosis in poor countries could help estimate the degree of HIV-induced immune damage.

## COMMENT BY JOSEPH F. JOHN, Jr., MD

Momentous is how I find the scope and vision of this

report. What a great contribution these workers and thinkers have given a world at the edge of an HIV abyss! Humans are notorious for their capacity for denial, and we have denied the extent and threat of the HIV epidemic from its outset. This publication in *Foreign Affairs*[2] should be parlayed as soon as possible into the medical literature. Had it not been for my occasional foray into the literature of international relations, I would have missed this report, also.

Well, here it is, and the question becomes, "What next?" What next indeed since the report misses giving the world a springboard to the massive infusion of money that is need to give us a chance to avoid the worst-case scenario. The enlightened initiative by the Bush administration is a start, but I find myself asking just how to create what is a new flood of dollars to fund global HIV—its prevention (that is best), its care (that is human), and its research (that is necessary) over the next 4 years.

If we do not follow the recommendations of the working group, in 4 years the world may look quite different. Those countries like Uganda in sub-Saharan Africa may start to benefit from their success not only in material but also in political fashion. Larger countries like China may find—like Africa found in the 1980s—that its workforce is decimated by HIV and that the cost of treating victims and the cost of lost work dismantles the Beijing economic miracle. The types of threats emerging to developed countries that a further dismemberment of the Third World by HIV would produce are too horrible to envision. Concepts like world order and global nationhood would certainly suffer.

What are we missing? Bridging the gap was stage one. That bridge, though shaky, has grown over the last decade, north south and east west. Closing the gap is next, making access to HIV prevention a reality for billions of people who lack it and budgeting enough new resources to make a difference felt.

In my opinion, the next phase would be the creation of financing mechanisms to pay for the scope of changes that the Global HIV Prevention Working Group has presented here. The financing cannot simply come out of existing federal budgets. New instruments and concepts need to be presented. For example, perhaps the model of state financing in the United States for Medicaid, AIDS Drugs Utilization Programs (ADUP), and creation of new medical programs through penny taxes on items like soda pop could be initiated. Maybe some of a national lottery proceeds could contribute sizably to the need. Maybe some of you readers have better ideas.

Our leaders need to understand the real and present danger of global HIV/AIDS and the impossibility of providing adequate support with current funding levels. The alternatives to missing the current opportunity for meaningful funding remain abhorrent to the medical community.

We in the IDSA should be proud of our society for addressing the issue of global HIV/AIDS and how to really help poor countries. Thanks to Vermund for closing the gap on what has become the global misery of HIV disease. There is a comprehensive report of the Consensus Statement written by Chris Collins available at http://www.idsociety.org/ME/HIVConferenceReport-Final.pdf. ■

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## *Special Feature*

# Neurotoxicity of Carbapenems

*By Jessica C. Song, MA, PharmD*

Carbapenems are a class of β-lactam antibiotics that offer broad-spectrum therapy for patients with a variety of infections, including skin/skin structure, intra-abdominal, lower respiratory tract, meningitis, urinary tract, and bone/joint infections.1-3 Since their introduction in the 1980s, there have been 3 carbapenems, imipenem/cilastatin (Primaxin IV®), meropenem (Merrem IV®), and ertapenem (Invanz®), approved by the Food and Drug Administration (FDA) for clinical use in the United States.

Soon after its introduction to clinical practice, imipenem/cilastatin was recognized to have a higher propensity to produce seizures compared with other β-lactam antibiotics, with one review of 2516 patients reporting an incidence of 1.5%.[4,5] However, subsequent reports showed a lower incidence of seizure, as the risk factors for this complication have been recognized by health care workers.[4-5] This article will review the mechanism of seizure provocation by carbapenems; review the incidence of seizures associated with carbapenems; review key risk factors for carbapenem-induced

seizures; and provide dosing recommendations for carbapenems in renally impaired patients.

## Mechanism of Seizure Provocation by Carbapenems

Carbapenem-induced convulsions appear to arise from interference with the inhibitory transmitter function induced by gamma-aminobutyric acid (GABA), thereby resulting in reduced inhibition of epileptic discharges.[4,6] One study showed that the concentration of meropenem required to inhibit 50% of GABA binding was 20-fold higher than that of imipenem.[7] Other proposed mechanisms of carbapenem-induced seizure may be related to its action on the α-amino-3-hydroxy-5-methyl-isoxazolepropionate (AMPA) and N-methyl-D-aspartate (NMDA) receptor complexes and the basicity of the amino functional group of the C-2 side chain (imipenem, meropenem, and ertapenem have different side chains attached to C-2). Differences in the C-2 side chain may result in varying binding affinities for GABA receptors in the central nervous system (CNS).[8]

## Key Risk Factors/General Features of Carbapenem-Induced Seizures

The seizure types described for patients treated with carbapenems have varied widely and include tonic-clonic generalized, focal, and grand mal, with tonic-clonic generalized seizure representing the most frequently occurring type.[7-19] The average time of seizure onset for imipenem was 7 days after the start of therapy (range, 1-29 days) in a report by Calandra and associates that evaluated data from phase III dose-ranging studies of imipenem (n = 1754).[11] Less information on the time of seizure onset is available for meropenem and ertapenem. Klugman and colleagues found that seizures were most likely to occur 3-4 days after the start of meropenem treatment in children with bacterial meningitis (n = 190).[7] Two patients experienced seizures 10 days after the start of ertapenem treatment in trials evaluating the efficacy of this drug for the treatment of community-acquired pneumonia (n = 478).[13,14]

Calandra et al found that renal insufficiency, *Pseudomonas* infection, dosages in excess of those recommended by the manufacturer, and CNS lesions (or history of seizures) increased the risk of seizures in patients treated with imipenem.[11] However, imipenem-induced seizures can occur in patients receiving appropriate doses (dose adjusted for renal insufficiency), as shown by Eng and associates, who reported 5 cases of imipenem-induced seizures.[9] Of note, quinolones, theophylline, metronidazole, ganciclovir, and cyclosporine may lower the threshold for seizures in patients concomitantly treated with imipenem.[5] In addition, other pharmacologic agents known to cause seizures (*see Table 1*) should be used with caution when combined with carbapenems.[20-22]

## Incidence of Seizures

The incidences of seizure associated with imipenem, meropenem, and ertapenem use are reported by the manufacturers to be 0.4%, 0.7%, and 0.5%, respectively.[1-3] However, Pestotnik and colleagues showed that appropriate dosing of imipenem resulted in a much lower frequency of seizures in a study of 1951 patients than previously reported in the literature. The frequency of seizures in their patients was 0.2%.[10] Moreover, safety data from clinical trials of ertapenem published after the prescribing information for this drug became available revealed a seizure incidence of 0.18%.[13-19]

Continued on page 187

**Table 1**

**Drugs Reported to Cause Seizures**

| Drug Class | Drug(s) |
|---|---|
| Antivirals | amantadine, rimantadine, acyclovir, ganciclovir, foscarnet |
| Beta-lactams | oxacillin, penicillin, piperacillin/tazobactam, cephalosporins |
| Quinolones | nalidixic acid, ciprofloxacin, levofloxacin, ofloxacin |
| Anticholinesterase agents | organophosphates, physostigmine, neostigmine |
| Antidepressants | amitriptyline, venlafaxine, fluoxetine, fluvoxamine, sertraline, bupropion |
| Antipsychotics | clozapine, chlorpromazine, haloperidol, quetiapine, risperidone, thioridazine |
| Anxiolytics | benzodiazepines (with abrupt withdrawal) |
| Beta-blockers | propranolol |
| Chemotherapy agents | etoposide, ifosfamide, cisplatinum, L-asparaginase, chlorambucil |
| Antimycobacterial agents | isoniazid, cycloserine |
| General anesthetics | ketamine, halothane, althesin, enflurane |
| Narcotic analgesics | fentanyl, meperidine, pentazocine, propoxyphene |
| Miscellaneous agents | baclofen, cimetidine, cocaine, cyclosporine, ergonovine, folic acid, levodopa, metronidazole, oxytocin, prednisone (with hypocalcemia), salicylates (in overdose), theophylline, metolazone, vitamin K oxide, zolpidem |

**Table 2**

## Safety Data from Clinical Trials of Ertapenem (n = 1644 Ertapenem-Treated Patients)[13-19]

| Reference | Drugs/Patient Population | Renal Dose Adjustment | Number of Patients Experiencing Seizures | Comments |
|---|---|---|---|---|
| Ortiz-Ruiz G, et al. (2002)[13] | ERT 1g IV q.d.<br>CTX 1g IV q.d.<br>Adult CAP patients (n = 498) | Patients with CrCl < 30 mL/min/1.73 $m^2$ received ERT 500 mg IV q.d. | 1/242 ERT-treated patients (0.41%) experienced a tonic-clonic seizure on day 10 of treatment | Patient was 89-year-old woman; recovered without receiving antiseizure medication. Electroencephalograph on study day 53 normal |
| Vetter N, et al. (2002)[14] | ERT 1g IV or IM q.d.<br>CTX 1g IV or IM q.d.<br>Adult CAP patients (n = 359) | Patients with CrCl < 30 mL/min/1.73 $m^2$ received ERT 500 mg IV q.d. Patients requiring HD or PD were excluded | 1/236 ERT-treated patients (0.42%) experienced 2 seizures on day 10 of treatment. Of note, on study day 9, dose of ERT increased to 2g IV q.d. due to suboptimal response to ERT 1g IV q.d. ERT D/C'd and patient recovered without sequelae | Patient was 76-year-old man with epilepsy and history of resected frontal meningioma. Valproic acid therapy stopped on day 5 due to tremors, and phenytoin started. Phenytoin level subtherapeutic on day 10 |
| Solomkin JS, et al. (2003)[15] | ERT 1g IV q.d.<br>P/T 3.375g IV q.6h.<br>Adult patients with complicated intra-abdominal infections (n = 633) | Patients with CrCl ≤ 30 mL/min or undergoing dialysis were excluded (type not specified). P/T dose adjusted according to PI | 1/323 ERT-treated patients (0.31%) experienced a grand-mal seizure. 1/310 P/T-treated patients (0.32%) experienced a seizure | No details on the seizure cases were provided (time of onset, age of patients, past medical history, etc) |
| Graham DR, et al. (2002)[16] | ERT 1g IV q.d.<br>P/T 3.375g IV q.6h.<br>Adult patients with complicated skin and skin/structure infections (n = 529) | Patients requiring HD or PD were excluded from the study | None of the patients experienced seizures | |
| Tomera KM, et al. (2002)[17] | ERT 1g IV q.d.<br>CTX 1g IV q.d.<br>Adult patients with complicated UTI (n = 582) | Patients with CrCl ≤ 30 mL/min or undergoing HD/PD were excluded | None of the patients experienced seizures | |
| Yellin AE, et al. (2002)[18] | ERT 1g IV q.d.<br>ERT 1.5g IV q.d.<br>CTX 2g IV q.d. + MET 500mg IV q.8h.<br>Adult patients with complicated intra-abdominal infections (n = 158) | | None of the patients experienced seizures | |
| Jimenez-Cruz F, et al. (2002)[19] | ERT 1g IV q.d.<br>CTX 1g IV q.d.<br>Adult patients with complicated UTI (n = 258) | Patients with CrCl < 30 mL/min received ERT 500 mg IV q.d. Patients requiring HD or PD were excluded | None of the patients experienced seizures | |

CAP = community acquired pneumonia; CTX = ceftriaxone; ERT = ertapenem; HD = hemodialysis; MET = metronidazole; PD = peritoneal dialysis; PI = prescribing information; P/T = piperacillin/tazobactam; UTI = urinary tract infection.

**Table 3**

**SCVMC Guide to Adult Antimicrobial Therapy 2003**

| Drug | CrCl > 50 mL/min | CrCl 10-50 mL/min | CrCl < 10 mL/min |
|---|---|---|---|
| Imipenem[a-c] | 500 mg IV q.6h. | 500 mg IV q.8-12h | 250-500 mg IV q.12h. |
| Ertapenem[a,b,d] | 1 g IV q.24h. | CrCl ≤ 30 mL/min: 500 mg IV q.24h. | 500 mg IV q.24h. |
| Meropenem[a,e] | 1g IV q.8h. | CrCl 26-50 mL/min: 1g IV q.12h. CrCl 10-25 mL/min: 500 mg IV q.12h. | 500 mg IV q.24h. |

[a]May be removed by hemodialysis, recommend to schedule dose after dialysis

[b]CrCl is normalized to mL/min/1.73 $m^2$ or mL/min/72 kg

[c]Sanford Guide (2003) recommends giving imipenem after hemodialysis and the recommended CAPD dose is 125-250 mg IV q 12h

[d]For patients on hemodialysis: If ertapenem is administered (500 mg IV) at least 6 hours prior to dialysis, no supplementary dose is necessary. However, if ertapenem (500 mg IV) is administered within 6 hours prior to hemodialysis, a supplementary dose of 150 mg is recommended after the dialysis session. No data on patients undergoing peritoneal dialysis or hemofiltration (continuous arteriovenous or venous-venous) is available.

[e]Sanford Guide (2003) recommends giving meropenem after hemodialysis and the recommended CAPD dose is 500 mg IV q 24h.

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Table 2 summarizes the key points of the ertapenem studies.

Cunha and associates[8] compared the safety data of meropenem with other antibiotics (including imipenem, ceftazidime ± tobramycin or amikacin, cefotaxime + metronidazole, ceftriaxone + amikacin, or clindamycin + gentamicin or tobramycin) from a database of 26 phase III studies. The frequency of seizures was 0.7% for both meropenem and imipenem, compared with a frequency of 0.2% for cephalosporin-treated patients. To date, no clinical trial comparing the incidence of seizures induced by ertapenem with that of imipenem or meropenem has been published.

## Carbapenem Dose Adjustment for Renal Impairment

Table 3 summarizes the dose adjustments required for renally impaired patients receiving carbapenems at Santa Clara Valley Medical Center.

## Conclusion

In summary, all carbapenems are potentially neurotoxic and may cause seizures. However, seizures have not been a major problem except for situations when dosing exceeds recommended guidelines. Therefore, it is important to individualize carbapenem regimens for patients' renal function and to use these drugs with caution in patients receiving other drugs known to cause seizures or in patients with a history of CNS disorders or seizures. ■

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# Azithromycin as Single-Drug Therapy for Community-Acquired Pneumonia

ABSTRACT & COMMENTARY

***Synopsis:*** *Azithromycin is an effective, single-drug therapy for mild-to-moderate community-acquired pneumonia.*

**Source:** Feldman RB, et al. Azithromycin monotherapy for patients hospitalized with community-acquired pneumonia. *Arch Intern Med*. 2003;163:1718-1726.

TO DETERMINE WHETHER AZITHROMYCIN ALONE (without an additional ß-lactam antibacterial agent) is an effective treatment for patients with mild-to-moderately severe community-acquired pneumonia, Feldman and associates performed this retrospective cohort study of patients hospitalized at the West Los Angeles Healthcare Center over a 3.5-year period ending in mid-2001.

Eligible patients included those admitted to the general medical ward with clinical symptoms and signs of pneumonia, as well as radiographic demonstration of pulmonary infiltrates that were not previously present and that appeared within the first 2 days of hospitalization. Excluded were patients immunosuppressed by virtue of HIV infection, neutropenia, malignancy, or medication, as well as patients with hospital-acquired pneumonia, mycobacterial infection, or other explanations for the pulmonary infiltrate. Patients transferred from other hospitals or hospitalized within the previous 2 weeks were also excluded. Patients who were initially admitted to the general medical ward but then transferred to the intensive care unit within 24 hours were assumed to have severe pneumonia and to have been misclassified for the purposes of this study and were not included in the analysis.

A total of 442 patients' records remained after the exclusion criteria were applied. The majority were white, but approximately 30% were black and 10% were Hispanic. Average age was mid-to-late 60s. As expected in a VA patient series, about 95% were male, and nearly half were current smokers.

All patients were assigned a pneumonia severity index score,[1] a scoring system using age, coexisting medical conditions, abnormalities of mentation and vital signs upon admission to the hospital, and laboratory and radiographic findings. Statistically, patients in classes I and II have a predicted mortality of < 1%, while patients in class III have a predicted mortality of < 4%. Patients in classes IV and V have predicted probability of death of 4-10% and > 10%, respectively.

In this VA study, patients were grouped according to the initial antibiotic regimen received (excluding the first dose of antibiotic usually given in the emergency department). During the time of this study, recommended empiric therapy for patients with less-than-severe pneumonia was azithromycin as monotherapy. As a result, the largest group of patients (221—exactly half) received azithromycin initially; 29% received an alternate American Thoracic Society (ATS)-recommended regimen,[2] and 21% received an initial regimen different from the ATS-recommended guidelines. (Inexplicably, identities of antibiotics received by these non-azithromycin groups were not specified.)

The groups were comparable with respect to age and other demographic features. Pneumonia severity index scores among the 3 groups were similar.

Patients receiving azithromycin as the initial therapy fulfilled early discharge criteria sooner and length of stay was shorter than in patients in the other 2 groups. Need to transfer to the intensive care unit and in-hospital mortality—markers for progressive disease—were similar in all 3 groups.

*Streptococcus pneumoniae* was the most frequent presumed pathogen, comprising 41% of all isolates from sputum, other respiratory tract sites, and blood. Eighty percent of *S pneumoniae* isolates were erythromycin-susceptible. Outcomes were similar irrespective of erythromycin susceptibility among these isolates.

In summary, Feldman et al concluded that azithromycin as single-drug therapy for hospitalized patients with mild-to-moderate community-acquired pneumonia was equivalent to other ATS-recommended regimens.

## COMMENT BY JERRY D. SMILACK, MD

The literature on community-acquired pneumonia is vast. A quick Medline search found 985 articles on the subject in the English language medical literature over the last 5 years. Comparison of results is confounded by such methodologic differences as definitions of pneumo-

nia, case entry criteria, measurement of outcome, institutional differences in quality of care, etc. Efforts to standardize medical therapy have advanced considerably in recent years by publication of guidelines by the Infectious Diseases Society of America,[3] the American Thoracic Society,[2] the Canadian Infectious Diseases Society and Canadian Thoracic Society,[4] and the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group.[5] In general, for the hospitalized patient not requiring intensive care, most guidelines call for a ß-lactam, such as a third-generation cephalosporin or a ß-lactam/ß-lactamase inhibitor combination, plus a macrolide, or monotherapy with an enhanced-activity fluoroquinolone. The ATS guidelines, on the other hand, offer several options for patients with no underlying cardiopulmonary disease or modifying risk factors: azithromycin or an antipneumococcal fluoroquinolone as monotherapy, or a combination of doxycycline and a ß-lactam.

The present VA study retrospectively analyzed the outcomes of patients admitted with a diagnosis of community-acquired pneumonia. Because hospital routine at the time called for azithromycin monotherapy, half of the patients received that regimen from the outset. However, since treating physicians were apparently not compelled to follow recommended treatment guidelines, other regimens were also used.

Feldman et al found that patients treated with azithromycin generally fared as well as patients treated with other ATS-recommended and nonrecommended regimens. They had shorter lengths of stay, met clinical stability and discharge criteria more quickly, and had equal or lesser need to return to the emergency room or require readmission following hospital discharge than the comparator patient groups.

Although Feldman et al state that the treatment groups were almost entirely comparable, it appears to this reviewer that patients treated with azithromycin alone were "less sick" overall than those in the group receiving other ATS-recommended regimens or those treated with non-ATS recommended regimens. For example, the azithromycin group had lower pneumonia severity scores (although differences just escaped statistical significance); over 55% were in classes I and II, whereas 43% and 42% of patients in the other 2 treatment groups were in these lowest severity index classes. Additional support for the notion that the azithromycin group might not have appeared to the treating physicians to be as ill was the fact that patients in this group were less likely to have blood cultures drawn and to have arterial $O_2$ assessment performed upon admission. In addition, patients admitted from a skilled nursing facility were more likely to receive non-ATS-recommended treatment, perhaps because the treating physicians felt they may be "sicker." Questions about comparability of the groups weaken the conclusions of this study.

Other randomized studies, both retrospective[6] and prospective,[7] have shown similar results even though details concerning methods of selection, analysis, and outcome were somewhat different. After reviewing all of these studies, one could conclude that patients hospitalized for community-acquired pneumonia, particularly in the absence of such significant risk factors as serious underlying disease, advanced age, recent nursing home exposure, and recent hospitalization or antibiotic exposure, can safely and effectively be treated with azithromycin as monotherapy. Of course, this begs the question: Could these patients be treated as outpatients? If so, all of the expert guidelines agree that either a macrolide or doxycycline, among other alternatives, is appropriate therapy. ■

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# Community-Acquired Methicillin-Resistant *Staphylococcus aureus*

ABSTRACT & COMMENTARY


***Synopsis:*** Staphylococcus aureus *is a versatile enemy. It is spreading in the community, as well as in the hospital, with increasing resistance to antibiotics. Its armamentarium now includes not only resistance to methicillin and vancomycin but also means of spread and pathogenic mechanisms we clearly need to know more about—and soon.*



**Source:** *Infect Control Hosp Epidemiol*. 2003;24:397-458, 460.


THE JUNE 2003 ISSUE OF *Infection Control and Hospital Epidemiology* contains a series of articles on community-onset infections due to methicillin-resis-

tant *Staphylococcus aureus* (MRSA). Although most of the studies are several years old, there are some important points to be made and ideas for future research. It is important to recognize that there has already been a lot of work done with 20,000 articles on MRSA referenced in Medline. It should also be noted that even the NNIS study indicates more than half of the nosocomial *S aureus* infections acquired in the hospital are due to methicillin strains.

The Baggett[1] study describes an outbreak of community MRSA (COMRSA) in rural southwest Alaska, where 240 cases are reported from 1999 to 2000. Eighty percent of the *S aureus* infections were reported as resistant, which was a dramatic increase from several years before. The infections caused were almost all skin and soft-tissue and were more likely in men. Only 19% of patients were hospitalized. Of the strains, it was remarkable that so many were susceptible to non-beta-lactam antibiotics. Virtually all strain were susceptible to tetracycline, rifampin, trimethoprim-sulfa, and ciprofloxacin. Seventy percent were reported as susceptible to clindamycin, although only 30% were susceptible to erythromycin.

Seal[2] reported an increase in MRSA from 13% in 1986 to 28% in 2000 of the *S aureus* strains isolated at the University of Chicago medical complex. This was accompanied by a comparable rate of increase in the resistance to macrolides, as well as ciprofloxacin, but not to gentamicin or trimethoprim-sulfa. The study also found the methicillin-resistant strains to be more resistant to other antibiotics than the methicillin-susceptible one.

Jernigan[3] cultured patients admitted to Grady Hospital in Atlanta and found essentially all could be traced to prior hospitalizations, but his study was done in 1998.

Fishbain[4] looked for acquisition of MRSA among patients hospitalized at Tripler Army Medial center in Honolulu and found only 1.7%, but the study period was short and the percent of admissions sampled low. Acquisition seemed to correlate with time in the hospital as well as the intensive care unit.

Calfee[5] sampled family members of patients with MRSA who returned home after being hospitalized in Charlottesville, Va. They found about 15% at least colonized, but the follow-up times were variable, and it was unclear whether the hospitalized patients were the source or not.

Campbell[6] sampled 62 children in Louisville, Ky, and found the hospital and community-onset strains the same by antibiogram testing.

Johnson[7] studied 26 COMRSA strains in Detroit and found there to be at least 3 clones by pulse-field electrophoresis.

Tambyah[8] found virtually all strains of MRSA isolated within 48 hours of admission in a large teaching hospital in Singapore in 1998 were health care-associated and resistant to clindamycin, gentamicin, and trimethoprim-sulfa.

Kenner[9] cultured 404 patients seen in the outpatient clinics at Tripler Army Medical Center and found 38% colonized with *S aureus* and 2% with MRSA. Risk factors for MRSA included male gender and recent hospital care. COMRSA strains were more likely to be susceptible to oral antibiotics.

Jernigan[10] also studied 494 patients in an outpatient clinic in Atlanta and found 24.7% colonized with *S aureus* and 3% with MRSA, but the survey was done in 1997-98. The MRSA strains were associated with prior hospitalization and chronic diseases.

Said-Salim[11] reviewed the available literature on COMRSA stains and found evidence of at least 30 geographically distinct strains.

Scarnato[12] found up to 3.3% of staff in a geriatric facility in France were at least colonized with MRSA and virtually all of them were nurses or nursing assistants.

Eckhardt[13] found evidence of spread of MRSA in a neonatal intensive care unit in Atlanta.

## COMMENT BY ALAN D. TICE, MD, FACP

It is clear from the reports in this issue that *S aureus* is a formidable and versatile microbe. It has successfully eluded many of our best antimicrobials and can carry a tool kit that makes it a deadly pathogen in many respects.[14]

The concept of community-acquired or community-onset strains is a difficult yet important one as it has been thought that most strains are bred in the hospital and may not survive long in the community. It would be nice if we could control the acquisition and spread of these strains in the hospital, but such is not the case. It is clear from the articles that strains can be carried home to set up a focus there—and then be brought back into the hospital—as was the case a few years ago.

What is also apparent is that there are distinct strains, or more likely sets of strains, of MRSA in the community that are not hospital acquired but may cause serious infections as well. They seem to be replacing the methicillin-susceptible strains and possibly some of the hospital-acquired strains as well, but it is not clear why. The origin of these strains is also uncertain, although there is talk of a Samoan strain.[15] Many also appear surprisingly susceptible to oral antibiotics, although their clinical value has not been adequately demonstrated. They pro-

duce primarily skin and soft-tissue infections that are eventually self-limited, although the sores and boils may be extensive and painful at times. It is interesting to see how many patients survive and even recover even though they have been on antibiotics that appear completely inactive by in vitro testing.

The definition of which MRSA strains are "health-care associated" and which are not is also problematic. A 48-hour window after admission does not help in many instances, as health care is so pervasive in our society. Most people are exposed to the medical care industry on a frequent basis—either through their own care or by employment or through other people close to them who are.

The classification of a strain of *S aureus* as MRSA vs MSSA is also limited, as it is only one component of this complex organism. Toxin production, survival factors, growth factors, and other pathogenic mechanisms may be more important in many instances. This may be even more important with the advent of vancomycin resistance.

It is obvious that *S aureus* is a major threat and that it is growing. We need a variety of means to respond. Means of more rapid identification and infection control are critical. Clinical trials of the older oral antibiotics are also urgently needed, although there are few pharmaceutical companies interested in supporting them. Understanding of how it causes disease and how to combat the processes would also be helpful. A vaccine would be great, but it is not on the near horizon.[16] ■

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**9. In a recent study concerning hospitalized patients with community-acquired pneumonia treated with azithromycin as a single-drug therapy, which of the following was *not* true?**

a. Patients had shorter lengths of stay.
b. Patients required readmission to the hospital more often.
c. Patients met criteria for discharge sooner.
d. In-hospital mortality was similar among the patient groups.

**Answer:** 9(b)

## 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: Christie Messina—Reader Questions, *Infectious Disease Alert*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. ■

## In Future Issues:

**Corticosteroids for Kawasaki Disease**

# UPDATES

By Carol A. Kemper, MD, FACP

## Transfusion-Associated WNV

**Source:** *Eurosurveillance Weekly*. 2003; 7(34).

THE CURRENT YEAR HAS SEEN THE reemergence of West Nile Virus in the United States, with further encroachment into Canada and Mexico, and an extension of the transmission season. In addition to the usual mode of transmission, human infection has been caused by percutaneous exposure to infected tissue or blood products, transplantation of infected organs, and via breast-feeding and the transplacental route. As of March 2003, the CDC had accumulated reports of 61 possible cases of transfusion-associated WNV infection in the United States. Of these, tests confirmed that at least 14 donors had resulted in 21 cases. The problem is that 5 of these 14 donors had no clue they were ill, and several of the remaining donors developed symptoms only after their donation. This suggests that individuals with subclinical infection may have sufficient levels of viremia to cause clinically significant disease in a susceptible host. Obviously, screening based on the presence of self-reported symptoms is not sufficient. Since July 1, 2003, using a newly developed nucleic acid test (NAT), the United States has been screening all potential blood donors for WNV. Thus far, a single positive donor has been detected.

The possibility of transfusion-associated WNV infection has also raised concerns in the United Kingdom and Europe, which presently do not screen blood donors, some of whom may have recently visited endemic areas. Ireland alone estimates that up to 10% of their donors may visit Canada or the United States during the summer months. As a result, the United Kingdom and many European countries have adopted various deferral policies, whereby travelers to high-risk areas are asked to defer donation for ~ 28 days. These policies are putting an additional squeeze on the pool of blood supplies in these countries, already limited by the presence of bovine spongiform encephalopathy in some areas. ■

*Audio Conference*

## Seasonale: A Revolutionary Contraceptive

EXTENDED HORMONAL CONTRACEPTION is drawing dramatic attention due to the desire of many women to reduce or eliminate the number of withdrawal bleeds associated with current birth control methods. The first extended-use oral contraceptive, Seasonale, was just approved by the FDA and is expected to have an enormous effect on family planners and OB/GYNs. This new therapy will reduce the number of periods a woman has to 4 a year. Researchers also are looking at extended use of the NuvaRing contraceptive vaginal ring and the Evra transdermal contraceptive patch.

To bring you up to speed with the exciting changes in this field, Thomson American Health Consultants offers ***Extended-use Contraception: What You Should Know About Seasonale and Other Options***, an audio conference on October 9, from 2-3 p.m., ET.

"I consider [Seasonale] to be the most important change in hormonal contraception since birth control pills initially became available," says Robert Hatcher, MD, MPH, editor of *Contraceptive Technology Update*, and professor of gynecology and obstetrics at Emory University.

Presenters will be Hatcher, who will act as moderator; Lee Shulman, MD, professor of OB/GYN at Northwestern University, Chicago; and Sharon Schnare, RN, FNP, CNM, MSN, a family planning clinician and consultant in Seattle.

After listening to this program, participants will be able to:

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- recognize potential problems with extended-use hormonal contraception; and
- identify best candidates for extended-use hormonal contraception.

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