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The Lengthening Shadow of MRSA

ABSTRACT & COMMENTARY

Synopsis: *The emergence of new clones of exfoliative toxin producing S aureus in Japan may be a harbinger of things to come.*

Source: Yamaguchi T, et al. Clonal association of *Staphylococcus aureus* causing bullous impetigo and the emergence of new methicillin-resistant clonal groups in Kansai district in japan. *J Infect Dis*. 2002;185:1511-1516.

BETWEEN JUNE AND SEPTEMBER 1999 EIGHTY-EIGHT *Staphylococcus aureus* strains isolated from skin swabs of outpatients with bullous impetigo were collected from 4 hospitals in Kansai district of Japan. A molecular epidemiological analysis was performed to reveal the clonal association of *S aureus* strains. Pulsed-field gel electrophoresis (PFGE) with cluster analysis, genetic and phenotypic characterizations, and antimicrobial susceptibility profiling of 88 *S aureus* strains were undertaken.

Three distinct clonal groups were identified: 2 of them carried the exfoliative toxin (ET) A gene (*eta*), and the other carried the ETB gene (*etb*). The former groups represent 2 *eta*-positive clonal groups that have not been described previously. All the strains in the more dominant *eta*-positive clonal group and some of the strains in the *etb*-positive clonal group were methicillin-resistant *S aureus* (MRSA) showing borderline-to-moderate resistance to β-lactams.

These MRSA strains are emerging as clonal groups that have not been detected in previous epidemiological studies of ET-producing *S aureus* in Japan. Thus, these new MRSA *eta*- and *etb*-positive strains thus pose a significant future threat and may manifest as bullous impetigo and/or staphylococcal scalded-skin syndrome (SSSS).

COMMENT BY JOSEPH F. JOHN, Jr, MD & RAJIV NAVAL-SRINIVAS, MD

Bullous impetigo is a localized skin infection without systemic symptoms caused by exfoliatin toxin-producing staphylococci. SSSS, its more severe cousin, first described by Ritter von Rittershain in 1878. SSSS encompasses a spectrum of clinical features

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INSIDE

with bullous impetigo being the most common clinical finding. The majority of cases of SSSS in the United States are due to Phage group II with 75% of them belonging to phage type 71. The blister formation is due to exfoliative toxins—ETA, ETB produced by *S aureus*. The gene producing the toxin ETA, *eta*, is encoded on the genome of a temperate phage (ϕETA), while the gene for ETB, *etb*, is encoded on large plasmids. ETA is a serine protease, which cleaves desmoglein 1, a protein connecting epidermal cells.

Not all strains possess genes for exfoliative toxins as these genes are acquired through horizontal transfer during evolution of *S aureus*. Management of SSSS currently relies on eradication of the exfoliatin-bearing strain from the focus of infection with penicillinase-resistant β-lactam antibiotic, assuming there is no MRSA in the population.

To understand the phenomenon of spreading methicillin resistance, we need to review the molecular biology of methicillin resistance. Methicillin resistance is defined as an oxacillin MIC of ≥ 4 mg/L or a methicillin MIC of ≥ 16 mg/L. Staphylococci have at least 2 essential penicillin binding proteins (PBPs), which have enzymatic activity and are responsible for cross-linking of the peptidoglycan cell wall. MRSA are characterized by the ability to produce an altered penicillin binding protein but, like other *S aureus,* constitutively produce penicillinase, coagulase, DNase, and enhanced amounts of catalase.

Staphylococci can become resistant to β-lactam agents, cephalosporins, and carbapenems by acquiring a chromosomally mediated *mecA* gene, which encodes an alternative supplementary target called PBP 2a or PBP 2′ that has low affinity for β-lactams.

The abnormal PBP 2a continues to function when PBP 1, 2, and 3 are inactivated by β-lactam antibiotics and generates a stable peptidoglycan. *mecA* is located on a large 30-40-kilobase DNA element in the chromosome, flanked by insertion sequence-like elements (IS431 and IS257) that trap additional unrelated drug resistance genetic determinants leading to multiple drug resistance.

Transfer of *mec* DNA to a susceptible *S aureus* has occurred in vitro and recently in vivo. The mechanism of transfer of *mec* DNA from a donor to a recipient is not completely understood. Until recently, horizontal transfer of *mec* was thought to be relatively rare but a recent population-based study of MRSA from Finland suggests that MRSA may emerge as a community-acquired pathogen as a consequence of horizontal acquisition of *mecA* gene by a previously susceptible *S aureus* strain.[1]

Yamaguchi et al's study of clonal association of *S aureus* isolated from bullous impetigo raises the spectre of global emergence of new *eta*- and *etb*-positive MRSA. A majority of the 88 isolates were positive for an ET gene and were MRSA while no strains possessed both *eta* and *etb*. PFGE analysis separated the 88 isolates into 4 clusters with *eta*-positive strains found in 3 clusters. The dominant clonal group was sub cluster IIIb composed of *eta* positive, *mecA* positive (27/28), coagulase type III that showed borderline-to-moderate resistance to β-lactam antibiotics with a narrow MIC range for each drug. The antibiotic susceptibility pattern of *etb*-positive MRSA was similar to that of *eta*-positive MRSA strains. The *eta*- and *etb*-positive strains were resistant to gentamicin but sensitive to fusidic acid and minocycline with wide variation in MICs to erythromycin and clarithromycin.

The emergence of the *eta*-positive MRSA clonal group was postulated by Yamaguchi et al to be due to

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phage conversion of *mecA* positive, coagulase type III strain and *etb* MRSA due to acquisition of *mecA* gene by *etb*-positive strains. The emergence of *eta*- and *etb*-positive MRSA groups with multiple drug resistance, particularly if proven to be a geographically more dispersed event, could cause serious clinical problems in infants and newborns with SSSS and may manifest differently in adults.

It has now been shown that infections caused by MRSA strains may be more difficult to manage and more expensive to treat.[2] The resultant increased vancomycin use could add further to the problem of antibiotic-resistant gram-positive bacteria. A similar study of SSSS in United States would shed more light on the prevalence of *eta*- and *etb*-positive MRSA in this hemisphere. ■

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Saucy Enterics

ABSTRACT & COMMENTARY

"What is food to one man is bitter poison to others."—Lucretius (99 BC-55 BC)

"Part of the secret of success in life is to eat what you like and let the food fight it out inside."—Mark Twain (1835-1910)

Synopsis: *Both enterotoxigenic and enteroaggregative E Coli were recovered from table-top Mexican sauces in Guadalajara restaurants.*

Source: Adachi JA, et al. Enteric pathogens in Mexican sauces of popular restaurants in Guadalajara, Mexico, and Houston, Texas. *Ann Intern Med*. 2002;136:884-887.

ADACHI AND COLLEAGUES IN HOUSTON COLLECTED samples of table-top Mexican sauces, including green and red salsas, guacamole, and pico de gallo from restaurants in the summer of 1998 to determine the frequency of their contamination by enteric pathogens. Seventy-one sauces were collected from 26 Guadalajara area restaurants popular with US travelers, as well as 25 sauces from 12 Mexican-style restaurants in Houston.

Escherichia coli was recovered in culture from 47 of 71 (66%) Guadalajara sauces at a median density of 1000 colony-forming units (CFUs) (range, 0-80,000 CFU) per gram. Ten of 25 (40%) of Houston samples yielded *E coli* with a median of 0.0 CFU/g. Both the frequency and the degree of contamination were significantly greater in the Guadalajara than in the Houston samples. The most consistently contaminated sauce in both cities was guacamole but, among the Guadalajara samples, the highest levels of contamination (median, 1000 CFU/g) were in pico de gallo. The mean pH of the sauces in the 2 cities did not significantly differ. Enterotoxigenic *E coli* (ETEC) were detected in 9% and enteroaggregative *E coli* (EAEC) in 44% of the sauces from Guadalajara that were tested for the presence of these organisms. Neither organism was detected in any of the Houston samples. No enteropathogens other than these 2 types of *E coli* were detected.

■ COMMENT BY STAN DERESINSKI, MD, FACP

Why is it that the things that make food taste good seem too often be bad for you? This study found that the piquant sauces provided at restaurants in cities in Texas and Mexico are commonly contaminated with enteric bacteria, but that the level of contamination was higher in the Mexican samples studied and enteric pathogens were isolated only from the latter. Adachi et al point out that, while the Houston sauces were refrigerated before being served, those in Guadalajara were prepared on-site and were not refrigerated and, in addition, may have been handled by more individuals than those in Texas.

A study of herbs and spices being sold in markets in Mexico found high levels of aerobic bacteria in most samples of garlic powder, cumin seed, and black pepper, with lower levels in oregano and bay leaves (Garcia). In addition, *Aspergillus niger* was found in 29% of samples, *Rhizopus* spp. in 19%, and *Penicillium* spp. and Cunninghamella in 8%. In fact, purchased spices in any country are not sterile. Thus, the European Spice Association specifications of quality minima for herbs and spices include the following:

- Salmonella absent in (at least) 25 g;
- Yeast & moulds 10^5/g target, 10^6/g absolute maximum;
- *E Coli*. 10^2/g target, 10^3/g absolute maximum.

Thus, while regulations are aimed at preventing importation of spices contaminated with enteric pathogens, relatively high concentrations of other microbes are considered acceptable.

In this study of prepared sauces, enteric pathogens were recovered from sauces at Guadalajara restaurants. Adachi et al point out that this is one of the first demonstrations of EAEC in food. Adachi et al have demonstrated that EAEC is a major cause of traveler's diarrhea in several regions and, in fact, is as common a cause of traveler's diarrhea in Guadalajara as ETEC.[1,2] ■

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Transmission of HCV From Surgeons to Patients

ABSTRACTS & COMMENTARY

Synopsis: *Molecular studies documented transmission of HCV from surgeons to patients; the risk of transmission during high-risk procedures in these look-back studies was 0.2-0.48%.*

Sources: Ross RS, et al. Risk of hepatitis C virus transmission from an infected gynecologist to patients. Results of a 7-year retrospective investigation. *Arch Intern Med*. 2002; 162:805-810. Ross RS, et al. Phylogenetic analysis indicates transmission of hepatitis C from an infected orthopedic surgeon to a patient. *J Med Virol*. 2002;66:461-467.

EIGHT WEEKS AFTER UNDERGOING A CAESAREAN SECtion delivery in December 1999, a 22-year-old woman developed acute icteric hepatitis C virus (HCV) infection. Risk factors for HCV infection were absent. One of her surgeons had been found 2 years previously to have chronic HCV infection and had had elevated serum transaminase levels as early as 1993 when he began working as a gynecologist in Itzehoe, Germany. The surgeon was viremic when tested several months after the surgical procedure with a concentration of 266,000 IU/mL. Both the patient and the surgeon were infected with HCV-1b and sequencing of the hypervariable region 1 of the viral genomes, together with phylogenetic analysis, demonstrated apparent identity of the viruses.

Of 2907 patients upon whom the surgeon had operated, 2285 (78.6%) responded to a questionnaire and were counseled and tested. Among the remainder, 33 had died, but none as the result of liver disease. Approximately one fifth of the 2338 gynecological and obstetric procedures were high risk for potential patient exposure to the surgeon's blood. These procedures included major interventions involving laparotomy, all hysterectomies, major repairs, and caesarean sections. One half of the procedures were medium risk, including cone biopsies, pelvioscopic procedures, perineal sutures, and episiotomies.

Seven patients were repeatedly HCV antibody positive, but 2 of these had no detectable HCV RNA by PCR in blood. Serological studies found that one of these was infected with HCV, but this method does not allow determination of the subtype. Three of the remaining 5 were infected with HCV 1a and 2 with HCV 1b. Molecular studies, however, demonstrated that the virus from the latter 2 differed from that of the index patient as well as the surgeon. Thus, the index patient was unique and the overall rate of transmission from surgeon to patients was 1 in 2286 or 0.04% (95% CI, 0.008-0.25%).

Separately, during July 2000, an orthopedic surgeon who specialized in traumatology and arthroplasty disclosed to the director of his German hospital that he was HCV-infected. At that time his blood HCV RNA concentration was 1.3 million IU/mL; he was infected with HCV subtype 2b. The timing of his infection acquisition was unknown, but it was determined that his serum liver enzyme concentrations were normal in 1997, and slightly abnormal in August 1999. Two hundred-seven of 229 patients who had undergone "exposure-prone" operations performed by the orthopedic surgeon beginning 26 weeks before August 1999 (the upper limit of the HCV incubation period), which was taken as the first evidence of HCV infection, were counseled and tested. Procedures considered exposure prone were open reduction of fractures, internal fixation, joint replacement, reconstruction and repair of ligaments, removal of hardware, and spine surgery.

Two of the 207 patients were infected with HCV subtype 1b and 1 with HCV subtype 2b. The latter, a 50-year-old man, had undergone a complicated total hip arthroplasty on March 21, 2000; he was known to have had normal liver enzyme levels in November 1999. Sequencing and phylogenetic analysis of the hypervariable region 1 demonstrated close relatedness to the virus infecting this patient and that recovered from the surgeon. Thus, the findings were consistent with intraoperative transmission of HCV from surgeon to patient and, if this was indeed the only instance of this, the transmission rate was 0.48% (95% CI, 0.04-1.15%).

■ COMMENT BY STAN DERESINSKI, MD, FACP

The reported frequency with which HCV is transmitted to a health care worker by an accidental injury with a contaminated needle is quite variable, ranging from 0-10%.[1] I

believe a reasonable estimate is approximately 3%. Thus, the risk of transmission of HIV, HCV, and HBV after such an injury is approximately 0.3%, 3%, and 30%—an easy and reasonably accurate progression to commit to memory. The actual risk in an individual case, however, is dependent upon a number of variables, including the HCV viral load and the volume of the inoculum.

The risk of transmission as the result of an individual percutaneous exposure in the opposite direction, from health care worker to patient, cannot be calculated from the data in the studies examined here. These lookback studies do, however, provide an initial benchmark with regard to the risk of such transmission per operative procedure. Unfortunately, the calculated transmission rates in these studies differ by an order of magnitude. Each study has deficits which make it difficult to assess the results with great accuracy. In the first instance, the study of transmission from the gynecologic surgeon was triggered by evidence of a transmission event, and, thus, potentially suffers from a bias tending to exaggerate the risk of transmission. On the other hand, the fact that more than one fifth of those exposed, including a number who had died, were never examined provides the potential for risk underestimation. Finally, while the overall risk of transmission in the obstetrics/gynecology setting was 1 in 2338 (0.04%), it was 1 in 488 (0.2%; 95% CI, 0.09-2.68%) when only high-risk procedures were taken into account, a value much closer to the 0.48% reported for high risk orthopedic procedures in the second study.

Ross and associates review 2 previous retrospective analyses of transmission to patients by cardiothoracic surgeons in which the calculated transmission rates were 2.3% (95% CI, 0.97-5.2%) and 0.36% (95% CI, 0.06-2.0%) during procedures most of which were likely high risk.[2,3] Thus, taken together, the reported risk of such transmission during high risk surgical procedures is in the range of 0.2% (obstetrics & gynecology), to 2.3% (cardiothoracic surgery). It is of interest that these results are also within the range reported for risk of transmission of HCV to health care workers as the result of a single sharps exposure.

It must be kept in mind that not all intraoperative transmission of hepatitis viruses is the result of direct transmission from surgeon (or anesthesiologist) to patient. A recently described outbreak of HCV infection in patients who had undergone gynecological surgery was recently reported but, rather than being the consequence of direct physician to patient transmission, it was most likely the result of contamination of a multidose vial of propofol.[4]

Reported instances of HCV transmission from health care worker to patient remain distinctly uncommon and, as a result, the US Centers for Disease Control (CDC) does not routinely recommend work restrictions for health care workers infected with HCV.[5] The CDC, the Society for Healthcare Epidemiology of America, and the British Advisory Group on Hepatitis do recommend, however, exclusion from patient care activity be considered for health care workers who have been documented to transmit HCV. In contrast, both German and Canadian regulations require that all HCV-infected health care workers be forbidden to perform exposure-prone procedures. ■

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Yellow Fever Acquired in Amazonas, Brazil

ABSTRACTS & COMMENTARY

Synopsis: *An American traveler returning from Amazonas, Brazil, died from yellow fever.*

Sources: Centers for Disease Control and Prevention. Fatal yellow fever in a traveler returning from Amazonas, Brazil, 2002. *MMWR Morb Mortal Wkly Rep*. 2002;51(15):324-325. Monath TP, Cetron MS. Prevention of yellow fever in persons traveling to the tropics. *Clin Infect Dis*. 2002;34:1369-1378.

A HEALTHY 47-YEAR-OLD MAN FROM TEXAS TRAVELED to Amazonas, Brazil, on a 6-day fishing trip in March 2002. He presented with abdominal pain, fever, and headache upon return, and subsequently developed intractable vomiting. His laboratory evaluation revealed leukopenia, anemia, thrombocytopenia, abnormal coagulation profile, renal failure, and liver failure. His IgM and IgG titers for yellow fever were negative. However, serum and postmortem liver samples tested positive for yellow fever by polymerase chain reaction.

The patient had not received pretravel evaluation, yellow fever vaccine, or malaria prophylaxis. He had slept on an air-conditioned fishing boat and used DEET. Among the 15 US travelers on the fishing trip, no one else became ill with fevers. Eight (53%) of the travelers had appropriate yellow fever vaccination

within 10 years and at least 10 days before arriving in Manaus. One traveler had been immunized 11 years prior to the trip; one traveler had been vaccinated 5 days before arrival, and one may have been immunized more than 30 years ago in the military. Four travelers had never been vaccinated against yellow fever, and 12 travelers did not take malaria chemoprophylaxis. According to the CDC report, the travel agent and outfitter appear to have underestimated the health risk for the group.

Monath and Cetron reviewed many of the issues regarding yellow fever in travelers. First of all, there is an increase in travel to areas where yellow fever is endemic. Secondly, the epidemiology of yellow fever in endemic countries is continually changing. Next, new concerns regarding vaccine safety have been raised since the report of severe multiorgan systemic failure in yellow fever vaccine recipients. Moreover, certified yellow fever vaccination centers tend to be located in urban areas, which requires motivation for travelers residing in rural areas who seek the vaccine. Finally, shortages in vaccine supply can contribute to inadequate vaccination.

Monath and Cetron estimated the risks associated with unvaccinated travelers. For someone visiting an area with epidemic yellow fever for 2 weeks, the risk of developing yellow fever infection is 1:267, and the risk of death is 1:1333. For the visitor to Africa, the risk of developing yellow fever infection is estimated to be 1:2000 for a 2-week trip, and the risk of death is 1:10,000. For the visitor to South America, the risk of yellow fever infection is estimated to be 1:20,000 and the risk of death is estimated to be 1:100,000. The highest risk occurs during the rainy season. In West Africa, the peak risk occurs from July to October, whereas in Brazil, it occurs from January to March.

Serious vaccine adverse reactions were also reviewed. These include hypersensitivity reactions (1 per 58,000-131,000 vaccinees), postvaccinal encephalitis (< 1 per 1,000,000), and multiorgan systemic failure (MOSF, 1 per 400,000).

Two other American and 2 European travelers died of yellow fever in recent years, 1996-1999, and none had received yellow fever immunization prior to their travel. Using a mathematical model, Monath and Cetron calculated yellow fever vaccine coverage in travelers, and estimated that vaccine coverage decreased by more than 50% from 1992 to 1998.

COMMENT BY LIN H. CHEN, MD

Yellow fever has reemerged. Outbreaks were reported predominantly in Africa: Cameroon, Ghana, Liberia, Nigeria, Sierra Leone, Gabon, and Kenya, but yellow fever has also resurged in South America, in Peru and Brazil.[1] Epidemics in Africa have affected the young, especially children younger than 15 years of age.[2] It is estimated that more than 200,000 cases occur annually in Africa, and less than 50% of the 34 African countries at risk have been able to finance some form of vaccination program for yellow fever.[2] Therefore, there are huge populations that are susceptible to the infection, and yellow fever epidemics can easily occur. Interestingly, 4 of the 5 American and European travelers who died of yellow fever since 1996 acquired their infections in South America.[3-5] This perhaps indicates an under-appreciation of the risk of yellow fever to travelers who go there.

Recent reports of severe adverse events (MOSF) have renewed concerns regarding the yellow fever vaccine (*See TMA Update* 2001;11:35-36).[6-8] The estimated incidence is 1 case per 400,000 vaccine recipients. On the other hand, Monath and Cetron noted that 190 million yellow fever vaccine doses have been distributed since the initial recognition of the syndrome in 1996, since which time 10 cases have been reported. Thus, the true incidence of the severe adverse events needs further elucidation.

Monath and Cetron suggest that the MOSF may probably develop only in patients who are receiving their primary vaccination. This may reassure the many patients who need repeat yellow fever vaccination. Monath and Cetron also report on a patient with chronic lymphocytic leukemia for whom IVIG was given, which contained protective levels of yellow fever neutralizing antibody. This passive protection may prove to be a good option for patients with contraindications to the yellow fever vaccine (ie, immunosuppression).

The case of fatal yellow fever in a traveler to Amazonas, Brazil, illustrates that some travel agents understate or underestimate potential health hazards. There is little motivation on the part of the travel agent to mention the need to see a travel medicine specialist. Nonetheless, the consequences of illnesses such as yellow fever and malaria in a traveler are severe. Travel medicine specialists should work with the travel agents to portray accurate risks to the travelers. ■

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CME Questions

1. **The emergence of which clonal group of Staphylococcus aureus in United States and worldwide could create a serious problem in management of SSSS in infants and newborns?**
   a. *eta* positive
   b. *etb* positive
   c. *eta* and *etb* positive
   d. *eta* or *etb* with *mecA* positive

2. **Which of the following statements is correct?**
   a. The epidemiology of yellow fever has not changed since the development of the vaccine.
   b. Since the 1980s, yellow fever epidemics have occurred predominately in Africa.
   c. The use of DEET and sleeping in air-conditioned accommodations should eliminate any risk of yellow fever.
   d. None of the above

3. **Which of the following is correct?**
   a. Enteroaggregative *E coli* does not cause traveler's diarrhea.
   b. Enterotoxigenic *E coli* has never been identified in food.
   c. The incidence of multi-organ system failure after yellow fever vaccination is estimated to be 1 in 400,00.
   d. Studies have failed to detect evidence of transmission of HCV from surgeons to patients.

In Future Issues:

Changing Patterns of New Tuberculosis Infections

UPDATES

By Carol A. Kemper, MD, FACP

Diagnosing TB: Are Fluoroquinolones a Problem?

Source: Dooley KE, et al. *Clin Infect Dis*. 2002;34:1607-1612.

The widespread use of fluoroquinolones—which are quite active against *Mycobacterium tuberculosis*—for the treatment of community-acquired pneumonia (CAP) has led to concerns that, in some instances, a diagnosis of TB may be missed or delayed. Dooley and colleagues examined 33 recent cases of pulmonary TB diagnosed within the United States, 24 (73%) of whom were first treated for presumed CAP (12 received a fluoroquinolone as monotherapy, 4 received a fluoroquinolone plus another antibacterial, and 7 received an antibiotic other than a fluoroquinolone). Dooley and colleagues compared the outcomes of 16 patients (48%) who received fluoroquinolone with those who did not. The groups were nearly identical at presentation, with a similar frequency of cough, fever, sweats, weight loss, and radiographic findings (13% in each group had cavitary disease).

There was a significant delay in the diagnosis of TB and in the initiation of antituberculous therapy in patients receiving flouroquinolones compared with those who did not receive flouroquinolones (median, 21 vs 5 days; $P = .04$). Patients receiving fluoroquinolones were more frequently discharged before a diagnosis of TB was made (63%) compared with those who did not receive fluoroquinolones (29%). This occurred despite the fact that specimens for AFB smear and culture were obtained within a similar time-frame for both groups, and the frequency of smear-positive disease was similar (31% vs 47%; $P > .20$). This may have been due to the rapid clinical response to fluoroquinolone therapy observed in some patients: 83% of patients receiving fluoroquinolone monotherapy had significant clinical improvement within an average of 3 days.

An important concern, not addressed by this study, was whether the empiric use of fluoroquinolone therapy impairs the ability to diagnose pulmonary TB, especially in the event that adequate specimens for smear and culture are not collected at presentation. In addition, fluoroquinolones are an important component of therapy in patients with multidrug resistant disease. While it is generally believed that a period of antibiotic exposure longer than the usual 10-14 days course of therapy for CAP is required to induce fluoroquinolone resistance, the widespread use of fluoroquinolones may eventually have a more global effect on the susceptibility of MTb to these agents. ■

VRSA Debuts in Michigan!

Source: Sievert DM, et al. *MMWR Morb Mortal Wkly Rep.* July 5, 2002.

This report describes the first clinical isolate of *Staphylococcus aureus* with high-level resistance to vancomycin (VRSA). The isolate was recovered from a 40-year-old diabetic with chronic renal failure on hemodialysis in Michigan. The patient had received multiple antibiotics (including vancomycin) for recurrent diabetic foot infections for about 1 year, when he developed MRSA bacteremia due to an infected arteriovenous graft. This infection was successfully treated with vancomycin and rifampin. Unfortunately, 2 months later, the patient developed a catheter exit site infection, cultures of which grew MRSA with high-level resistance to vancomycin (MIC > 128 mg/mL). One week later, cultures of a foot ulcer grew VRSA plus VRE. Both isolates remained sensitive to linezolid and quinupristine/dalfopristine.

Molecular studies confirmed that the *S aureus* isolate had acquired the *vanA* resistance gene, possibly from its neighboring VRE. Conjugative transfer of glycopeptide resistance genes from enterococci to *S aureus* has been demonstrated in vitro. *S aureus* isolates with low-level resistance to vancomycin have been popping up in many different countries, most recently England, but this is the first clinical isolate with evidence of the *vanA* gene.

Strict infection control practices have been instituted at the dialysis center, and, thus far, this appears to be an isolated case with no evidence of transmission. This sentinel case provides an opportunity to re-evaluate infection control practices at your center. While limiting transmission of these organisms is important, improved strategies to effectively decolonize patients chronically infected or colonized with MRSA should be explored—especially at dialysis centers where the reliance on vancomycin is so heavy. Sievert and associates also suggested that hospital laboratories should begin routinely performing MICs to vancomycin on MRSA isolates. ■

PHARMACOLOGY WATCH

Study Concludes Premarketing Drug Trials Underpowered

The phrase: "Never be the first to prescribe a new drug" may be sage advice, according to a new study. More than 10% of new drugs (56 of 548) approved between 1975 and 1999 were withdrawn from the market or given black box warnings indicating serious side effects. Half of the withdrawals occurred in the first 2 years of the drug's introduction while half of the black box warnings occurred within the first 7 years. A recent study concluded that premarketing drug trials may be underpowered to detect serious adverse drug reactions, and that many drugs have limited postmarketing follow-up. It is only after the use of these medications is expanded to large numbers of patients that trends are discovered. This study suggests that the FDA should consider raising its threshold for approving new drugs, especially when safe and effective therapies already exist. They also suggest that clinicians should be wary of new drugs and should immediately report adverse drug reactions to Medwatch, the FDA's adverse drug reporting program (*JAMA*. 2002;287:2215-2220). In an accompanying editorial, physicians from the FDA said that many of the warnings were the result of ongoing clinical studies such as the Cardiac Arrhythmia Suppression Trial. In general the FDA's evaluation process is improving. They do however agree that physicians should carefully contemplate prescribing a new drug—especially when safe alternatives are available (*JAMA*. 2002;287:2274-2275).

Sildenafil to Receive Competition

Sildenafil (Viagra-Pfizer) may soon be in for some tough competition as Lilly's tadalafil (Cialis) nears approval. The drug has received an approvable letter from the FDA for the treatment of erectile dysfunction and needs only completion of additional clinical pharmacology studies, manufacturing inspections, and finalization of labeling to receive approval. Tadalafil is reported to have a quicker onset of action than sildenafil. Lilly, which is marketing the drug in partnership with Seattle-based Icos pharmaceuticals, feels that a 2003 launch is likely.

New Thrombolytic Therapy Study

Patients with pulseless electrical activity do not benefit from thrombolytic therapy, according to a new study. A total of 233 patients with cardiac arrest and pulseless electoral activity were randomized to receive tissue plasminogen activator or placebo along with CPR. The proportion of patients returned a spontaneous circulation of 21.4% in the t-PA group vs. 23.3% in the placebo group (P = 0.85; 95% confidence interval, -12.6-8.8). The basis of study was assumption that coronary thrombosis or pulmonary thromboembolism are common causes of acute cardiac arrest and pulseless electrical activity. The study, however, found no benefit of fibrinolyis with t-PA in these patients (*N Engl J Med*. 2002;346:1522-1528).

COX-2 Findings Criticized in BMJ

An editorial in the June 1 edition of the *British Medical Journal* severely criticizes the findings of the Celecoxib Long-term Arthritis Safety Study (CLASS) trial (*JAMA*. 2000;284:1247-1255). That study, which was sponsored by, and has been widely publicized by, celecoxib's manufacturer Pharmacia, showed that the COX-2 inhibitor celecoxib, when compared with traditional nonsteroidal anti-inflammatory drugs (NSAIDs), was

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associated with the lower incidence of symptomatic ulcers and ulcer complications. The authors of the editorial argue however that the CLASS data reported in the JAMA article actually referred to the combined analysis of the results of the first 6 months of 2 separate and longer trials, both of which had different protocols, outcomes, and durations. With re-review of the data, almost all ulcer complications in the second half of the trial were in users of celecoxib. Also when the predefined definition of ulcer complications was used, a nonsignificant trend in favor of diclofenac was found. Perhaps more significantly, the *JAMA* paper reported only the first 6 months of data, when data up to 12 months were available to the researchers, at which time the rate of ulcer complications for celecoxib was equal to that of traditional NSAIDs. This editorial points out that the VIGOR trial comparing the upper GI toxicity of rofecoxib and naprosyn in patients with rheumatoid arthritis found an unequivocal benefit for the other COX-2 inhibitor, Rofecoxib and over a traditional NSAID (*N Engl J Med*. 2000;343:1520-1528). The authors point out not only the flaws in the CLASS data, but their disappointment in the use of the data in marketing efforts (*BMJ*. 2002;324:1287-288).

Salmeterol Aids Pulmonary Edema Victims

The beta adrenergic agonist salmeterol helps protect mountaineers against high-altitude pulmonary edema. Beta agonists, along with causing bronchodilation, also facilitate clearance of alveolar fluid in the lung, the primary cause of high-altitude pulmonary edema. In a recent Swiss study, 37 mountain climbers who were subject to pulmonary edema were randomized to receive salmeterol or placebo in a double-blind fashion. After a rapid ascent to 4500 m, 74% of those in the placebo group developed pulmonary edema vs. 33% in the salmeterol group (P = 0.02). Subjects in the study were also evaluated for nasal transepithelial potential difference, a marker of transepithelial sodium water transport in the distal airways. The results from susceptible individuals were compared to the results from mountaineers not prone to pulmonary edema. The mountaineers prone to pulmonary edema were found to have a low nasal potential difference value. It is speculated that this may also be the case of patients for prone to pulmonary edema from such conditions as congestive heart failure and acute respiratory distress syndrome. It is suspected that this mechanism may be an appropriate target for therapy with inhaled beta agonists (*N Engl J Med*. 2002;346:1631-1636).

Azithromycin vs. Vitamin C for Bronchitis

Azithromycin is one of the most popular antibiotics for the treatment of upper respiratory tract infections. However, a recent study suggests that it is no more effective than vitamin C in treating acute bronchitis. A total of 230 patients were randomized to receive azithromycin (Zithromax Z-Pack) for 5 days or vitamin C also for 5 days. Patients also received liquid dextromethrophan and albuterol inhalers spacer. After 7 days, 89% of patients in both groups had returned to normal activities. There's no difference in the incidence of adverse effects. Eighty-one percent of patients reported benefit from the albuterol inhaler. The authors conclude that azithromycin is no better than vitamin C in the treatment of acute bronchitis and suggest that similar studies should be done to identify the best treatment for this disorder (*Lancet*. 2002;359:1648-1654).

FDA News

The FDA has approved a new angiotensin II receptor blocker (ARB). Olmesartan medoxomil (Benicar—Forest Laboratories) is a once-a-day ARB that is approved for monotherapy or in combination with another antihypertensive. It will be available in 5-, 10-, and 20-mg tablets. It will be the seventh ARB approved for use in this country.

The Nonprescription Drug Advisory committee for the FDA will soon consider omeprazole (Prilosec) for over-the-counter status. AstraZeneca is proposing an over-the-counter 20 mg dose of omeprazole be taken for 14 days for symptoms of frequent heartburn.

The same committee recently proposed loratidine's (Claritin) switch to OTC for the treatment of urticaria. Final action on loraditine is expected to occur on November 28, 2002.

Drugs receiving expanded indications from the FDA:

Sertraline (Zoloft) has been approved for premenstrual dysphoric disorder, joining its cousin SSRI fluoxetine in having this indication.

QVAR inhaler, a nonfluorocarbon-based beclomethasone inhaler, has been approved for adults and children up to age 12; now the FDA has expanded the indication to children ages 5-11.

The FDA has approved a 35 mg once-a-week dose of residronate (Actonel) for the treatment of osteoporosis. Residronate joins alendronate (Fosamax) with a once-a-week formulation for this indication. ■