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INSIDE

In a Community Near You: MRSA

SPECIAL FEATURE

By Stan Deresinski, MD, FACP

THE EVOLUTION OF ANTIBIOTIC RESISTANCE IN *Staphylococcus aureus* is an epic saga. Resistance to penicillin was first reported in the 1940s, at a time when the drug still remained in short supply. No reliable effective therapy against penicillin-resistant strains was available until the introduction of methicillin in 1960. There was no time for complacency, however, since resistance to this semisynthetic penicillin was reported the very next year. First detected in the United Kingdom, methicillin-resistant *S aureus* (MRSA) was soon identified on the continent, with subsequent worldwide spread, causing an ever-increasing number of nosocomial infections. Instead of producing the plasmid-mediated penicillinase that accounts for penicillin resistance, these isolates had acquired an extra penicillin binding protein, PBP 2a, which retained its transpeptidase activity in peptidoglycan synthesis but had reduced affinity for binding of ß-lactam antibiotics.

In 1968, the first description of a hospital outbreak of MRSA infection in the United States was reported from Boston City Hospital.[1] MRSA then expanded its reach, eventually establishing its current niche in hospitals to the extent that the majority of nosocomial isolates of *S aureus* in the United States are now methicillin resistant. More recently, *S aureus* with reduced susceptibility and, in 2 cases, high-level resistance, to vancomycin have made their appearance.[2]

A similar, albeit delayed, progression of staphylococcal resistance has occurred in the community. The proportion of community-acquired *S aureus* resistant to penicillin has increased progressively over the decades, reaching 90%. MRSA also appeared in the community, but, in most instances, the affected patients had had contact with health care facilities. The association with health care may be indirect; contacts of individuals with hospital-acquired MRSA are at a significantly increased risk of MRSA colonization.[3]

Beginning in the middle of the last decade, however, a dramatic change began taking place, with the occurrence of MRSA infections in otherwise healthy individuals with none of the previously known

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risk factors. These infections, mostly of skin and skin structures, were most commonly identified in children and often occurred in clusters. Outbreaks were reported in Native Americans, prisoners, and competitive athletes. The virulence of these infections was forcefully brought to our attention by a report of the deaths of 4 previously healthy children with community-acquired MRSA (CA-MRSA) infection.[4] The CA-MRSA strains, which are distinct from the hospital strains, have accelerated their rate of spread, reaching all regions of the United States and, in some areas, have become dominant community pathogens. For instance, a retrospective review of 60 children with community-acquired *S aureus* infection admitted to a Houston hospital found that 45% of the isolates were methicillin resistant (*IDSA 799*).

In northern California, outbreaks of CA-MRSA infections have been identified in county jail prisoners, in men who have sex with men, and in at least one athletic team. Six percent of homeless youth in San Francisco are colonized with CA-MRSA (*IDSA 255*).

CA-MRSA differs in a number of important ways from the 6 major pandemic clones of MRSA that account for nearly 70% of isolated strains.[5] These differences are found in the nature of the gene cassette coding for methicillin resistance, in the carriage of genes encoding resistance to antibiotics of other classes, and, probably, in virulence.

The molecule that accounts for methicillin resistance, PBP 2a, is encoded by the *mecA* gene. This gene is carried on a large mobile genetic element called staphylococcal cassette chromosome *mec* (SCC*mec*) that is integrated in the chromosome of MRSA. Four distinct types of SCC*mec* are known with types SCC*mec* I, II, and III found in most hospital-associated MRSA. SCC*mec* I and II generally also encode resistance to other antibiotics, accounting for the usual multidrug-resistant phenotype of hospital MRSA. One or the other of these genes is believed to have been introduced into *S aureus* at least 20 times, with the resultant emergence of methicillin resis-

Table 1.

CA-MRSA: Case Definition

- The patient's isolate was obtained in an outpatient setting or < 48 hours after hospital admission.
- The patient has no history of hospitalization, renal dialysis, surgery, intravenous therapy, or residence in a long-term care facility during the year before infection.
- The patient has no history of injection drug use, prior MRSA colonization, or MRSA infection.

Table 2.

CDC Recommendations for Prevention of Staphylococcal Skin Infections Among Sports Participants

- Cover all wounds. If a wound cannot be covered adequately, consider excluding players with potentially infectious skin lesions from practice or competitions until the lesions are healed or can be covered adequately.
- Encourage good hygiene, including showering and washing with soap after all practices and competitions.
- Ensure availability of adequate soap and hot water.
- Discourage sharing of towels and personal items (eg, clothing or equipment).
- Train athletes and coaches in first aid for wounds and recognition of wounds that are potentially infected.
- Encourage athletes to report skin lesions to coaches, and encourage coaches to assess athletes regularly for skin lesions.

Source: *MMWR Morb Mortal Wkly Rep. 2003;52:793-795.*

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Table 3.

MRSA Types

SCCmec Type	Size (kB)	Cassette Carries Other Resistance	Hospital or Community	PVL
I	-	-/+	H	-
II	52	+++	H	-
III	67	+++	H	-
IV	21-24	-	C	+++

tance in at least 5 phylogenetically distinct lineages.[6] In contrast, CA-MRSA carries SCC*mec* type IV, a genetic element significantly smaller than the other 3 and which does not carry other antibiotic resistance genes. Most CA-MRSA maintains susceptibility to tetracyclines, trimethoprim/sulfamethoxazole, and clindamycin. Some strains that are reported by the laboratory to be susceptible to clindamycin but resistant to erythromycin may, however, exhibit inducible resistance to clindamycin, a phenomenon that can be detected with the "D test."[7]

While being less likely to be multidrug resistant than hospital strains, clinical observations and molecular studies suggest CA-MRSA may be more virulent. Thus, sequencing of the entire genome of a single CA-MRSA strain (MW2) that caused fatal sepsis in a 16-month-old girl from North Dakota[4] detected 19 virulence genes not detected in the genomes of 5 hospital MRSA strains. These include a number of superantigens, such as staphylococcal enterotoxin H and the amphipathic bicomponent leukotoxin, Panton-Valentine leukocidin (PVL).

PVL, which appears to be carried on temperate phage, has been detected in the vast majority of SCC*mec* IV CA-MRSA isolates. It has been associated with increased severity of skin infections and with necrotizing pneumonia.[8,9] In addition to lysing leukocytes by forming pores in their cell membranes, intradermal injection of PVL causes demonecrosis in experimental animals.[10] In addition, some (but not all) studies suggest that CA-MRSA has greater replicative fitness as reflected in shorter doubling times than hospital strains.[11]

The increasing incidence of infections with MRSA, both community and hospital acquired, have a number of important implications.

- It is increasingly important that cultures be obtained in outpatients with possible staphylococcal infections.
- In outpatient community-onset staphylococcal infection prior to the availability of susceptibility data, consideration may be given to the use of antibiotics other than ß-lactams.
- In all patients with MRSA infection or colonization, strenuous efforts must be made to avoid transmission to other patients. Most such transmission occurs via the hands of health care workers. Wash your hands!
- Antibiotic use, both appropriate and inappropriate, leads to the emergence of antibiotic-resistant bacteria. In the case of MRSA, this is the consequence not only of the use of ß-lactams but also fluoroquinolones. Only use antibiotics when indicated. ■

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The Vice of VRSA

ABSTRACT & COMMENTARY

Synopsis: *The results of genetic analysis of a strain of* S aureus *with high-level resistance to vancomycin suggest that this resistance was the consequence of genetic transfer from a VRE to an MRSA, each present in and on the unfortunate patient who served as the incubator.*

Source: Weigel LM, et al. Genetic analysis of a high-level vancomycin-resistant isolate of *Staphylococcus aureus*. *Science*. 2003;302:1569-1571.

A CULTURE TAKEN FROM AN EXIT-SITE INFECTION from a hemodialysis catheter of a 40-year-old Michigan woman on June 14, 2002 (*see Table 1*), resulted in the isolation of a strain of methicillin-resistant *Staphylococcus aureus* (MRSA) that also had high-level resistance to vancomycin (MIC = 1024 µg/mL). This resistance was due to the expression of the *vanA* gene, previously only detected in vancomycin-resistant enterococci (VRE). Weigel and colleagues examined this first vancomycin-resistant *S aureus* (VRSA) in an attempt to reconstruct its genetic history.

The organism was confirmed to be *S aureus* by genetic sequencing, and pulsed-field gel electrophoresis (PFGE) demonstrated it to belong to the most commonly identified pulsed-field type in US hospitals, designated USA100. Vancomycin resistance was confirmed by PCR as being *vanA*-mediated. The VRSA was also resistant to aminoglycosides, ß-lactams, fluoroquinolones, macrolides, rifampin, and tetracycline but was susceptible to linezolid, quinupristin/dalfopristin, and trimethoprim/sulfamethoxazole.

The VRSA contained a single 57.9 kb plasmid (pLW1043). Two other isolates from the same patient, an MRSA and a VRE, were also examined. The antibiogram of the VRSA and MRSA isolates differed only in the resistance of the former to vancomycin and teicoplanin, and the 2 isolates both belonged to the same pulsed-field type, USA100. The MRSA contained a single 47 kb plasmid (pAM829), while the VRE contained 2 plasmids, 45 kb and 95 kb in size. Restriction analysis demonstrated that the plasmids from the VRSA and the MRSA were very similar, although the VRSA plasmid was 11 kb larger (the approximate size of Tn1546). Hybridization experiments localized *vanA* to a 7.1 kb fragment on the VRSA and VRE plasmids but absent in that of the MRSA. Study of the the fragment common to both was consistent with its identity with the *VanA* coding region of Tn1546, the prototypical Van encoding transposon element found on plasmids in VRE.

Table 1.

Patient Number 1

The 40-year-old woman from whom these isolates were obtained had diabetes mellitus and end-stage renal disease for which she was receiving chronic hemodialysis. She had had a series of infections, including a chronic foot ulcer. In March 2001, MSSA was isolated from an amputation wound, while 2 months later MRSA and vancomycin-susceptible *Enterococcus faecalis* were isolated from a foot ulcer. In attempts to treat the latter, during the first months of 2002, she had received the following antibiotics: vancomycin, gentamicin, ampicillin/sulbactam, piperacillin/tazobactam, levofloxacin, clindamycin, cefazolin, trimethoprim/sulfamethoxazole, tobramycin, and metronidazole. In April she received vancomycin and rifampin for treatment of MRSA bacteremia associated with an abscess of an AV graft. She then developed a series of infections at the exit site of temporary hemodialysis catheters, the third of which yielded VRSA. Culture of plantar ulcers at that time contained VREF and VRSA. The VRSA cleared after treatment with trimethoprim/sulfamethoxazole.

Source: *MMWR Morbid Mortal Wkly Rep. 2002;51:565-567.*

Table 2.

***S aureus* Vancomycin Susceptibility Classification**

Category	MIC (µg/mL)
Susceptible	= 4
Intermediate (VISA, GISA)	8-16
Resistant (VRSA)	= 32
Heteroresistant	= 4 with resistant subpopulations

Source: *Fridkin SK. Clin Infect Dis. 2001;32:1018-1025.*

These data were interpreted to indicate that the MRSA plasmid had acquired Tn1546, converting the organism to a VRSA. It was felt likely that conjugative transfer of the VRE plasmid to the MRSA had been followed by excision of Tn1546 from that plasmid and its subsequent integration into the preexisting MRSA plasmid. Direct transduction was an alternative possibility.

COMMENT BY STAN DERESINSKI, MD, FACP

The first report of an *S aureus* isolate with reduced susceptibility to vancomycin appeared in 1997. That strain had an MIC of 8 µg/mL; only a small number of strains with similar MICs of 8-16 µg/mL have been isolated since.[1] By current US CDC criteria (*see Table 2*), such strains are designated as "vancomycin-intermediate *S aureus* (VISA)." More commonly detected, and a possible cause of failure of vancomycin therapy, is heterore-

Table 3.
History of *S aureus* Resistance

Year Reported	Reduced Susceptibility to	Associated Gene	Mechanism	Designation
1948	penicillin	*bla*	Hydrolysis of β-lactam ring	MSSA
1961	methicillin	*mecA*	Altered target*	MRSA
1997	vancomycin	None	Excess, altered target	VISA
2002	vancomycin	*VanA**	Altered target**	VRSA

*VanA was first detected in *E faecium* in 1988.

**Replacement of alanine with lactate in the disaccharide pentapeptide cell wall precursors.

sistance. All strains of VISA are morphologically altered, with a thicker than normal cell wall, and the thickness of the cell wall correlates with the vancomycin MIC.[2] Resistance to vancomycin, which is lost on serial passage, is apparently the result of altered murein monomers with increased affinity for vancomycin, together with either increased monomer synthesis or reduced cell wall turnover, the consequence of which is sequestration of vancomycin preventing its interaction with its target.[3]

VRSA is a totally different story, with stable high-level resistance to vancomycin as a consequence of an MRSA having acquired a *vanA* gene from an enterococcus in an individual coinfected with MRSA and VRE. A second *vanA*-containing VRSA, isolated in culture from a Pennsylvania man in September 2002, presumably had acquired this resistance gene in a similar manner. Both VRSA strains belong to pulsed-field type USA100, which represents 44% of *S aureus* isolated in the United States and is typically multidrug resistant. To date, all but one US VISA also belong to USA100.[4]

This second VRSA strain is also multidrug resistant but, like the first VRSA, retains susceptibility to trimethoprim/sulfamethoxazole, linezolid, and quinupristin/dalfopristin. It is of interest that this isolate is also susceptible to the investigational glycopeptides, oritavancin and dalbavancin, or to daptomycin.[5] Mupirocin was active but was only bacteriostatic. The 2 VRSA-infected patients were successfully treated with trimethoprim/sulfamethoxazole.

There was no evidence of spread of either of these VRSA strains to other individuals, and no additional strains have appeared. But you can bet VRSA will be back. ■

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Antiviral Drug Resistance: Implications for Post-Exposure Prophylaxis in Health Care Workers with Occupational HIV Exposure

ABSTRACT & COMMENTARY

Synopsis: *In a multicenter study of occupational HIV exposures, 38% of source patients had genotype mutations associated with resistance to antiretroviral drugs. Recent antiretroviral treatment history was highly associated with resistance.*

Source: Beltrami EL, et al. Antiretroviral drug resistance in human immunodeficiency virus-infected source patients for occupational exposures to healthcare workers. *Infect Control Hosp Epidemiol*. 2003;24:724-730.

BELTRAMI AND COLLEAGUES ENROLLED HEALTH CARE workers with percutaneous exposure to HIV, along with the source patients for the exposures, in tertiary care medical centers in 5 US cities. They collected antiretroviral treatment histories from source patients. In addition, they collected source patients' blood for RNA viral load. HIV-1 isolates were submitted for genotyping in order to identify mutations associated with primary drug resistance.

They enrolled a total of 64 HCW-patient pairs. Four-

teen patients had undetectable viral loads, and thus virus was not available for genotyping. Of the 50 isolates genotyped, 19 (38%) had 1 or more (range, 1-6) mutations associated with primary drug resistance. Of the 50 patients, 26 had taken and 23 had not taken antiretroviral agents within the 3 months prior to the exposure incident. No drug treatment history was available from 1 patient. Of the 26 isolates from patients having received antiretroviral therapy, 16 (62%) had at least 1 primary drug resistance mutation. Of the 23 isolates from patients without recent antiretroviral treatment, 3 (13%) had at least 1 primary drug resistance mutation.

Multivariate analysis was performed on 5 drugs that are included in the CDC's current postexposure prophylaxis regimens: lamivudine, zidovudine, efavirenz, nevirapine, and nelfinavir.[1] Resistance to a specific drug was related to current or previous (within 3 months) use of that drug or of another drug of the same class. The results were similar when agents used within the preceding year were analyzed.

Beltrami et al recommend that when a health care worker sustains a percutaneous exposure from a source patient known to be HIV positive, postexposure prophylaxis should include 1 or more agents with which the source patient has not been treated. If that is not possible, an attempt should be made to select agents with which the source patient has not been treated within the preceding 3 months.

COMMENT BY ROBERT MUDER, MD

Although a health care worker's risk of acquiring HIV infection after a percutaneous exposure to blood from an HIV-positive source patient is low (0.3%), the US Public Health Service recommends the initiation of postexposure prophylaxis (PEP) in order to reduce the risk further.[1] Although there are no controlled trials of PEP, the estimated efficacy is approximately 80%, based on indirect evidence and animal models. The recommended regimes contain 2 or 3 antiretroviral drugs; ideally, PEP should be started within 24 hours of exposure. The relatively high prevalence of primary drug resistance mutations in HIV from patients who have received antiretroviral therapy could potentially compromise the efficacy of antiretroviral therapy. At the time of a percutaneous exposure incident, the viral genotype of the source patient is likely to be unavailable, and the appropriate testing can't be performed within the 24-hour window in which PEP should be initiated.

Beltrami et al show evidence that the source patient's recent history of antiretroviral therapy is highly correlated with the presence of primary drug resistance mutations. It's not perfect; for example, 13% of treatment-naïve patients had virus with drug resistance mutations. Nevertheless, treatment history is likely to be obtainable in a timely fashion and offers at least a rational basis for adjusting the agents used in PEP. Whether such an approach will reduce the incidence of occupationally acquired HIV infection will probably never be demonstrated by a clinical trial, but at present it seems to be a highly logical approach. ■

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ICAAC/IDSA/ASTMH 2003

CONFERENCE COVERAGE

The following summary of selected abstracts from 3 meetings will be published in multiple parts. The 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) met in Chicago September 14-17, 2003. The Infectious Disease Society of America (IDSA) met in San Diego October 9-12, 2003. The American Society of Tropical Medicine and Hygiene met in Philadelphia December 3-7, 2003.
— Stan Deresinski, MD, FACP

Gram-Positive Pathogens

Antibacterials, *Staphylococcus*, *Enterococcus*, Group B *Streptococcus*, Anthrax

Dalvabancin

Dalbavancin, an investigational glycopeptide with once-weekly dosing, is active against many Gram-positive organisms, including the Pennsylvania vancomycin-resistant *S aureus* (VRSA) isolate. In a phase 2 randomized trial, dalbavancin, given as a 1-gram IV dose followed by a 500-mg dose 1 week later, appeared to be at least as effective as the standard-of-care comparator agents chosen by the treating physician (*IDSA 172, 173, 299*).

Daptomycin

Daptomycin is a cyclic lipopeptide antibiotic for intravenous administration whose activity is limited to Gram-positive organisms but includes methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-

resistant enterococci (VRE). It recently received US FDA approval for the treatment of complicated skin and skin-structure infections due to susceptible Gram positives. Its mechanism of action has remained incompletely defined, although it appears to bind to the bacterial cell membrane via its fatty acid tail, followed by a decrease in membrane potential (*Antimicrob Agents Chemother*. 2003;47:1318). Transmission electron micrography was consistent with the cell membrane as being the target of daptomycin and with bactericidal activity occurring without gross lysis of the bacterial cell (*ICAAC C1-2135*).

Daptomycin was active in vitro against enterococci and *S aureus* resistant to either linezolid or quinupristin/dalfopristin. It was more rapidly and completely bactericidal against susceptible staphylococci and streptococci than was either cefazolin or vancomycin in peritoneal dialysate fluid in vitro and is bactericidal against vancomycin-intermediate *S aureus* (VISA) strains. Daptomycin was also bactericidal at 8 µg/mL against 5 of 6 strains of *Enterococcus faecium* resistant to both vancomycin and linezolid. The postantibiotic effect of daptomycin against staphylococci and pneumococci lasted 1.0-6.2 hours (*ICAAC C1-1643, A-1152, C1-1641, C1-1638, A-1172*).

When compared in clinical trials to either a semisynthetic penicillin or vancomycin, daptomycin was as successful as these agents in the treatment of complicated skin and skin-structure infections due to *S aureus*, including both MRSA and methicillin-susceptible *S aureus* (MSSA), as well as against streptococcal infections (*IDSA 296, 297*).

Linezolid

The introduction and use of an antibiotic is inevitably followed by the emergence of bacterial resistance to the agent. At one institution, all vancomycin-resistant *E faecium* (VREF) were susceptible to linezolid at concentrations < 2 µg/mL prior to the introduction of this antibiotic into use. In the period immediately after its introduction, 2 of 12 strains had a linezolid MIC = 4 µg/mL. One of these 2 strains was examined and found to have the typical G2576U mutation in domain V of 1 of 6 23S rRNA gene copies. Elsewhere, an outbreak of linezolid-resistant *E faecium* bloodstream infections involved 6 patients in an oncology unit. Resistance to linezolid may also be observed among staphylococci. An *S aureus* isolate with reduced susceptibility to linezolid (MIC = 8 µg/mL) associated with mutations in 2 of 5 copies of the 23S rRNA gene was the cause of fatal ventilator-associated pneumonia (*IDSA 216, ICAAC K-1112, K-1405*).

Linezolid, which is bacteriostatic against staphylococci and enterococci, was less effective than vancomycin in the treatment of endocarditis due to either MRSA or glycopeptide-intermediate *S aureus* (GISA) in a rabbit model. Linezolid was, however, synergistic with imipenem in a rabbit model of MRSA endocarditis (*ICAAC B-316, B-1093*).

Oritavancin

Oritavancin, like dalbavancin, a second-generation glycopeptide, was active in vitro against VRE with either *VanA* or *VanB* phenotypes. Three to 7 days of treatment with oritavancin was as effective as a similar duration of treatment with vancomycin, followed by cephalexin to complete a total of 14 days in patients with complicated skin/skin-structure infections. Oritavancin, which was given for a mean of 5.3 days vs 10.9 days in the comparator group, was significantly better tolerated (*ICAAC C1-1640, L-739a*).

MRSA—Detection

A major drawback to efficient management of MRSA-infected patients is the delay, usually of at least 48 hours, in the identification of methicillin resistance by classical microbiological techniques. The IDI-MRSA™, a real-time PCR assay with same-day turn around, had a sensitivity of 98% and specificity of 100% for the detection of MRSA directly on nasal and rectal swabs in 2 studies. The total assay time to process the samples was 3-4 hours (*ICAAC K-1394, 1748*).

Bacteremia—*S Aureus*

Eighty-five percent of cases of bacteremic *S aureus* pneumonia were hospital acquired. Of the total of 55 cases, 34 were due to MRSA and 21 to MSSA. Only 48% of patients infected with MRSA infection received effective antibiotic therapy within 48 hours of admission (*ICAAC K-765*).

In a prospective study of *S aureus* bacteremia, 158 of 245 patients had blood cultures drawn every 2-3 days after the start of therapy, until they were negative. The median time to blood culture positivity was 15.2 hours (range, 4-53 hours). The mean duration of bacteremia was 4.0 ± 6.4 days (range, 8-59 days). In 65% of patients, bacteremia had cleared by day 3, while it persisted for 4-7 days in 23% and for > 7 days in 12%. Risk factors for persistence for 4-7 days, on multivariate analysis, were the presence of an orthopedic prosthesis and rapid growth in blood culture (< 15 hours to positive culture). Predictors of persistence for > 7 days were an endovascular source of infection and treatment with vancomycin, especially in endocarditis (*ICAAC K-763*).

In patients with *S aureus* bacteremia, a time to blood culture growth detection of 16 hours or less was associat-

ed with an increased likelihood of an endovascular source (including endocarditis and IV catheter infection), persistence of bacteremia for more than 4 days, and the development of metastatic foci of infection (*IDSA 307*).

Twenty-eight patients with bacteremic pneumonia due to *S aureus* were identified; 43% were community acquired. The pneumonia was believed to be secondary to the bacteremia in two-thirds of cases. Nine patients had endocarditis, 5 had osteomyelitis, 5 had septic arthritis, and 2 had epidural abscess. The mortality was 18% (*IDSA 270*).

Of 320 prospectively identified adult inpatients with *S aureus* bacteremia, 45 (14%) had soft-tissue infection as the source. Among 29 patients in this group with repeated blood cultures, the mean duration of bacteremia was 2.5 ± 2.9 days (range, 1-13 days); bacteremia persisted for > 4 days in 17%. The duration of bacteremia was inversely related to the incubation time to initial blood culture positivity. Nine patients received predominantly oral therapy (*IDSA 271*).

MRSA—Epidemiology

It was estimated by the CDC that approximately 120,000 hospitalizations with a diagnosis of MRSA infection occur annually in the United States. These include approximately 30,000 septicemias and 27,000 pneumonias. In a network of 8 community hospitals, only 18% of cases of MRSA infection or colonization were nosocomially acquired, but most of the rest were health care associated (*IDSA 563, 562*).

Analysis of the SCOPE-MMIT Antimicrobial Network data revealed a persistent and significant association between hospital levofloxacin use and the prevalence of MRSA. This is consistent with a number of other studies that have identified fluoroquinolone use as a risk factor for nosocomial acquisition of MRSA (*Emerg Infect Dis*. 2003. www.cdc.gov/ncidod/EID/vol9no11/03-0284.htm). It is also consistent with the observation that fluoroquinolones select MRSA from heteroresistant populations in vitro. Relevant to this finding, it was reported that garenoxacin exposure was associated with lesser selection of oxacillin-resistant clones from a population of *mecA*-positive MRSA in vitro than were ciprofloxacin, levofloxacin, or gatifloxacin. In addition, it was reported that a 95% reduction in fluoroquinolone use in a French hospital was associated with a trend toward a reduced frequency of MRSA isolation (*ICAAC K-1743, K-1399, C1-64*).

But not all reports agree with this putative role of fluoroquinolones in the epidemiology of MRSA infections. One group reported that neither the use of fluoroquinolones nor antimicrobials of other classes was associated with an increased risk of subsequent MRSA bloodstream infection in a matched case-control study (*ICAAC K-1742*).

When tested 3 or more months (median, 16 months) after successful MRSA decolonization, only 3 of 37 (8%) patients were again colonized with their original strain, and 1 individual had acquired a new MRSA strain. One potential reason for this failure may be continued gastrointestinal tract colonization—38 of 107 (36%) MRSA carriers had positive rectal swabs for MRSA (*ICAAC K-1749, K-1401*).

An MRSA outbreak in a burn unit occurred despite standard burn-wound precautions and targeted isolation but was terminated after implementation of preemptive barrier precautions with all patients in the unit. Separately, the use of intranasal mupirocin was believed to have terminated an MRSA outbreak, not affected by other control measures, in a neonatal ICU (*ICAAC K-582, K-1744*).

A metaanalysis of 10 studies found that the use of mupirocin was associated with a substantial reduction in *S aureus* infections in dialysis patients (*ICAAC K-1746*).

MRSA—Community Acquired

Acquisition of MRSA in the community has exploded in frequency. One-half of MRSA isolated from patients with systemic infections in 2002-2003 was community acquired (CA-MRSA) and carried the staphylococcal cassette chromosome type IV (SCC*mec* IV) in a Houston study. Consistent with the usual lack of multidrug resistance in CA-MRSA isolates containing SCC*mec* IV, all were susceptible to trimethoprim-sulfamethoxazole. Similarly, the proportion of community-acquired *S aureus* bacteremic episodes in Darwin, Australia, due to MRSA increased from 9% in 1998 to 20% in 2001. Empiric antimicrobial therapy was inappropriate in 80% of episodes. The isolates contained type IV SCC*mec* and were not multidrug resistant (*IDSA 258, ICAAC L-619*).

A retrospective review of 60 children with community-acquired *S aureus* infection admitted to a Houston hospital found that 45% of the isolates were methicillin resistant. MRSA was more likely to be associated with deep-skin infections than was MSSA, while the latter was more often associated with respiratory infection. The length of stay was 3 days longer in MRSA-infected patients, who were also more likely to have received inappropriate initial antimicrobial therapy (*IDSA 799, 801*).

Four outbreaks of CA-MRSA were identified in Los Angeles County in 2002. Those involved a group of 5 infants recently discharged from a newborn nursery, 2 members of an athletic team, a number of men who have sex with men (MSM), and 934 county jail inmates. Almost 10% of the 934 LA county inmates with CA-MRSA infections were hospitalized for a mean of 10

days. Pulsed-field gel electrophoresis revealed the same predominant clone in each outbreak (*IDSA 263, 264*).

Community-onset MRSA infection was detected in 35 adult outpatients—30 males, 4 females, and 1 transgender male-to-female. Compared to the general clinic population, MRSA patients were significantly more likely to be MSM. Among the MSM, the site of the skin abscess was consistent with the possibility of sexual transmission, involving the groin, genitals, buttocks or rectum, mouth, or face (*ICCAC L-1602a*).

Examination of MRSA isolates from jail inmates in both San Francisco and Los Angeles determined that they are SCC*mec* type IV and are of a single clone bearing the Panton-Valentine leukocidin (PVL) virulence factor (*Infectious Disease Alert*. 2002;22(6):44; *Emerg Infect Dis*. 2003;9:978-984). Separately, analysis of national MRSA isolates found that PVL is common only in community-onset isolates, while toxic shock syndrome toxin (TSST) was detected primarily in one hospital-associated lineage. Other novel MRSA strains that could not be typed by SCC*mec* analysis are also circulating in San Francisco. These strains have antibiotic-resistance patterns similar to the strains carrying SCC*mec* type IV (*ICAAC K-1393, C2-1980, IDSA 259*).

Another study in San Francisco found that *S aureus* containing SCC*mec* type IV, which has been associated with community-onset MRSA, was widely detected in both hospital and community settings. Furthermore, these strains are capable of capturing multiple antibiotic resistance determinants. In a separate study in which 6% of 308 homeless youth in that city had nasal colonization with CA-MRSA containing SCC*mec* type IV, emerging resistance to macrolides and fluoroquinolones was found (*ICAAC C2-1983, IDSA 255*).

The optimal choice of antibiotic for treatment of CA-MRSA remains a matter of discussion. However, many subcutaneous abscesses caused by community-onset MRSA were effectively treated with incision and drainage in the absence of effective antibiotic therapy (*ICAAC G-1541*).

MRSA—Treatment

Fifty-six percent of 161 erythromycin-resistant, clindamycin-susceptible *S aureus* isolates in Baltimore demonstrated inducible clindamycin (MLS) resistance. Elsewhere, 79% of *S aureus* and *S epidermidis* with a clindamycin-susceptible, erythromycin-susceptible phenotype exhibited inducible resistance to clindamycin. The authors conclude that laboratories should either test for inducible clindamycin resistance or report these strains as being resistant or potentially resistant to clindamycin. This approach may have prevented a reported case of failure of clindamycin therapy in an infection due to an isolate with inducible clindamycin resistance (*IDSA 485, ICAAC C2-87, IDSA 485*).

Six of 21 (29%) *S haemolyticus* isolates demonstrated vancomycin heteroresistance, but this did not appear to adversely affect therapeutic outcomes. The presence of the accessory gene regulator (*agr*) in MRSA has been associated with glycopeptide-intermediate susceptibility (*J Infect Dis*. 2003;187:929). Persistence of MRSA infection despite therapy with vancomycin was associated in 4 of 5 patients with the presence of *agr* group II MRSA. Treatment with quinupristin/dalfopristin plus vancomycin was successful in 3 of the 4, with eradication of the organism in 1.5, 4, and 4.5 days (*IDSA 218, 486*).

Biofilm plays a critical role in many infections, particularly those involving foreign material such as vascular access catheters. Minocycline, rifampin, and quinupristin/dalfopristin were significantly more active than either vancomycin or linezolid against MRSA and VRE embedded in biofilm. In addition, ramoplanin was bactericidal against *S epidermidis* and *S aureus* growing in biofilm (*ICAAC C1-118, C1-119*).

VRE

Confirming the results of previous studies, a meta-analysis found that vancomycin resistance is an independent predictor of death in patients with enterococcal bloodstream infection (*IDSA 491*).

In further evidence of the potential for antibiotic-fed food animals to be the source of antibiotic-resistant bacteria in humans, interspecies transfer of the *vanA* operon from poultry-derived *E faecium* to human-derived *E faecalis* occurred at high frequency in the GI tract off human flora-associated mice (*ICAAC C1-16*).

Hand washing is, of course, critical to prevention of VRE transmission. VRE carriage on the hands of health care workers was transient or intermittent, but not persistent. Environmental contamination may also be important in the epidemiology of VRE. Thus, VRE contamination by patient carriers in an outpatient hemodialysis unit was frequently detected on chairs or couches, the gowns of health care workers, and on patient hands. But bathing ICU patients with a 2% chlorhexidine-impregnated washcloth system was associated with decreased patient skin, environmental, and health care worker hand VRE contamination when compared with soap and water bathing (*ICAAC K-1105, K-1107, K-1108, K-1107*).

Some studies have suggested that the use of piperacillin/tazobactam is associated with a decreased risk of colonization with VRE when compared to cephalosporin or ticarcillin/clavulanate use. This observation was apparently confirmed by one group that

reported that VRE acquisition decreased in association with a formulary change from ticarcillin/clavulanate to piperacillin/tazobactam. Two other papers did not confirm this finding. Thus, VRE colonization in an ICU was detected in 24% of patients after receipt of piperacillin/tazobactam and 25% after cefepime. In one study, previous receipt of vancomycin, piperacillin-tazobactam, advanced generation cephalosporins, and gatifloxacin were each associated with an increased risk of acquisition of VRE (*ICAAC K-1429, IDSA 490, ICAAC K-1417*).

In a setting in which linezolid and quinupristin/dalfopristin (QD) have been used for 5 years, 2.6% of VREF were nonsusceptible to linezolid, and 15.5% were resistant to QD (*ICAAC K-1409*).

VREF are susceptible to ramoplanin, an orally administered, nonabsorbable glycolipodepsipeptide (*IDSA 167*).

Streptococcus agalactiae

Adults 65 years and older are colonized with group B streptococci at rates similar to younger populations but are more likely to carry type V, the leading cause of invasive infection with this organism in the elderly. Furthermore, healthy elderly individuals often lack type V-specific IgG in serum. A group V vaccine conjugated to tetanus toxoid was found to be safe and immunogenic in healthy elderly adults (*IDSA 529, 519*).

Anthrax

In vitro studies demonstrated that chloroquine and plasma inter-alpha inhibitor each rescued murine peritoneal macrophages from anthrax lethal toxin-induced cytoxicity (*IDSA 709, 712*).

Levofloxacin and linezolid were each effective in the treatment of inhalational anthrax in murine models of infection. In a primate model, both ciprofloxacin and levofloxacin were therapeutically effective. However, 3 of 10 monkeys became ill and died after the 30-day period of treatment, presumably as the consequence of germination of residual spores (*ICAAC A-306, B-3300, B-331a*).

Two hundred individuals potentially exposed to anthrax in a US bioterror event received both antibiotics and anthrax vaccine. There were no serious adverse events attributable to the vaccine. However, most of 15 anthrax survivors assessed 1 year after infection reported significant functional impairment and evidence of psychological distress (*IDSA 831, 833*).

Hyperimmune human serum is being explored as a potential therapeutic in anthrax. The antiprotective antigen IgG concentration measured by ELISA in plasma obtained from individuals vaccinated against anthrax correlated with its functional activity in a toxin-neutralization assay (*IDSA 832*). ■

CME Questions

1. **By CDC criteria, to be designated vancomycin resistant, an isolate of *S aureus* must have an MIC of:**
   a. ≥ 128 µ/mL.
   b. ≥ 64 µ/mL.
   c. ≥ 32 µ/mL.
   d. ≥ 16 µ/mL.

2. **Which of the following types of *S aureus* contain a gene cassette virtually identical to that seen in vancomycin-resistant enterococci?**
   a. MRSA
   b. VISA
   c. VRSA
   d. Heteroresistant VISA

3. **Which of the following is correct with regard to CA-MRSA?**
   a. They have been demonstrated to be less virulent than hospital-associated MRSA.
   b. They are less likely to be multidrug resistant than are hospital-associated MRSA.
   c. They seldom cause skin-structure infections.
   d. Clindamycin susceptibility can be predicted from the result of the susceptibility/resistance of CA-MRSA to erythromycin.

4. **A health care worker has sustained a percutaneous injury with a needle used to draw blood on a patient with known HIV infection who is receiving antiretroviral therapy. Based on the USPHS guidelines, postexposure prophylaxis for the health care worker is indicated. Which of the following statements is true?**
   a. The health care worker should begin treatment with zidovudine and lamivudine within 24 hours.
   b. The source patient's recent antiretroviral treatment history should be reviewed; postexposure prophylaxis should include at least 1 drug that the patient has not previously received.
   c. The source patient's blood should be sent for HIV genotyping; postexposure prophylaxis should be delayed pending the results.
   d. The source patient's blood should be sent for HIV RNA viral load determination; postexposure prophylaxis should be delayed pending the results.

Answers: 1(c); 2(c); 3(b); 4(b)

In Future Issues:

Ventilator-Associated Pneumonia

UPDATES

By Carol A. Kemper, MD, FACP

Drug Users Battle Tetanus

Sources: *Eurosurveillance Weekly*. 2003;7; ProMED-mail Post. November 30, 2003.

An outbreak of tetanus involving 6 (and possibly 7) injection drug users in England and Wales has officials concerned that others may be at risk. Six of the cases occurred during the past 3 weeks and were spread throughout the country, suggesting contamination of some type of drug—possibly heroin. While the specifics of the cases, including the types of drugs involved, are not known, 4 of the cases were females (in their early 20s) and 3 were male. The seventh possible case occurred in July, when a female IVDU presented to the emergency room with trismus and died of respiratory failure before a diagnosis was made.

At least 2 of the cases were known to have been vaccinated, and 1 person received tetanus toxoid 9 years ago. Even fully vaccinated individuals with dirty wounds remain at risk for tetanus; hence, the recommendation for tetanus immune globulin in tetanus-prone wounds.

Persons with tetanus generally present with complaints of abdominal rigidity and tightening of the jaw muscles, which quickly progresses to painful spasms, dysphagia, and progressive respiratory failure. Autonomic dysfunction is common. The case fatality rate in recent series has varied from 18% to 29% and depends on prompt recognition of infection and treatment, with aggressive debridement of affected wounds, antibiotics, supportive care, and tetanus immune globulin. While the site of infection may not be obvious, clinicians should have a low index of suspicion in injecting drug users who "skin pop" or "muscle" drugs.

A similar outbreak of *Clostridium novyi* infection in 108 heroin users (44 of whom died) occurred in England, Wales, and Ireland in 2000. Infection was strongly associated with subcutaneous or intramuscular injection. The Western United States, and in particular California, has also been experiencing a decade-long outbreak of wound botulism in black-tar heroin users. Most of the cases have similarly occurred in individuals who shoot heroin subcutaneously or intramuscularly—although 1 person reported only snorted drug. Despite the best efforts of narcotics experts, epidemiologists, and microbiologists, the source of the outbreak and mechanism of contamination of the black-tar heroin has not been discovered. ■

Did Alexander the Great Die of WNV Encephalitis?

Source: Marr J, Callsher CH. *Emerg Infect Dis*. 2003;9:1599-1603.

Could Alexander the Great's sudden demise in Mesopotamia in 323 B.C. from a 2-week febrile illness, culminating in coma and flacid paralysis, have been the result of West Nile virus (WNV) infection? Theorizing that WNV, which has been responsible for a series of well-known outbreaks in the Middle East over the past 60 years, has been endemic in the area for hundreds of years, these authors provide the following case presentation: AG was a vigorous, healthy 32-year-old man, although he drank heavily, loved to bathe, and had sustained a penetrating right chest wound one year earlier. He was born in Macedonia and had traveled extensively throughout the Middle East, Northern Africa, and the Mediterranean. About 5 years earlier, he had a self-limited febrile illness of unknown cause. Shortly after returning to Babylon on the shores of the Euphrates River—just south of modern-day Baghdad—in May 323 B.C., AG developed progressive fever and chills, transient back pain, and abdominal pain. Over the next 2 weeks, he developed increasing thirst, progressive delirium, aphonia, and gradually slipped into coma with flaccid paralysis.

Previous authors have speculated that he may have been poisoned (not likely to result in sustained fever for 2 weeks), while others have suggested various infectious etiologies, such as typhoid fever, schistosomiasis, bacterial sepsis, pneumococcal pneumonia, malaria, etc. Of those proposed, influenza A, polio, or a viral encephalitis seem most plausible. The authors point to a passage in *Plutarch* for a possible clue: Upon entering the gates of the city, a flock of ravens were seen "flying about and pecking one another, and some of them fell dead in front of him." Considered a bad omen at the time, the birds may have been more than just a harbinger, but an actual vector. WNV is an important case of death in wild birds, especially crows, and diseased birds often exhibit bizarre behavior, such as circling, disorientation, abnormal posturing, and impaired vision.

WNV, therefore, appears a likely candidate for AG's demise. During the 2000 outbreak of WNV infection in Israel, which affected more than 400

individuals, encephalitis occurred in more than half of recognized cases. Fever, cognitive changes, abdominal pain, and flaccid paralysis were common symptoms. Most of the recent Israeli cases occurred later in the year, in July through September, although a few were reported in June. However, it is believed that human illness generally follows natural infection in mosquitos and birds. Hence, the possible importance of *Plutarch*'s ravens. ■

Multidrug Resistance Threatens Cape Town

Source: ProMED-mail Post. November 21, 2003.

South Africans are no strangers to tuberculosis (TB)—a country with the highest prevalence of AIDS/HIV, and about 225,000 reported cases of TB last year. However, multidrug-resistant TB remains relatively uncommon in Africa, compared with places like Russia and Southeast Asia. Recent data from Gambia, Botswana, and Ethiopia indicate that resistance to a single drug occurs in 4-6.3% of new cases and 20-22.8% of retreatment cases, while multidrug resistance (defined as resistance to both INH and rifampin) occurs in 0.5-1.2% of new cases and 9-12% of retreatment cases. Resistance to ethambutol has been uncommon.

Against this backdrop, a new drug-resistant "superstrain" of TB has been identified in the Western Cape area of South Africa, termed DRF150. DRF150, which is resistant to all 4 TB drugs commonly used, has been identified in about 60 cases from 72 clinics located in 3 communities in and around Cape Town during the past 14 months. Additional cases have been found in Western Cape, the Northern and Mpumalanga Provinces, and Nairobi, Kenya, although it is not clear whether these are the same genotypic strain. This new multidrug-resistant strain appears to be different from another MDR strain present in South Africa, Beijing/W, which has been increasingly recognized as a cause of multidrug resistance in Russia and other countries. A 2001 prison outbreak in Archangel, Russia, was largely due to this strain and was significantly associated with resistance to both streptomycin and ethambutol.

Africa can ill afford an increase in the prevalence of MDR-TB. For example, treatment of MDR-TB in South African costs about 30,000 RAND (about $4600 USD), mostly because of the necessary prolonged hospitalization, while routine TB treatment costs about 200 RAND (about $30 USD). At present, about 20% of the South African TB budget is spent treating 2% of the cases with MDR-TB. The occurrence of these "mini-outbreaks" of MDR-TB, as one expert called them, should command worldwide attention and prompt efforts at control. ■

Fosamprenavir Released by US FDA

Source: GlaxoSmithKline "Dear Healthcare Professional" letter. 2003; Package insert, October 2003.

Fosamprenavir, a prodrug of amprenavir, which is rapidly hydrolyzed to the active compound by cellular phosphatases in the gut, is the newest protease inhibitor to be approved by the US FDA for treatment of HIV. The singular advantage of the newer formulation is lower pill burden; whereas the earlier formulation of amprenavir requires 8 150-mg tablets twice daily (16 tablets/d), the newer formulation can be administered as a single 700-mg tablet twice daily or once daily when boosted with ritonavir (the twice-daily regimen, boosted with ritonavir, is recommended for protease inhibitor-experienced patients). There is some speculation that fewer tablets (hence fewer gel caps) may be associated with a lower incidence of GI side effects and diarrhea compared to amprenavir.

In clinical trials, treatment responses at 48 weeks appeared to be somewhat better in treatment-naïve patients receiving fosamprenavir compared to nelfinavir (66% and 69% for FOS and FOS/r, respectively, vs 52% and 68% for nelfinavir) and was associated with significantly less diarrhea. Rates of adverse reactions and discontinuation were otherwise similar. In protease inhibitor-experienced patients, virologic responses were similar in patients receiving 1 of 2 doses of fosamprenavir/r (700 mg/100 mg twice daily or 1400 mg/200 mg once daily) vs lopinavir/r (400 mg/100 mg twice daily).

Genotypic studies were performed in 61 treatment-naïve patients with virologic failure during treatment with either fosamprenavir or fosamprenavir/r. Five of 29 subjects receiving fosamprenavir without ritonavir had evidence of V32I, L33F, M46I/L, I47V, and 154L/M alone or in combination. No genotypic mutations were detected in the remaining 32 patients. Most of the protease inhibitor-experienced patients who responded to fosamprenavir had previously received nelfinavir and indinavir, with baseline resistance mutations to D30N (95%), N88D/S9 (91%), and L90M (52%).

Fosamprenavir can be administered with or without food. Amprenavir is metabolized by the P450 3A4 (CYP3A4) enzyme system and is not affected by renal impairment. It has several important drug interactions and should not be coadministered with triazolam, ergotamines, propulsid, or midazolam. Fosamprenavir contains a sulfonamide moiety, although clinical data thus far suggest a similar incidence of rash in patients with or without a history of sulpha allergy. Nonetheless, the package insert advises the cautious use of fosamprenavir in those with a history of sulpha allergy. ■

PHARMACOLOGY WATCH

Vioxx Might Control Postoperative Knee Pain

Oral rofecoxib (Vioxx) may have a role in controlling postoperative pain patients undergoing knee surgery. Researchers in Chicago enrolled 70 patients who were undergoing total knee arthroplasty and randomized them to rofecoxib 50 mg the day prior to surgery, 1-2 hours prior to surgery, and for 5 days postoperatively, then 25 mg daily for another 8 days; or matching placebo at the same times. The main outcome was postsurgical analgesic consumption and pain scores, as well as nausea and vomiting, joint range of motion, sleep disturbance, and patient satisfaction with analgesia and hematologic anticoagulation parameters. Rofecoxib resulted in significantly reduced use of epidural analgesia and in-hospital opioid consumption ($P < .05$). Pain scores were also lower in the rofecoxib group while in the hospital ($P < .001$) as well as 1 week after discharge ($P = .03$). Rofecoxib also resulted in less postoperative nausea, a decrease in sleep disturbance, as well as increased knee flexion at 1 month—including a shorter time in physical therapy to achieve effective joint range of motion. The drug had no effect on warfarin usage or INR levels postoperatively. Interestingly, Buvanendran and colleagues did not include changes in renal function or evidence of GI intolerance in the study analysis. They did conclude however that rofecoxib is effective at reducing postoperative pain and opioid consumption after major orthopedic surgery (*JAMA*. 2003;290:2411-2418).

Echinacea Has No Value for URIs

Just in time for winter, another study showed that *Echinacea* has no value for reducing the duration or severity of upper respiratory tract infections (URIs). The herbal remedy is commonly used worldwide for this indication. In this study of children in the Pacific Northwest, 707 URIs occurred in 407 children over 2 years. Three hundred thirty-seven URIs were randomized to treatment with *Echinacea* while 370 were assigned to placebo. *Echinacea* was begun at the onset of symptoms and continued throughout the infection for maximum of 10 days. Data analysis showed there was no difference in the duration of URIs with *Echinacea* or placebo ($P = .89$), and there was no difference in the overall estimate of severity of URI symptoms ($P = .69$). There was also no statistically significant difference between the 2 groups for peak severity of symptoms, number of days of peak symptoms, number of days of fever, or parental global assessment of severity of URI. Rash occurred during 7.1% of URIs treated with *Echinacea* and 2.7% of those tree with placebo ($P = .008$). The study concludes that *Echinacea* was not effective in treating URI symptoms in patients 2 to 11 years old but was associated with an increase in skin rash (*JAMA*. 2003;290:2824-2830).

Valsartan, Captopril Have Similar Benefits

Valsartan and captopril have similar benefits in patients with myocardial infarction complicated

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by left ventricular systolic dysfunction, heart failure, or both, according to a new study. Previous studies have shown that ACE inhibitors reduce mortality and cardiovascular morbidity in this group, but it was unclear if angiotensin receptor blockers (ARBs) conveyed the same benefit. In this international study, nearly 15,000 patients with myocardial infarction were randomized to valsartan, captopril, or a combination of valsartan and captopril. The primary end point was death from any cause. The median follow-up was just more than 2 years. During that time, the death rate in all 3 groups was remarkably similar (979 of 4909 deaths valsartan, 958 of 4909 deaths captopril, 941 of 4885 deaths combination [hazard ratio valsartan vs captopril 1.0; 97.5% CI, 0.9-1.11; $P = 0.98$], [hazard ratio valsartan and captopril vs captopril, 0.98; 97.5% CI, 0.89-1.09; $P = 0.73$]). The valsartan plus captopril group had the most drug-related adverse events, while in the monotherapy groups valsartan was associated with more hypotension and renal dysfunction, while cough, rash, and taste disturbance were more common with captopril. Pfeffer and associates conclude that valsartan is as effective as captopril in patients with myocardial infarction who are at high risk for cardiovascular events, but combining valsartan with captopril did not offer an advantage (*N Engl J Med*. 2003;349:1893-1906).

In-patients Likely to Continue Lipid Use

In-patients who are started on lipid-lowering therapy following coronary intervention are 3 times more likely to continue on the drugs compared to patients who are started on the same therapy as outpatients. Using data from the EPILOG trial in which patients underwent percutaneous coronary intervention for stable or recently unstable coronary artery disease, 175 patients were discharged from the hospital on lipid-lowering therapy and 1951 were discharged on no lipid-lowering therapy, with the intent to start them on treatment as outpatients. After 6 months of follow-up, 77% of patients who were started in the hospital were still taking lipid-lowering therapy compared with only 25% of those who were discharged without lipid-lowering therapy ($P < .001$). Aronow and colleagues suggest that initiation of lipid-lowering therapy in the hospital is effective strategy to enhance subsequent use of the drugs in these high-risk patients (*Arch Intern Med*. 2003;163:2576-2582).

More on Metformin/Lactic Acidosis

When it comes to the relationship between metformin and lactic acidosis, the emperor may have no cloths. The drug, which has been used to treat type 2 diabetes for more than 40 years, has always carried with it the stigma that it may cause lactic acidosis in at-risk patients. Metformin hydrochloride is a biguanide that is similar in structure to phenformin hydrochloride, which was withdrawn from the market because of a documented risk of lactic acidosis. Metformin increases glucose oxidation without substantially affecting fasting lactate production and peripheral tissues unlike phenformin, and the true rate of metformin-associated lactic acidosis has never been demonstrated. Recently, researchers from Stanford performed a thorough review of the literature on this topic and performed a meta-analysis on 194 studies involving nearly 37,000 patient years in the metformin group and 30,000 patient years in the nonmetformin group. No cases of fatal or nonfatal lactic acidosis were found in either group. Their conclusion is that there is no evidence that metformin therapy is associated with an increased risk of lactic acidosis or with increased lactate levels compared with other antihyperglycemic treatments (*Arch Intern Med*. 2003;163:2594-2602). The study is important because metformin is an effective treatment for type 2 diabetes, and has some unique properties including stabilizing weight gain or even facilitating weight loss. The drug has also recently become multisource (generic) and is affordable for diabetic patients who must pay for their medications.

FDA Notes

The FDA has approved tadalafil (Cialis), Eli Lilly and Icos Corp's entry into the lucrative phosphodiesterase inhibitor market. With the success of sildenafil (Viagra), and newcomer vardenafil (Levitra) already generating huge profits, Cialis is being touted as a longer acting, less expensive alternative for the treatment of erectile dysfunction. The drug, which exerts its effect over 36 hours, has already been dubbed "the weekend drug" in Europe, where it as been available for some time.

Bristol-Myers has received approval to market the first chewable oral contraceptive for women. The product is a new formulation of Ovcon 35 (norethindrone and ethinyl estradiol), which is spearmint flavored and can be chewed or swallowed whole. If chewed than swallowed, the woman should drink a full 8 oz of liquid immediately afterward to make sure the entire dose reaches the stomach. ■