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First Report of Linezolid Resistance in *Staphylococcus aureus*

ABSTRACT & COMMENTARY

Synopsis: *A Staphylococcus aureus isolate with an MIC to linezolid > 32 mg/L was isolated from a peritoneal dialysis patient who had received prolonged linezolid therapy for MRSA peritonitis.*

Source: Tsiodras S, et al. *Lancet.* 2001;358:207-208.

An 85-year-old patient receiving peritoneal dialysis developed MRSA peritonitis. Because of a history of vancomycin allergy, he was treated with oral linezolid, 600 mg every 12 hours. The dialysis catheter was left in place. Over the ensuing 3 weeks, multiple MRSA isolates susceptible to linezolid (MIC = 2 mg/L) were recovered from the peritoneal fluid. One month after linezolid was started, the patient was readmitted with symptoms of recurrent peritonitis. Peritoneal fluid cultures yielded MRSA with a linezolid MIC > 32 mg/L on 3 separate occasions. During the remainder of the hospitalization, the patient received multiple antibiotics, including quinupristin/dalfopristin, ampicillin, azithromycin, gentamicin, and levofloxacin as treatment for MRSA, as well as for *Enterococcus faecalis* isolated from blood and *Pseudomonas* isolated from peritoneal fluid. The peritoneal fluid was ultimately sterilized, but the patient subsequently died. A total of 11 linezolid-susceptible isolates obtained during linezolid therapy were identical by pulsed field gel electrophoresis (PFGE). The 3 resistant isolates differed from the susceptible isolates by more than 6 bands—but were themselves closely related—differing by no more than 1 band. The resistant isolates showed a single G to T mutation at the same position in 23S rRNA-encoding DNA sequence.

COMMENT BY ROBERT MUDER, MD

This disturbing, but not unexpected, report follows closely after the report of the emergence of linezolid resistance in vancomycin-resistant *Enterococcus faecium* in the same journal.[1,2] As in the prior report, isolation of a linezolid-resistant strain occurred following

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prolonged linezolid therapy. However, the linezolid-resistant *S aureus* was clearly not clonally related to the original susceptible strain. It is not clear whether this strain was acquired during therapy, or emerged from a different susceptible strain that had been unapparently colonizing the patient.

The latter may be more likely, as Tsiodras and colleagues identified no other linezolid-resistant *S aureus* isolates in their facility. At present, many laboratories do not routinely perform susceptibility testing of *S aureus* against linezolid, assuming universal susceptibility. While the occurrence of a single episode of resistance may not be sufficient to alter current practices, it would be prudent to test selected MRSA isolates for linezolid susceptibility. At a minimum, this should be done when linezolid is used to treat life-threatening infections such as staphylococcal bacteremia or pneumonia, or when the clinical or microbiologic response to linezolid is inadequate. ❖

References

1. Gonzales RD, et al. *Lancet.* 2001;357:1179.
2. Muder R. Update: *Infectious Disease Alert.* 2001;20: 117-118.

Are Patients Dissatisfied if They do not get an Antibiotic for a Respiratory Infection?

ABSTRACTS & COMMENTARY

Synopsis: *Patient education can overcome their prejudice toward antibiotic therapy for acute bronchitis.*

Sources: Gonzales R, et al. *Eff Clin Pract.* 2001;4:105-111; Sargent J, Welch HG. *Eff Clin Pract.* 2001;4:136-138.

Gonzales and colleagues provide follow-up information on patient satisfaction after a study that documented the value of a patient education campaign on antibiotic prescribing.[1] The intervention led to a drop in antibiotic prescriptions for acute bronchitis from 74% to 48% in outpatient clinics in the Kaiser Permanente system in Denver, Colo, during the winter of 1997-1998.

This study involved 2 clinics, both of which had an office-based program to reduce antibiotic prescribing that consisted of exam room posters, fact sheets, and a 1-hour educational session for clinicians. The intervention clinic also had the benefit of direct patient education with direct mailings to patients, refrigerator magnets, self-care guidelines, CDC brochures on antibiotic use, and a letter from the clinic director. The period under study was the winter of 1998-1999. No new direct patient contact was made, but there was some reinforcement of the prior messages through newsletters and another hour lecture for clinicians on how to say "No."

Records of patients seen at the clinic with a diagnosis of acute bronchitis were reviewed. Satisfaction was assessed with a telephone questionnaire, to which 416 patients responded. One hundred fifty patients were excluded because of missing data or a good reason to get an antibiotic because of another respiratory infection. Antibiotics were used less frequently in the "intervention" clinic, but the percentage receiving antibiotics rose to 64% from 48% the year before. Nonetheless, the control clinic remained higher, with 85% of patients receiving prescriptions.

Patients were interviewed within 4 weeks of evaluation. Sixty-nine percent in the intervention clinic and 63% in the control clinic indicated their level of satisfaction with care was "very good" or "excellent." Further analysis was done

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to determine satisfaction factors but only a limited correlation was found with age and duration of symptoms.

COMMENT BY ALAN D. TICE, MD, FACP

This is a follow-up study with some interesting observations and insight provided in the accompanying editorial. While patient satisfaction has not been reported to correlate with antibiotic prescriptions, physicians commonly report it as a reason why they prescribe antibiotics. This article again demonstrates satisfaction with care among those who did not get prescriptions compared with those who did. It is, however, the first to demonstrate no difference in satisfaction even though there was clearly a change in prescribing. In fact, there was a suggestion that there was a higher rate of satisfaction in the intervention clinic in which antibiotics were less frequently prescribed.

How important a factor patient satisfaction or demands are in the decision to prescribe antibiotics is up for debate. Certainly, time with a patient providing evaluation, education, and assurance correlate well with satisfaction with care. Beyond that, there appears to be little indication that patients feel they know more about antibiotic prescribing than the physician.

What is also interesting about the study is that more than half of the patients received an antibiotic for an illness in which such therapy is not indicated. Is that the fault of the physician or the patient?

As Sargent and Welch point out in the editorial, there are many factors responsible for antibiotic use besides the patient's wishes. A simple rule is not adequate for the complexity of factors that must be considered in evaluating an infection. Risks of therapy must be weighed against the possibility of serious disease that would easily respond to early therapy but not later on. The risk of a lawsuit for an infection that might have responded to an antibiotic not prescribed is far higher than one in which the drug was prescribed. The cumulative effect on antimicrobial resistance in society is a subtle one and not often appreciated by an ill person or even a physician who is trying to help. It is not an easy situation these days in this litigious society and creates a difficult choice between the individual and society with the rising tide of antimicrobial resistance.

In essence, the decision to prescribe an antibiotic lies with the physician, although the relationship with the patient is essential, and the desire of a patient to receive an antibiotic may be moderated by a careful evaluation, education, and assurance. ❖

Reference

1. Gonzales R, et al. *JAMA.* 1999;281:1512-1519.

Can Antibiotic Prescribing to Children be Reduced?

ABSTRACT & COMMENTARY

Synopsis: *An educational outreach program, based on CDC materials, was effective in reducing unnecessary antibiotic use in a pediatric population.*

Source: Finkelstein JA, et al. *Pediatrics.* 2001;108:1-7.

Finkelstein and colleagues performed a randomized clinical trial involving 12 practices affiliated with 2 managed care organizations to determine whether educational outreach based on the CDC program of judicious antibiotic use was associated with decreased antibiotic use in children younger than 6 years of age. Physicians in the practices assigned to the intervention group participated in 2 meetings outlining the CDC recommendations and also received information concerning their prior prescribing rates. They also received instruction on the importance and means of distinguishing between acute otitis media and otitis media with effusion. Parents whose children were cared for at the intervention sites received a CDC brochure on antibiotic use by mail and were exposed to supporting materials displayed in waiting rooms.

Almost two-thirds of antibiotic prescriptions were for otitis media; 9.2% were for illnesses caused by viral infection. Antibiotic prescription rates during a pre-intervention baseline year varied significantly—especially among children from 3 to < 36 months of age in whom the number of antibiotic courses per person year of observation ranged from 1.61 to 3.73. Clinics randomly assigned as controls prescribed fewer antibiotic courses than did the experimental group during the baseline year.

The primary analysis included 8815 patients who were cared for in both the baseline and intervention years. Multivariate analysis demonstrated an adjusted intervention effect of a 16% (95%; CI = 8-23%) reduction in children 3 to < 36 months of age and a 12% (95%; CI = 2-21%) reduction in antibiotic administration to the older children.

COMMENT BY STAN DERESINSKI, MD, FACP

In the comment by Dr. Tice in the preceding contribution, he reviews a paper indicating that patient education can reduce their expectation of antibiotic therapy and enhance their level of satisfaction when appropriately denied such therapy. Dr. Tice ends his comment by pointing out that concerns about litigation may drive some antibiotic use and also by indicating that it is the

physician who is the ultimate key in reducing unnecessary antibiotic use.

Programs, such as that of the CDC, undoubtedly provide physicians with some degree of protection in the medicolegal arena—authoritative statements often win the day in that setting. The study reviewed here demonstrates that the CDC intervention is also effective in its primary aim, the reduction of unnecessary antibiotic use.

The data on antibiotic use in this study was extracted from automated pharmacy claims data. This method would not account for any provision of antibiotic samples to patients at the point of care, a potential confounding factor.

Finkelstein et al also do not mention anything about patient-informed consent. Since this was not a randomization of individual patients to therapy or no therapy, it would seem that this is acceptable. However, a full discussion of the need for patient consent when they are participating in what is, after all, a clinical trial, would be welcome. This actually extends to the entire issue of "managed care," which has been an experimental procedure in which a large proportion of the American population has participated, in most cases without realizing its experimental nature—although many of them have become aware of the adverse results. ❖

New Drug for Treatment of Cytomegalovirus

ABSTRACT & COMMENTARY

Synopsis: *Valganciclovir, a prodrug of ganciclovir, is effective in the treatment of CMV retinitis after oral administration.*

Source: *Am J Health Syst Pharm*. 2001;58:946, 948.

Roche has obtained approval for the marketing of valganciclovir (Valcyte), an oral prodrug of ganciclovir. Valganciclovir, like intravenous ganciclovir, is indicated for treatment of cytomegalovirus (CMV) retinitis in patients with AIDS. Currently, oral ganciclovir is only indicated for maintenance therapy after suitable induction therapy with intravenous ganciclovir. While no comparative clinical data are available on the efficacy of valganciclovir for maintenance therapy of CMV retinitis, the blood levels of ganciclovir following valganciclovir support its use. Compared to the higher recommended doses of oral ganciclovir, a 900-mg dose of valganciclovir produces a similar AUC and a higher Cmax. While both intravenous and oral ganciclovir are indicated for prevention of CMV infection in high-risk solid-organ-transplant recipients, valganciclovir has not yet been evaluated for this indication.

Ingested, valganciclovir is rapidly converted to ganciclovir by esterases in the intestinal wall and liver. The bioavailability of valganciclovir is significantly higher than ganciclovir capsules, and because the bioavailability is increased by a high-fat meal, it should be taken with food. It is eliminated renally as ganciclovir through glomerular filtration and active tubular secretion. The dose must be adjusted in patients with renal dysfuction and it cannot be given to hemodialysis patients because it is not available in a small enough dosage form. Like ganciclovir, patients should be monitored closely for the risks of granulocytopenia, anemia, and thrombocytopenia, and it should not be administered to patients if the absolute neutrophil count is less than 500 cells/µL, the platelet count is less than 25,000/µL, or the hemoglobin is less than 8 g/dL. Because of the teratogenicity of valganciclovir and ganciclovir, the usual cautions regarding pregnancy, breast-feeding, and the need for adequate contraception apply.

In an open-label study that was used to gain approval for the drug, 160 AIDS patients with newly diagnosed CMV retinitis were randomized to receive induction therapy with either oral valganciclovir or intravenous ganciclovir. The dosage of valganciclovir was 900 mg twice daily for 21 days, followed by 900 mg once daily for 7 days. (For comparison, the maintenance dosage of oral ganciclovir is 1000 mg 3 times daily, due to its lower bioavailability.) The dosage of intravenous ganciclovir was 5 mg/kg twice daily for 21 days, followed by 5 mg/kg once daily for 7 days. The progression of retinitis was determined on the basis of masked review of retinal photographs taken at baseline and week 4, and was nearly identical in both groups with approximately 80% of the patients remaining stable. Additionally, all adverse effects such as diarrhea, nausea, headache, vomiting, abdominal pain, pyrexia, insomnia, peripheral neuropathy, parasthesia, and retinal detachment occurred at similar rates between the 2 groups.

The product is available as 450-mg tablets and because of potential toxicities, the tablets are not to be broken or crushed. Complete product information is available at http://rocheusa.com/products/valcyte/pi.html.

COMMENT BY THOMAS G. SCHLEIS, MS, RPh

Valganciclovir does appear to offer an advantage over oral ganciclovir in that it can be used as induction therapy in the treatment of CMV retinitis. The other advantage is that it can be administered once daily as maintenance therapy, unlike oral ganciclovir, which must be given 3

times daily. This would be expected to increase compliance in a population that is already burdened with numerous and complex medication regimens.

The comparative costs of intravenous and oral ganciclovir vs. valganciclovir for a 70 kg patient are shown in Tables 1 and 2.

From the cost comparison, it is interesting to note that intravenous ganciclovir is actually the least expensive in terms of drug costs, although the other costs associated with intravenous therapy such as catheters, supplies, and personnel costs would still make it the most expensive therapy. In most cases, however, oral medications are usually less expensive than their intravenous counterparts. For maintenance therapy, the cost of oral ganciclovir and valganciclovir is similar and the advantage of once daily administration makes valganciclovir the obvious choice.

In summary, oral valganciclovir now makes it possible to treat CMV retinitis and provide maintenance therapy without the need for intravenous therapy. The advantage of once daily administration and similar cost makes it the preferred choice for maintenance therapy, although it currently does not have FDA approval for this indication. ❖

Table 1

Comparative Costs of Intravenous and Oral Ganciclovir vs. Valganciclovir for a 70 kg Patient*

Medication	Therapy	Total Daily Dosage (70 kg person)	Total Daily Average Wholesale Price*
IV Ganciclovir	Treatment of CMV retinitis	5 mg/kg q 12 h = 700 mg	$51.94
Oral Ganciclovir	Treatment of CMV retinitis	N/A	N/A
Valganciclovir	Treatment of CMV retinitis	900 mg q 12 h = 1800 mg	$115.12

*Based upon MediSpan™ Average Wholesale Pricing of $927.43 for 25 vials of 500 mg ganciclovir for injection, $1541.58 for 180 capsules of oral ganciclovir, and $1726.56 for 60 tablets of valganciclovir.

Table 2

Comparative Costs of Intravenous and Oral Ganciclovir vs. Valganciclovir for a 70 kg Patient*

Medication	Therapy	Total Daily Dosage (70 kg person)	Total Daily Average Wholesale Price*
IV Ganciclovir	Maintenance therapy for CMV retinitis	5 mg/kg q 24 h = 350 mg	$25.97
Oral Ganciclovir	Maintenance therapy for CMV retinitis	1000 mg 3 times daily = 3000 mg	$51.36
Valganciclovir	Maintenance therapy for CMV retinitis	900 mg q 24 h	$57.56

*Based upon MediSpan™ Average Wholesale Pricing of $927.43 for 25 vials of 500 mg ganciclovir for injection, $1541.58 for 180 capsules of oral ganciclovir, and $1726.56 for 60 tablets of valganciclovir.

Wall-Mounted Gel Dispensers Improve Compliance with Hand Antisepsis Guidelines

ABSTRACT & COMMENTARY

Synopsis: *The availability of rinse-free alcohol gel from wall-mounted dispensers resulted in a 32.8% increase in the rate of hand antisepsis 2-6 weeks after installation.*

Source: Earl ML, et al. *Am J Nurs.* 2001;101(3):26-33.

Although it is common knowledge that the hands of health care workers can carry disease-causing organisms from one patient to another, compliance with hand antisepsis guidelines remains poor. During the past decade, rinse-free alcohol-based antiseptic gels that require neither soap nor water have been developed as an alternative means of hand cleansing. Earl and colleagues postulated that ready access to such gels would increase rates of compliance with hand antisepsis guidelines.

The study was conducted in 2 units, a 20-bed SICU and 13-bed MICU, located in a university-affiliated tertiary care facility. Phase I established baseline rates of compliance. During 30 days of observation, 1090 episodes were observed that required hand antisepsis and compliance was 39.6%. Subsequently, in Phase II, 73 gel dispensers (Kimcare Instant Hand Sanitizer, Kimberly-Clark Corp.) were installed inside and outside patient rooms, and observations were conducted to establish the short-term effect of the intervention. During 25 days, 1091 episodes were observed that required hand antisepsis, and the overall rate of compliance increased 32.8%, with the rate of hand antisepsis increasing significantly ($P < 0.001$) in the SICU. Rates also increased in the MICU but not significantly ($P = 0.09$). Slightly more than half of all observed instances of hand antisepsis involved the use of gels (62.8% nursing personnel, 61.6% physicians, 52.4% ancillary personnel). Gel dispensers located in the

hallways were 30 times more likely to be used than those mounted inside patient rooms.

Phase III was conducted 10-14 weeks after the dispensers were installed to test long-term effects of the intervention. Over 30 days, 834 episodes were observed that required hand antisepsis. Compliance increased an additional 8.4% to 43.9% above baseline. In all phases of the study, ancillary personnel had the highest compliance with hand antisepsis (83.5%), followed by nursing personnel (56.9%) and physicians (43.7%).

COMMENT BY LESLIE A. HOFFMAN, PhD, RN

Waterless alcohol-based hand hygiene products are available in a variety of different formulations, including gels, rinses, and foams. In Europe, where they are known as hand gels, they have been used in health care facilities for many years. Typically containing an alcohol compound plus an emollient, gels are thought to work against microorganisms by denaturing proteins, thereby destroying cell walls. When used at full strength, they are the most effective and fastest way to reduce microbial counts on the skin. Reluctance to use these gels largely results from the belief that they are drying to the skin, but studies reveal that they are actually less drying than soap and water cleansing.

In this study, the simple action of placing gel dispensers inside and outside of patient rooms increased compliance with hand antisepsis 43.9% above baseline (soap and water only). More importantly, this increase was sustained over the 3-month observation interval. While the study lacks blinding, knowledge of the study did not appear to be a factor motivating improved rates of hand antisepsis. Compliance rates were determined by 5 observers, all public health graduate students, who recorded episodes of patient contact and noted whether hand washing occurred. Observation sessions were scheduled at varied times of the day and night in order to obtain an accurate representation of all shifts. Unit managers, but not unit staff, were informed about the purpose of the study. If asked, the observers stated they were conducting an infection control study for the epidemiology unit.

Several findings suggest that convenience may have been the primary factor motivating change. Sinks in patient rooms were located a distance from the bed area. Gel dispensers were placed in convenient locations on the wall next to each bed and just outside the door. Of note, gel dispensers located outside the room were 30 times more likely to be used than those inside the room were. Finding a sink and washing the hands with soap and water requires more time than using a conveniently placed gel dispenser. Findings of this study support that gel dispensers placed at opportune locations—eg, inside and just outside patient rooms—may be a practical method of encouraging hand antisepsis by ICU personnel and, thereby, reducing nosocomial infection rates. ❖

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Pharmacology Update

Twinrix—A New Vaccine for Hepatitis A and B

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

The fda recently approved a vaccine that provides dual protection against hepatitis A and B. Marketed as Twinrix by GlaxoSmithKline Pharmaceuticals, the vaccine combines inactivated hepatitis A vaccine with hepatitis B recombinant vaccine, the antigenic components in Havrix and Engerix B, respectively. The combination reduces the number of injections needed to immunize patients to both viruses from 5 to 3.

Indications

Twinrix is indicated for the active immunization of adults (18 years of age or older) against disease caused by hepatitis A virus and infections by all known subtypes of hepatitis B virus.[1]

Dosage

The primary immunization for adults is 1 mL given intramuscularly in 3 doses at 0, 1, and 6 months. The injection should be given in the deltoid region, not in the gluteal region. Administration in the gluteal region may result in a suboptimal response.[1] Each 1 mL dose of Twinrix contains 720 ELISA units (EL.U) of inactivated hepatitis A virus and 20 mcg of recombinant hepatitis B surface antigen (HbsAg).

Potential Advantages

The combined vaccine offers more convenience and potentially better compliance. Twinrix requires 3 injections and 3 sites compared to 5 injections and 5 injection sites (2 for hepatitis A and 3 for hepatitis B).

Potential Disadvantages

Safety and effectiveness of Twinrix have not been

established in pediatric patients. The effectiveness in patients age 65 years and older has also not been established.[1]

Comments

The immunogenicity and safety of Twinrix has been demonstrated in more than 1500 subjects. After the completion of the 3-dose regimen, seroconversion was detected in more than 98% of subjects against both hepatitis A and B.[1,2] In a comparative trial, Twinrix was at least as effective as Havrix and Engerix-B administered separately.[1] The antibody titers achieved with Twinrix were actually higher than that achieved with Havrix. This may be attributed to a difference in dosing. Twinrix is given as 3 doses of 720 EL.U at 0, 1, and 6 months while Havrix is given as 2 doses of 1440 EL.U at 0 and 6 months.

The most frequent reported side effects are local soreness and headache or fatigue. These were similar to that reported with Havrix or Engerix-B.[1]

Clinical Implications

Hepatitis B is a viral infection with serious consequences including acute hepatic necrosis, chronic active hepatitis, and cirrhosis of the liver. Chronic hepatitis B infection has been linked to hepatocellular carcinoma. The main modes of transmission are parenteral drug abuse, unprotected sex, visits to high-prevalence countries, exposure to infected body fluids, and high-risk occupations or settings. The CDC estimates that there are 1-1.25 million chronic carriers of hepatitis B in the United States. These persons can infect others in the community. Currently, vaccination is routine in children. This strategy will not only protect persons from infection but reduce disease incidence by reducing transmission.

Hepatitis A is one of the most frequently reported vaccine preventable diseases and is considered a major public health problem.[3] The main mode of transmission is fecal-oral. Contaminated food or water or infected food handlers are a major source of transmission. Unlike hepatitis B, there is no routine childhood vaccination for hepatitis A. Twinrix offers a vaccine for adults who have not been vaccinated with either hepatitis A or B, and is recommended for those at risk of exposure to these viruses. These include travelers to endemic areas (who often are immunized against hepatitis A but rarely against hepatitis B), those with chronic liver disease, high-risk workers (laboratory, sanitation workers, medical personnel), employees of day-care centers, correctional facilities, persons with at-risk behavior (homosexuals, parenteral drug users), military personnel, persons with clotting-factor disease (eg, hemophiliacs), and those in close contact with individuals with hepatitis A.

Twinrix provides a convenient vaccine for the immunization against preventable diseases caused by hepatitis A and B in adults. The duration of protection is at least 4 years.[1] ❖

References

1. Twinrix Product Labeling. GlaxoSmithKline Pharmaceuticals. May 2001.
2. Thoelen S, et al. *Vaccine.* 1999;17:1657-1662.
3. CDC. *MMWR Morb Mortal Wkly Rep.* 1999;48(no. RR-12):18-29.

Dr. Elliott is Chair, Formularly Committee, Northern California Kaiser Permanente, Assistant Clinical Professor of Medicine, University of California-San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, Calif.

CME Questions

10. Patient dissatisfaction in not receiving an antibiotic is a major reason they are prescribed.
a. True
b. False

11. A campaign to reduce antibiotic prescribing can be much more successful if patients rather than just physicians are educated.
a. True
b. False

12. When rinse-free alcohol gel dispensers were mounted inside and outside patient rooms, ICU personnel:
a. used gel dispensers inside the room more frequently.
b. used gel dispensers outside the room more frequently.
c. did not change rates of compliance with hand antisepsis.
d. improved short-, but not long-term compliance with hand antisepsis.
e. None of the above

13. Which is *not* true about Twinrix?
a. It is less effective than both vaccines given individually.
b. It is not approved for children.
c. It requires 3 injections.
d. It is given at 0, 1, and 6 months.

In Future Issues:

The Pseudomonas Hot-Foot Syndrome

UPDATES

By Carol A. Kemper, MD, FACP

Counterfeit Malaria Drug in SE Asia

Sources: Newton P, et al. *Lancet.* 2001;357:1948-1950; *Wall Street Journal*. June 26, 2001;International section: A16.

Artesunate, derived from the Chinese herb of the same name, is one of the oldest antimalarials in southeast Asia, where it is frequently used in the suppression of falciparum malaria. Most artesunate in southeast Asia is manufactured by Guilin Pharma in China. Studies have shown that quality control standards for the manufacturing and distribution of many antimalarials in southeast Asia are often lacking. Pills and tablets are often found to contain inadequate or expired drug.

Newton and colleagues found evidence of a widespread and large-scale manufacturing and distribution operation of counterfeit artesunate in southeast Asia. Overall, 39 of 104 (38%) samples purchased from shops and pharmacies in Myanmar, Cambodia, Vietnam, Laos, and western Thailand contained no artesunate. The problem is so significant Newton et al report that one organization, which was thrilled to lay their hands on 100,000 tablets of artesunate, subsequently discovered they were fake.

Newton et al determined that counterfeit drug could be distinguished from the real thing based on a number of features in the packaging, including the printing, the bar code, an inadequate or absent company hologram, as well as lower cost. Many fake pills had the "AS" logo stamped only on 1 side of the tablet—not both—as with the real drug. Interestingly, the fake artesunate has been manufactured with a bitter taste, reminiscent of chloroquine (compared to the chalky taste of artesunate), as if the manufacturer wanted people to believe they were taking a "true" antimalarial. A "red dye" test, which is based on a reaction between an alkali-decompensation product of artesunate and a salt, can also differentiate fake from true drug.

The European union is currently sponsoring a program to combat the distribution of fake artesunate in SE Asia, which has been field-tested with success in 2 rural provinces of Cambodia. Artesunate and mefloquine are packaged together in a tamper-proof box, intended to thwart the separate sale of the drugs at greater profit. They are also field-testing a rapid test for malaria right at the pharmacy, where most people purchase their drugs without first seeing a doctor. However, Newton et al stressed the need for more stringent governmental control, pointing out that while there have been no prosecutions for the manufacture, distribution, or sale of fake antimalarials, Vietnam has given prison sentences of up to 20 years for illegal trafficking of fake Viagra! ■

Fungal Infections and Cardiac 'Devices'

Source: Nurozler F, et al. *Ann Thorac Surg.* 2001;71:614-618.

Nurozler and colleagues from Columbia University in New York report on their 10-year experience with fungal infection in 165 persons who received implantable left ventricular assist devices (LVAD). A total of 112 patients received vented electric devices (VED) and 53 patients received pneumatic devices (PD). Almost half of the patients received antibiotics for complicating bacterial infections. While only 5 patients had evidence of fungal infection at the time the devices were implanted, 37 (22.4%) patients subsequently developed fungal infections, more than 90% of which were candidal. Device-related infections were found in 18 (10.9%), with positive cultures of the LVAD pocket, mediastinum, drive-line site, or of the explanted device. Patients with pneumatic devices were more likely to have drive-line infection. In contrast, patients with VEDs were more likely to have pocket and mediastinal infections.

Fungal endocarditis occurred in 5 (3%) patients, all of whom had positive fungal cultures from the blood-contacting surfaces of the device at explantation. Three of these were due to *C albicans*, 1 due to *C parapsilosis*, and 1 developed sepsis from *Syncephalastrum racemosum*. All 5 infections were difficult to diagnosis; echocardiograms were negative for vegetations or pannus formation in all 5 cases (most likely because of the reflective properties of the devices that limit the sensitivity of echo). Only 1 patient had positive blood cultures, despite gross histologic evidence of complicating fungal infection of the device itself in 2 cases. One patient died acutely when the outflow tract of the device became obstructed from fungal matter, and another had an embolic cerebrovascular event with evidence of a large fungal ball obstructing the outflow tract at explantation, although he had no hemodynamic signs of outflow obstruction. Clinical signs of fungal infection were nonspecific, and included fever, weight loss, and sepsis, although fever may not always be present.

In addition to the presence of a prosthetic device in immediate contact with blood, LVAD may significantly affect cell-mediated immunity. Given the high rate of fungal colonization and severe infection in patients with LVAD, patients with continued fever or sepsis should probably receive Amphotericin B plus broad-spectrum antibacterials. ■