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INSIDE

Treatment of Legionnaires Disease

ABSTRACTS & COMMENTARY

Synopsis: *Levofloxacin was at least as effective as macrolide therapy in the management of Legionnaire's disease.*

Sources: Mykietiuk A, et al. Clinical Outcomes for Hospitalized Patients with *Legionella pneumonia* in the Antigenuria Era: The Influence of Levofloxacin Therapy. *Clin Infect Dis*. 2005;40:794-799; Blazquez Garrido RMB, et al. Antimicrobial Chemotherapy for Legionnaires Disease: Levofloxacin vs Macrolides. *Clin Infect Dis*. 2005;40:800-806.

MYKIETIUK AND COLLEAGUES REPORT THAT 139 (7.2%) OF 1934 prospectively evaluated adults without severe immunocompromise admitted over an approximately 8-year period to a university hospital in Barcelona because of community-acquired pneumonia (CAP) had evidence of *Legionella* infection. According to hospital guidelines, patients with CAP received empiric therapy with a lactam with or without a macrolide or, as an alternative allowed from 1998 on, levofloxacin alone. Of those with a urine antigen test positive for *L. pneumophila* serogroup, 1 received specific therapy with either a macrolide with or without rifampin or with levofloxacin.

Appropriate therapy was administered to 120 patients with legionellosis, including 40 who received levofloxacin (500 mg daily) and 80 treated with either erythromycin (1gm IV 6 hourly) or clarithromycin (500mg IV 12 hourly). Approximately one-fourth of patients in each group also received corticosteroids. The case fatality rate was 2.5% in levofloxacin recipients and 5% in those given macrolides (P = NS), and complications occurred in 25% in each group. Levofloxacin therapy was, however, associated with a shorter time to defervescence (2.0 vs 4.5 days; P <.001) and clinical stability (3 vs 5 days; P = .002), as well as median time to discharge (8 days vs 10 days; P = .518).

In a second report, Blazquez Garrido and colleagues describe the results of therapy in another observational, prospective, nonrandomized study of patients with Legionnaires disease in a setting of a community outbreak in Murcia. Antibiotic therapy was chosen by

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the clinicians attending the patients. Of the 292 patients included in this analysis, 65 received clarithromycin or azithromycin and 143 received levofloxacin, with 45 of the latter also receiving rifampin.

All but one patient, a levofloxacin recipient, survived. While there was no difference in outcome between treatment groups in patients with mild-to-moderate infection (Fine groups I-III), the frequency of complications was higher in macrolide than in levofloxacin recipients (27.1% vs 3.4%; $P = .02$), and the duration of hospitalization was longer (11.3 days vs 5.5 days; $P = .04$). A comparison of 45 patients who received levofloxacin alone, with 45 who received it in combination with rifampin, found that the latter group had more complications, as well as a longer duration of fever and of hospital stay.

COMMENT BY STAN DERESINSKI, MD, FACP

Although both of these studies were prospective, neither randomly assigned the antibiotic treatment, making the results potentially corrupted by confounding. For instance, in the experiment reported by Mykietiuk et al, all the patients given levofloxacin received it in the latter years of the study, and it is possible that other changes in management introduced at the same time may have improved outcomes. Thus, strictly speaking, the results can only be used to generate hypotheses for future randomized trials. Since, however, results of such trials are not likely to be available for quite a while, if ever, we are left to make the best use of this information for our patients that we can.

Perhaps the most interesting thing about these results is the extraordinarily low mortality in these patients with *Legionella* infection, a disease previously associated with mortality rates of 5% to 25% in immunocompetent patients. This apparent improvement in outcome is likely related, at least in part, to the routine inclusion of antibiotics with activity against this organism in published guideline recommendations for the empirical management of CAP, as well as other changes in practice that have occurred over time. In addition, the availability of the urine antigen test for the detection of infection due to *L. pneumophila* serogroup 1 has probably allowed for the diagnosis of less severe cases than in the past.

These studies suggest that levofloxacin therapy of *Legionellosis* is at least as effective as treatment with a macrolide. In fact, while ultimate cure rates are similar, levofloxacin therapy may be associated with a lower incidence of complications and more rapid clinical improvement, including more rapid derfervescence. However, it is possible that not all macrolides have similar efficacy in this infection; only a minority of patients given a macrolide received azithromycin. A recent publication reported that a favorable outcome was achieved in 22 of 23 patients with *Legionella pneumophila* infection treated with azithromycin for a mean duration of 8 days.[1] Also of note, is the finding by Blazquez Garrido et al of lack of evidence for benefit from the addition of rifampin to levofloxacin therapy. The addition of rifampin, in fact, may have had a negative effect.

The rank order of in vitro activity against *L. pneumophila* serogroup 1 is reported to be fluoroquinolones > ketolides > macrolides, whether using broth dilution susceptibility testing or examining intracellular efficacy.[2] All the available respiratory fluoroquinolones are active in vitro against *L. pneumophila*, and each is likely to be effective in the treatment of pneumonia due to this organism. None, however, have as much published clinical experience available to demonstrate this efficacy as does levofloxacin. In addition to the studies discussed here, a compilation of cases from clinical trials found that there were no deaths among 75 patients with legionellosis treated with levofloxacin.[3] Of note, is that treatment with 750 mg for 5 days appeared to be as

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efficacious as 500mg for 7-14 days; in a trial comparing 750 for 5 days and 500 for 10 days, 11 of 11 of the former and 3 of 3 of the latter were cured.[4] ■

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High Rate of Cytomegalovirus Transmission in Breast Milk

ABSTRACT & COMMENTARY

Synopsis: *Cytomegalovirus (CMV) is frequently transmitted via breast milk and poses risk for infant infection and symptomatic disease, especially for preterm infants. CMV is preferentially shed in breast milk without detectable CMV in peripheral blood.*

Source: Meier J, et al. Human Cytomegalovirus Reactivation During Lactation and Mother-to-Child Transmission in Preterm Infants. *J Clin Microbiol.* 2005;43:1318-1324.

HUMAN CYTOMEGALOVIRUS (CMV) SHEDDING IN BREAST milk was prospectively studied in 73 mothers and their 89 preterm infants in Berlin, Germany. Gestational age was 24-33 weeks (median, 28 weeks) and birthweight was 380-2010 g (median, 1,119 g). Feeding was initiated as early as possible, usually by 24-48 hours of life. Only blood products from CMV-seronegative donors were used for transfusions. Breast milk, pharyngeal (endotracheal, if intubated) aspirates, and urine were collected at day 3 of life, day 7, and then weekly through 64 days, and tested by PCR and viral culture.

By PCR, 48 of 73 (66%) mothers shed CMV in breast milk, which corresponds to the CMV seroprevalence of about 60% in the German population. The maternal CMV serostatus was known for 28 women; 19 of 20 (95%) seropositive women shed CMV in breast milk, compared to 1 of 8 (13%) seronegative women, suggesting acute CMV in one mother. Peripheral blood mononuclear cells were tested from 13 seropositive mothers with CMV in breast milk, and 6 seronegative who were also negative for CMV in breast milk. Only 2 of 13 (15) seropositive mothers had detectable virus in blood.

Overall, 20 of 73 (27%) mothers shed CMV in breast milk, and 21 of 89 (24%) infants acquired CMV. The transmission rate from CMV-positive mothers to their offspring was 38% (21 of 55 mother-infant pairs, including one set of twins). Postnatal CMV infection was confirmed in 12 of the 22 infected infants by negative urine PCR for CMV within the first 2 weeks, followed by positive urine PCR. The remaining 9 infants had positive urine PCR for CMV within the first 2 weeks of life, suggesting possible congenital infection. Only 2 of the 22 infected infants developed symptomatic disease, one with a sepsis-like illness and another with hepatitis and icterus.

■ COMMENT BY HAL B. JENSON, MD, FAAP

Human CMV virolactia, or virus in breast milk, appears to be much more frequent than previously appreciated. In this study, nearly all lactating women who are seropositive (19 of 20, 95%) shed CMV in breast milk, as detected by PCR. Interestingly, this did not correlate with maternal CMV viremia, as only 2 of 13 seropositive women tested had CMV detected in peripheral blood. These results suggest that CMV replication may occur preferentially in breast tissues, which may represent a distinct virological compartment from bone marrow granulocytes and monocytes that are known to harbor latent CMV. These findings are consistent with other studies that CMV DNA in breast milk results from local virus replication rather than systemic virus replication and the transmission of virus via the egress of maternal leukocytes in breast milk.

Symptomatic CMV disease was documented in 2 of 22 infected infants (9%), or 2 of 12 (17%) infected infants with confirmed postnatal infection. Although this study used PCR, which may detect DNA but not infectious virus, the documented infections in 22 infants without another source supports the conclusion that viral DNA in breast milk represents intact CMV virions.

If extrapolated to all preterm infants, there is a large vulnerable population with a significant risk of symptomatic disease. If confirmed by larger studies, these results suggest that maternal breast milk for preterm

infants should possibly be routinely frozen, pasteurized, or otherwise treated before use in preterm infants during the first few weeks of life. Although treatment should diminish the risk of postnatal, or acquired, CMV infection transmitted via breast milk, treatment would likely also adversely affect the immunoglobulins, leukocytes, and other immunological constituents in breast milk. ■

Purpura Fulminans Due to *Staphylococcal aureus*

ABSTRACT AND COMMENTARY

Synopsis: *Five cases of purpura fulminans related to infection with* Staphylococcal aureus *were identified in Minnesota during 2000-2004.*

Source: Kravitz GR, et al. Purpura fulminans due to *Staphylococcus aureus*. *Clin Infect Dis*. 2005;40:941-947.

KRAVITZ AND COLLEAGUES IDENTIFIED 5 CASES OF purpura fulminans associated with *Staphylococcus aureus* infection in the Minneapolis-St. Paul area during the period 2000-2004. Three of the patients died, and 2 recovered with significant sequelae. Three of the 5 cases had *Staphylococcal aureus* isolated from blood cultures, and 2 patients had staphylococci isolated from the respiratory tract, with negative blood cultures. This latter finding suggested to Kravitz et al that the pathogenesis of purpura fulminans, in these cases, may be due to exotoxin production by the organisms and/or host factors. Three isolates demonstrated production of *Staphylococcal enterotoxin* C (SEC), one toxic shock syndrome toxin-1 (TSST-1), and one *Staphylococcal enteroxin* B (SEB). In addition, all 3 of the SEC-expressing isolates also demonstrated the presence of Panton Valentine leukocidin (PVL).

■ COMMENTARY BY DEAN WINSLOW, MD, FACP

Purpura fulminans is generally considered by most clinicians to be synonymous with meningococcemia. However, it most likely represents a subset of the syndrome of symmetric peripheral gangrene (defined as ischemic necrosis simultaneously involving distal portions of 2 or more extremities, in the absence of proximal arterial obstruction), which can be seen in association with a variety of bacteremic and nonbacteremic infections, as well as cardiogenic shock, other low flow states, vasospasm, Raynaud's, cold agglutinin disease, primary polycythemia, and venomous snake bites.[1] In addition to meningococcemia, symmetric peripheral gangrene has occasionally been seen in association with bacteremic infection due to *S. pneumoniae*, other streptococcal species, *S. aureus*, various gram negative organisms, and *Aspergillus*.[2] Purpura fulminans has also been described in association after relatively benign, non-bacteremic infections seen in childhood, including scarlet fever, streptococcal pharyngitis, varicella, and measles.[3]

The pathogenesis of infection-associated symmetric peripheral gangrene/purpura fulminans is complex. Although often associated with DIC, shock (rather than DIC) may be the more important factor in symmetric peripheral gangrene. Histologic examination of the skin often shows a Schwartzman-like reaction with hemorrhage, perivascular cuffing, and intravascular thrombosis.[3] Acquired or transient deficiencies of protein C and/or protein S have been identified in some patients with purpura fulminans, and the lesions are quite similar grossly and histologically to that seen in patients with congenital deficiencies of these clotting factors who develop warfarin-associated skin necrosis.[4]

Superantigens are pyrogenic exotoxins that induce massive cytokine release by bypassing the normal specific interaction between T-cell receptor, antigen, and the MHC class II receptor by directly binding to the external portion of the V beta domain of MHC class II.[5] Staphylococcal superantigens include TSST-1 and several Staphylococcal enterotoxins. In the 5 cases of purpura fulminans associated with *S. aureus* described by Kravitz et al, all isolates expressed one or more of these superantigens, raising speculation that they may be playing a pathophysiologic role. Clearly more research will need to be done to define the role of these and other bacterial virulence factors and host factors.

It is also clear that while purpura fulminans due to *S. aureus* is probably not a new syndrome, the occurrence of these 5 cases during a short period of time in Minnesota should raise awareness of clinicians to this entity. In addition, it will be interesting to see if interventions such as administration of activated protein C or intravenous immunoglobulin (which could potentially neutralize various superantigens) may prove useful in the future. ■

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Biofilm

ABSTRACTS & COMMENTARY

Synopsis: *Growth in biofilm is associated with dramatic changes in gene expression by* S. epidermidis.

Sources: Yao Y, et al. Genomewide Analysis of Gene Expression in *Staphylococcus epidermidis* Biofilms: Insights into the Pathophysiology of *S. epidermidis* Biofilms and the Role of Phenol-Soluble Modulins in Formation of Biofilms. *J Infect Dis*. 2005;191:289-298; Kocianova S, et al. Key Role of Poly-Gamma- DL-Glutamic Acid in Immune Evasion and Virulence of *Staphylococcus epidermidis*. *J Clin Invest*. 2005;115:688-694.

Staphylococcus epidermidis CONTINUES TO BE A troublesome pathogen, mainly due to its ability to form biofilms that protect this species and allow it to express unique features that guarantee its survival. The main molecules involved in biofilm formation are under intense study. In the present study, the group at the Rocky Mountain NIH laboratory used a microarray representing all the known *S. epidermidis* genes in a strain known as 1457 to determine the gene usage in planktonic versus biofilm stages. Two types of non-biofilm experiments were done, and the expression values averaged. The first involved planktonic bacteria grown in flasks. The second used non-adherent bacteria recovered from the statically grown cultures in polytstyrene dishes.

Analysis of gene usage involves a complex software analysis. In all the open reading frames (ORFs) of 2633 *S. epidermidis* genes were annotated. RNA was extracted from planktonic and biofilm bacteria, reverse transcribed into cDNA and displayed on a microarray.

Microarray experiments yield an immense amount of data. The results of this large undertaking using just one strain of biofilm-forming *S. epidermidis* produced some expected and unexpected results. Planktonic cells generally behave in an aggressive, proinflamatory, metabolically active manner and use aerobic respiration. Biofilm cells behave the opposite: nonagressive, avoiding immune responses, and using a low metabolic quotient.

So as might be expected in these staphylococcal biofilms, down-regulated genes include those of global regulatory systems, adhesion factors, and aerobic production of energy. Many other proteins, some hypothetical, are also downregulated.

Of note from this study, is a family of proteins called phenol-soluble modulins (PSMs) that are upregulated in planktonic bacteria and downregulated in biofiilms. Yao and colleagues also measured PSMs in planktonic versus biofilm bacteria and found the PSMs many times higher in the former.

Upregulated genes include those of osmoprotection, one global regulator, fermentation, chaperone or stress response, and several others. Some of the more interesting ones were Drp35, an antibiotic resistant determinant, a zinc resistance protein CzrB, and the CapC, one of the proteins of the poly-gamma glutamate biosynthesis complex. These data suggest that *S. epidermidis* sees the biofilm as a hostile environment and mobilizes genes that allow it to resist that hostile environment.

In a related article also by Yao et al, the organism is the focus. There is an anionic, extracellular polymer known to be secreted by strains of *Bacillus* known as poly- -DL-glutamic acid (PGA). In this accompanying, exhaustive work, PGA was shown to shelter *S. epidermidis* from high salt concentration. There are a series of genes known as the cap genes, and the sequence of capBcapCcapAcapD that is present in *Bacillus anthrasis* has the same sequence in *S. epidermidis*. Yao et al showed that PGA can be seen by immunoscanning electron microscopy to stick to the surface of the bacteria and helps the bacterium resist high salt concentrations, up to 2 M NaCl.

They showed further that the cap products helped the staphylococci stick to subcutaneous catheters and that PGA assists in resisting innate immune attack by bacterial peptides. The capB and capD genes were present in a wide variety of coagulase-negative staphylococcal strains, including *S. simulans*, *S. caprae*, *S. warneri*, *S. capitis*, *S. haemolyticus*, and *S. hominis*.

COMMENT BY JOSEPH F. JOHN, JR., MD

The work by Yao et al, and that of other groups around the world, is leading to a holistic view of the bacterial biofilm. Biofilms are important medically, since they form an apparently protective environment for pathogenic bacteria.

That biofilms protect bacteria within the biofilm is too simplistic a view that does not take into account the response of the bacteria to the biofilm environment. The current papers demonstrates that biofilms develop through a multistep process in which the bacterium in question alters its viability traits to survive the biofiolm

enviornment. Aggressive metabolically active genes are turnes off, immune evasion, and fermentation genes are turned on. If this sounds like the production of a spore in spore-forming bacteria, the ring is true. Gene products, like PSMs, may even inhibit biofilm formation and, thus, must be downregulated, either directly or through global regulators like agr.

At the same time, the paper by Kocianova and colleagues. shows that the coagulase-negative staphylococci have some newly found weapons, namely PGA. It sounds like PGA may be so central to infections with these particularly sticky bacteria that pharmacologic or immune tools to block PGA or the genes that encode it should be developed soon. *S. epidermidis* continues to be the no. 1 isolate from blood in hospitalized patients. We are starting to understand much better the molecular pathogenesis of these pesky commensals as evidenced by these 2 sophisticated papers. ■

Influenza in Travelers

ABSTRACT & COMMENTARY

Source: Mutsch M, et al. Influenza Virus Infection in Travelers to Tropical and Subtropical Countries. *Clin Infect Dis*. 2005;40:1282-1287.

Synopsis: *Influenza is the most frequently encountered vaccine-preventable infection in travelers to the tropics and subtropics.*

MUTSCH AND COLLEAGUES PROSPECTIVELY evaluated the incidence of influenza virus infection among 1450 visitors to tropical and subtropical countries who attended the University of Zurich Travel Clinic. Among these travelers, 289 (19.9%) reported a febrile illness and 211 of these provided paired serum samples. Paired samples were also obtained from 321 matched controls from among the remaining travelers who did not develop a febrile illness. Only 12% had evidence of pre-travel immunity to circulating influenza viruses.

Forty travelers had serological evidence of acute influenza virus infection, with 22 having antibody titer increases of fourfold or greater (probable cases) and the remaining 18 having 2.0- to 3.9-fold increases (possible cases). The infection was asymptomatic in 13 of the 40 subjects. Approximately two-thirds of infections occurred in individuals 20 to 39 years of age. The overall attack rate was 2.8% (1.2% if only probable cases are considered. Travelers to Africa, Asia, and Latin America were affected; only travel to the Indian subcontinent appeared to constitute an excess risk of influenza virus infection relative to all other destinations. Infections were acquired throughout the year in all seasons.

COMMENT BY STAN DERESINSKI, MD, FACP

I recently was called to a local hospital Emergency Department to see a previously healthy 38-year-old male who presented with a sore throat, fever, and severe headache that had started 36 hours after return from a one-month trip to rural Vietnam and Thailand. The immediate concern was that he had avian influenza, which, fortunately, proved to not be the case. He did, however, have acute influenza virus infection (PCR repeatedly detected both influenza A and B while only influenza B was recovered on culture). He had received no vaccinations prior to travel. Influenza vaccination could have prevented the entire costly episode.

The results of the study under review indicate that influenza is the most frequently encountered vaccine-preventable infection in travelers to the tropics and subtropics, where influenza cases may occur throughout the year. In temperate regions of the Southern Hemisphere, the influenza season occurs from April through September. In temperate climates of either hemisphere, exposure to influenza may occur when groups from various geographic areas congregate, as on cruise ships.

The US CDC recommends that pre-travel influenza vaccination be recommended for "persons at high risk for complications of influenza" who did not receive the vaccine during the preceding fall or winter if:[1,2]

- travel is planned to the tropics
- travel is planned with large groups of tourists at any time of year, or
- travel is planned to the Southern Hemisphere during April-September.

The receipt of pretravel vaccine does not eliminate the recommendation for vaccination the following autumn, since the duration of protection may potentially proved inadequate in some cases and, more saliently, because vaccine composition is likely to have changed. Vaccine composition is, to some extent, a wild card in general for travelers, since the available vaccine may not contain appropriate components protective against the virus encountered.

There is no data available regarding benefits of revaccination of individuals before summer travel who were vaccinated during the previous fall or winter.

Two-thirds of cases of influenza detected by Mutsch et al occurred in individuals 20 to 40 years of age, with presumably most being healthy enough to not qualify as being at high risk of complications of influenza and, therefore, not included in the group for whom the CDC recommends pretravel influenza immunization. It seems

to me that pretravel influenza vaccination should not be restricted to high risk individuals, but should be considered for many others as well. ■

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BOOSTRIX®, TdaP for Adolescents

By Stan Deresinski, MD, FACP

In the United States, children receive 5 doses of combined tetanus-diphtheria-acellular pertussis vaccine between the ages of 2 months and 6 years. While otherwise quite effective, the resultant immunity is transient, so that by the time adolescence is reached, many vaccinees are once again at risk of acquiring infections with *Bordetella pertussis*. As a consequence, pertussis is a not infrequent cause of persistent cough in adolescents in adults. Seroepidemiologic studies indicate that approximately 2% of adults and adolescents are infected each year, and that between 800,000 and 3.3 million develop clinical illness as a consequence each year in the United States.[1]

On May 3, 2005, BOOSTRIX®, a trivalent product containing tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine was approved by the US FDA. It is indicated for active booster immunization against tetanus, diphtheria, and pertussis as a single dose for individuals in adolescents 10 to 18 years of age. It is administered in a 0.5 cc dose into the deltoid muscle.[2]

The antigens contained in BOOSTRIX® are each identical to those contained in the version previously approved for use in primary immunization of infants, INFANRIX®. In addition to the tetanus and diphtheria toxoids, this acellular vaccine contains 3 pertussis antigens isolated from *Bordetella pertussis* grown in broth culture. These are inactivated pertussis toxin (PT), formaldehyde-treated filamentous hemagglutinin (FHA) and pertactin, a 69 kD outer membrane protein. Each of the 5 antigens is individually adsorbed onto aluminum hydroxide. The vaccine contains no preservative.

The efficacy evaluation of BOOSTRIX® was based on the demonstration of immunogenicity in adolescents relative to standard Td for adults and to standard 3 dose primary immunization INFANRIX® in infants. An effective booster response to tetanus toxoid and diphtheria toxin was achieved in response to BOOSTRIX® in 89.7% and 90.6%, respectively, compared to 92.5% and 95.9%, respectively, in response to adult Td. BOOSTRIX® administration to adolescents resulted in effective booster responses of to PT, FHA, and pertactin, in 84.5%, 95.1%, and 95.4%, respectively. The frequency of adverse events did not differ from that observed after administration of standard Td.

There is no data available regarding the use of BOOSTRIX® for primary immunization or for completion of a primary series. No immunogenicity data is available regarding the immunogenicity of BOOSTRIX® when administered together with other vaccines.

Contraindications to the use of BOOSTRIX® include hypersensitivity to any of its components, as well as progressive neurologic disorder (until stabilized) or the occurrence of encephalopathy within 7 days of a previous dose of any pertussis vaccine not otherwise explained. Its risk-benefit should be carefully considered for individuals who have previously had any of the following apparent reactions to a pertussis-containing vaccine within 48 hours of receipt: temperature > 40.5°C, collapse or shock-like state (hypotonic-hyporesponsive episode), persistent inconsolable crying lasting > 3 hours. Also of concern is a history of seizures with or without fever occurring within 3 days of vaccine receipt, or Guillain-Barré syndrome within 6 weeks. Intramuscular injections, as required with this vaccine should not be administered to individuals with significant coagulopathies. Also, "Persons who experienced serious Arthus-type hypersensitivity reactions following a prior dose of tetanus toxoid usually have high serum tetanus antitoxin levels and should not be given Td or TdaP vaccines or even emergency doses of Td more frequently than every 10 years, even if the wound is neither clean nor minor."

The ability to safely and effectively boost immunity to pertussis is a valuable contribution to public health. ■

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Measuring Temperature Postoperatively Appears to Be a Waste of Time

ABSTRACT & COMMENTARY

Synopsis: *The positive predictive value for infection of an aural temperature > 38°C measured post-operatively was found to be only 12%, indicating the practice is of limited value.*

Source: Vermeulen H, et al. Diagnostic Accuracy of Routine Postoperative Body Temperature Measurements. *Clin Infect Dis*. 2005;40:1404-1410.

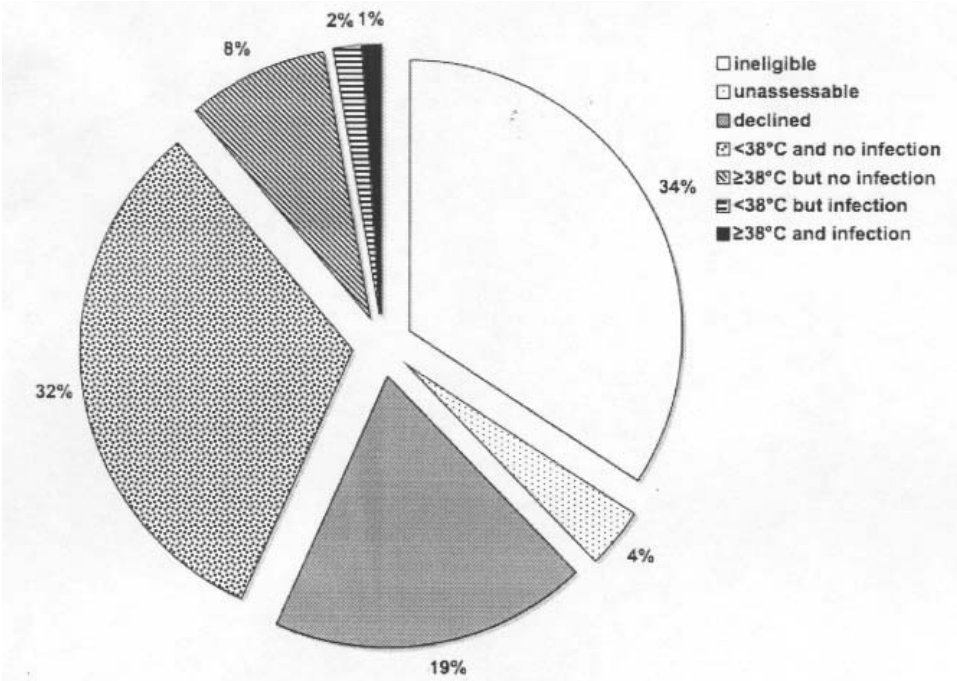
THIS WAS A PROSPECTIVE STUDY INVOLVING 308 consecutive patients who had surgery, and whose body temperature was measured twice-daily for up to 14 days after surgery. A temperature of > 38°C was considered a positive test result and postoperative infection was diagnosed microbiologically or on clinical grounds as defined by the CDC. The physician, nurses, and patient were all blinded to the results of the temperature measurements. A total of 2282 measurements for 284 patients were analysed and 19 [7%] of them had infection. Using temperature curves showed that a temperature ³ 38°C exhibited a sensitivity of 37%, a specificity of 80% and a likelihood ratio of 1.8 for a positive test results and 0.8 for a negative test result. Using each measurement as an independent result yielded positive and negative predictive values of 8% and 90%, for a cut-off value of ≥ 38°C. Nineteen patients had an infection and, of the 8 patients with severe infection, the temperature remained below 38°C before diagnosis. On the basis of these results, Vermeulen and colleagues advise abandoning measuring the temperature routinely after surgery except when there is good reason to expect infection.

COMMENT BY J. PETER DONNELLY, PhD

Measuring temperature to monitor patients is embedded in hospital practice and has a long history mainly because of the not unreasonable belief that infection is accompanied by inflammation, which, in turn, is manifest by an elevated body temperature. Indeed, as Vermeulen et al state, information about body temperature is considered essential to support clinical judgment and confirm signs of infection. It is considered nothing short of heresy to even doubt the value of this time-honoured practice. Aside from the issues around how, when, and where the body temperature should be measured, few question the validity of the practice, let alone conduct a study to estimate the performance characteristics. Vermeulen et al are therefore to be commended for attempting this study at all, and to be congratulated for persuading their ethics committee to approve it and their colleagues for going along with it. That the conviction that taking the temperature is a good thing was apparently shared by almost a fifth of the patients who declined to participate in the study. The attrition rate also shows how difficult and disheartening it can be to test long held convictions afresh (*See figure 1*), since in order to recruit sufficient numbers of patients, almost twice as many patients had to be approached. We are not told the fate of those who were not eligible, but is seems reasonably fair to assume that they fared no worse than those who participated lending further credence to both the low infection rate and the poor per-

Figure 1

Disposition of patients recruited to the study.



Source: Vermeulen H et al. Diagnostic Accuracy of Routine Postoperative Body Temperature Measurements. Clin Infect Dis. 2005;40:1404-1410.

formance of monitoring the temperature.

Like any other surrogate test, the utility of measuring body temperature is dependent upon the prevalence of the event it corresponds to, in this case, infection. Experience shows that surrogate tests are generally poor when prevalence is low, as in this case. Indeed, reliance on an elevated temperature may well have meant a delay in diagnosing infections and, hence, starting treatment soon enough, since 6 of the 8 patients with severe infection did not develop a temperature ≥ 38°C until afterwards. Whether these results would be replicated in other settings remains to be seen. Nevertheless, it would seem worthwhile to look critically at the practice of taking the temperature in other areas of clinical practice to at least determine its utility in the interests of evidence-based medicine, if not of the individual patient at risk of developing infection. ■

Diagnosing Intravascular Device Related Bacteremia

ABSTRACT & COMMENTARY

Synopsis: *In a meta-analysis of studies assessing methodologies for the diagnosis of intravascular-device related blood stream infections, paired quantitative blood cultures drawn from the catheter and a peripheral site are the most accurate. However, numerous other methods, including quantitative catheter culture, semi-quantitative catheter culture, and differential time to blood culture positivity have sufficient sensitivity and specificity to be clinically useful.*

Source: Safdar N, et al. Meta-Analysis: Methods for Diagnosing Intravascular Device-Related Bloodstream Infection. *Ann Intern Med*. 2005;142:451-466.

INTRAVASCULAR, DEVICE-RELATED BLOODSTREAM INFECTION (IDR-BSI) are a major source of morbidity and mortality. An estimated 250,000 infections occur annually in the United States, with an attributable mortality of 12-25%.[1] Accurate diagnosis is essential to management of IDR-BSI. A number of diagnostic methods have been proposed and evaluated in clinical studies, but there is no consensus as to the most accurate method of diagnosis.

Safdar and colleagues reviewed the English-language literature published between 1966 and 2004 for studies evaluating methods for diagnosis of IDR-BSI. The 51 studies included in the meta-analysis compared the method being evaluated against a reference standard, and contained sufficient data to allow calculation of sensitivity and specificity. Safdar et al studied 8 diagnostic methods commonly used in clinical practice (*See Table 1*). They calculated the overall sensitivity and pooled specificity of each method, and determined summary measures of accuracy using receiver operating curves and log odds ratio. They also assessed test accuracy for long term (tunneled, cuffed, or implanted) catheters and short term cathers. Because different studies used different reference standards for the evaluation of individual tests, Safdar et al performed multiple subgroup analyses according to the type of reference standards used.

The most accurate tests were paired quantitative culture and quantitative blood culture through the device. Of the methods requiring catheter removal, quantitative catheter segment culture was the most accurate. However, the other tests studied had acceptable performance with sensitivity and specificity generally exceeding 75%. Not surprisingly, all tests showed better performance with increasing prevalence of IDR-BSI, and all tests showed a negative predictive value of > 95% at a prevalence of 20%. There was a significant difference in accuracy when certain tests were applied to short-term catheters compared with long-term catheters. Semiquantitative catheter culture was more accurate when applied to short term catheters; differential time to culture positivity was more accurate when applied to long-term catheters.

Based on their findings, Safdar et al recommended that diagnostic testing for IDR-BSI be performed when the probability of IDR-BSI was significant, eg > 0.2. For short term catheters, they recommended quantitative or semi-quantitative catheter segment culture combined with 2 blood cultures, with one drawn peripherally and one drawn through the catheter. For long-term catheters, they recommended paired quantitative blood cultures as the most accurate method, but noted that differential time to positivity of paired blood cultures provided similar sensitivity with adequate specificity.

■ COMMENT BY ROBERT MUDER, MD

Given that IDR-BSI is so frequent and extracts such a heavy toll, it's surprising that there is no consensus as to the best diagnostic approach. Safdar et al are to be commended for undertaking such an ambitious analysis, and for providing the infectious disease community with credible estimates of the performance of individual tests that can be used to formulate rationale diagnostic strategies. Their analysis has a number of limitations, which they point out. The studies used different reference standards, and subgroup analyses revealed significant heterogeneity in test performance based on the reference standard used. The analysis did not take into account the potential effect of previous administration of antimicrobials. However, the results appear sufficiently robust that these weaknesses would appear to be relatively minor.

In practice, one issue that needs to be considered is the laboratory effort required to perform individual tests. Quantitative tests, such as quantitative paired cultures and quantitative catheter segment culture, are more accurate

Table 1

Evaluation of diagnostic methods for intravascular device-related bloodstream infections

Pooled Diagnostic Method (95% CI)	Catheter Removal Required	Overall Sensitivity (95% CI)	Specificity
Qualitative catheter segment culture	Yes	0.90 (0.83-0.97)	0.75 (0.72-0.78) (Any growth, broth culture)
Semi-quantitative catheter segment culture	Yes	0.85 (0.81-0.89)	0.86 (0.85-0.87) (> 15 colonies, role plate)
Quantitative catheter segment culture	Yes	0.83 (0.78-0.88)	0.89 (0.87-0.91) (> 1000 colonies after sonication or flush)
Qualitative blood culture through device	No	0.87 (0.80-0.94)	0.86 (0.83-0.89) (Any growth)
Quantitative blood culture through device	No	0.77 (0.69-0.85)	0.90 (0.88-0.92) (> 100 colonies)
Paired quantitative blood cultures	No	0.87 (0.83-0.91)	0.99 (0.98-1.0) (Culture through catheter >3-5x colony count of peripheral culture)
Acridine orange leukocyte cytospin	No	0.72 (0.60-0.84)	0.93 (0.89-0.97) (Any organisms visualized after lysis and stain)
Differential time to blood culture positivity	No	0.85 (0.78-0.92)	0.83 (0.79-0.87) (Culture drawn through catheter positive > 2 h before peripheral culture)

than their semi-quantitative or qualitative counterparts, but require considerably more time and effort to perform. Thus, tests such as differential time-to-blood culture positivity and semi-quantitative catheter culture are attractive since they provide acceptable accuracy with minimal impact on the laboratory workload. ■

Reference

1. O'Grady NP, et al. Guidelines for the Prevention of Intravascular Catheter-Related Infections. *MMWR*. 2002;51(RR10):1-29.

CME Questions

19. Which of the following is correct?

a. Levofloxacin is less effective than clarithromycin in the treatment of legionellosis.
b. *Legionella pneumophila* is susceptible to fluoroquinolones in vitro.
c. Effective treatment of *Legionellosis* with levofloxacin requires the addition of rifampin.
d. The mortality rate in immunocompetent patients with pneumonia due to *Legionella pneumophila* treated with levofloxacin is >25%.

20. Which is true of acquired CMV infections in infants?

a) It is rare
b) Most infection is transmitted by fecal-oral spread
c) Most cases are asymptomatic
d) Preterm infants are at lower risk of symptoms
e) Febrile seizures are a common manifestation

21. Which is most true of biofilms development?

a. It occurs only on plastic polymers
b. It does not resist high salt environments
c. It is a complex multistep process
d. It is easily penetrated by antibiotics

Answers: 19. (b); 20. (c); 21. (c)

In Future Issues:

Antibiotic Management Team

UPDATES

By Carol A. Kemper, MD, FACP

Nosocomial Transmission of Invasive Group A Strep

ProMED-mail post, March 5, 2005; www.promedmail.org

On march 5, 2005, the *Arizona Republic* newspaper reported spread of invasive Group A streptococcal infection to a health care worker at the Flagstaff Medical Center, resulting in severe infection requiring hospitalization. The case patient was hospitalized in early February with necrotizing fasciitis and streptococcal toxic shock syndrome (STSS). Within 6 days, a health care worker, who apparently had contact with the case patient, developed pneumonia, bacteremia, and STSS. Further details were not provided, and the mechanism of transmission (contact vs air) was not known.

Transmission of invasive Group A streptococcal infections has been described in the nosocomial setting, nursing homes, rehab facilities, and even within households. Generally, the risk of transmission is believed to be low, especially in young, healthy individuals.

In an attempt to identify the risk of secondary transmission of these infections, the Ontario Group A Streptoccocal Study Group examined 323 cases of invasive streptococcal infections from 1992 to 1993, for an estimated annual incidence of ~1.5/100,000. Necrotizing fasciitis occurred in 6%. Risk factors for invasive disease included older age and chronic underlying disease, such as diabetes, malignancy, HIV-infection, varicella infection, and alcohol abuse. Of the 323 cases, 45 (14%) occurred in the nosocomial setting and 13 (4%) occurred in nursing homes, often in smaller clusters. Two cases occurred in household contacts, for an estimated risk of 3.2/1000, ~ 200 x the risk of the general population. This data suggest that patients hospitalized with invasive streptococcal infection (eg, fasciitis, bacteremia, and STSS) should be isolated. The value of screening and treatment of household contacts has not been examined, although the spread of invasive disease-causing isolates may be difficult to demonstrate. ■

Durability of HBV Vaccination

McMahon BJ, et al. *Ann Intern Med*. 2005;142:333-341.

The durability of hepatitis b vaccination has not been well delineated. While some experts recommend that health care workers receive a single booster vaccination at 8 to 10 years, there are no formal recommendations for this in the health care setting. Furthermore, the durability of vaccination in all these little kids now receiving vaccine is not known, and there are no guidelines for reassessment of titers or repeated vaccination later in life. Although one can measure persistence of anti-HBs antibody, the loss of detectable antibody (> 10 IU/L) over time does not necessarily imply loss of protection, as cellular immunity may provide a sufficiently protective role.

Longitudinal studies suggest that even when anti-HBs wane over time in heavily vaccinated populations, breakthrough infections are uncommon. McMahon and colleagues examined 1578 Alaskan natives who received 3 doses of HBV vaccine at the age of 6 months or older in 1981-1982. Slightly more than half (53%) were available for reassessment 15 years later, during which mean plasma levels of anti-HBs decreased from an initial level of 872 IU/L to 27 IU/L. Higher levels of initial anti-HBs, male age, and age greater than 4 at the time of vaccination were associated with higher antibody levels 15 years later.

During the 15 years of follow-up, 16 documented and 8 possible breakthrough HBV infections occurred (1.26 per 1000 person-years), all of which were asymptomatic. Breakthrough infections were significantly more frequent in vaccine non-responders than responders. Interestingly, 2 persons were infected with wild type HBV and 4 were infected with wild type HBV and HbsAg variants.

Children who received HBV vaccine when they were less than 4 years had the fastest decline in antibody levels—meaning that just as they'll be reaching their late teens and 20s, and becoming sexually active and potentially at risk for transmission of HBV—their titers will have waned. This leaves open the question of whether and when children vacci-

nated at a young age may require booster vaccination. ■

Did Shakespeare Have Syphilis?

Ross JJ. *Clin Infect Dis*. 2005;40: 399-404.

SYPHILIS WAS WIDESPREAD IN England by the 16th century, especially in London. Shakespeare moved to London about this time, leaving behind his pregnant wife in Stratford, and by the early 1590s, had gained enormous wealth and popularity. But, he spent his later years in social isolation, and died bloated, bald, and chronically ill.

Dr. Ross, who has obviously spent considerable time analyzing Shakespeare's plays and sonnets, theorizes that Shakespeare's evident knowledge of bawdy sex, frequent references to venereal disease, and his familiarity with symptoms of STDs suggest the bard may have had first hand knowledge of STDs such as gonorrhea and syphilis. As just one example, Dr. Ross points to a total of 55 lines in "Measure for Measure" alluding to STDs. His writings are full of references to "cankers," "hoar leprosy", "limekilns in the palms" (possibly a reference to secondary syphilis), and "incurable bone-ache" (possibly syphilitic periostitis).

The sonnets also display frequent references to "burning love," which when viewed in a different light, may refer to the dysuria of gonorrhea rather than unrequited amour. The poet seeking a remedy for the "new fire" acquired from his mistresses "eye" and "love's fire heats water," again possible references to dysuria and gonorrhea.

Although many conditions could be interpreted similarly, Dr. Ross maintains they are more than likely references to symptoms of STDs, especially when interpreted in light of his bawdy humor and later misogyny. Dr. Ross pushes his argument further, postulating that Shakespeare's later years were plagued by tremors, agitation, an inconstant temper, social isolation, and alopecia—all of which could have been the result of mercury poisoning—a common Elizabethan treatment for syphilis. ■

Mortality in HCV/HIV Co-Infection

El-Sarag HB, et al. *Clin Gastroenterol Hepatol*. 2005;3:175-183.

IN ORDER TO EXAMINE THE IMPACT on mortality of HCV infection among HIV-infected patients, El-Sarag and colleagues from the Houston Veterans Affairs Medical Center and Baylor College performed a retrospective cohort study of HIV-infected patients between 1991-2000. A second separate analysis was performed for a similar group of patients identified after September 1996, following the introduction of highly active antiretroviral therapy, which became readily available about that time (the HAART era).

A total of 18,081 HIV-infected patients were identified for the initial analysis, of whom 5320 had HCV/HIV co-infection. A total of 1642 patients were excluded because of pre-existing liver disease. Patients were censored as of September 1996, to ensure no possible effect of HAART. In Cox multiple regression analysis, the HCV/HIV co-infection group had an adjusted mortality about half that of those HIV-infected patients without HCV (hazard risk ratio 0.55, $P < .0001$), after controlling for sex, age, year of diagnosis, and severity of HIV disease. For patients identified during the HAART era, the adjusted hazard ratio mortality for co-infection to HIV mono-infected pts. was .83 ($P = .003$).

These data suggest—somewhat provocatively—that patients with HCV co-infection had lower levels of mortality than patients with HIV-infection alone, which flies against popular belief. Earlier studies suggest that HCV co-infection increases mortality in HIV disease, or at a minimum has little effect. El Sarag et al suspect that some of the variation between this and earlier study results may be attributable to the VA population, which is older, had ready access to health care, are more likely to be drug abusers, and less likely to be men who have sex with men, which may influence the timing and detection of infections of these two. Possible additional sources of variation between this and earlier studies may be due to differences in proportions of those with HCV-related liver disease, severity of HIV disease (CD4 count data was not available), and other comorbidities.

Interestingly, most of the difference between the hazard ratios for the 2 analyses could be accounted for by the improved survival in the HIV-monoinfected group as the result of HAART. Interestingly, there was little change in the mortality of co-infected patients before and after the introduction of HAART—a significant finding of its own, and confirming other reports that patients with HCV infection have a blunted immune response to the introduction of HAART. ■

PHARMACOLOGY WATCH

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

Is Nesiritide Associated with a Higher Death Rate?

Nesiritide, Scios' intravenous recombinant form of human B-type naturetic peptide, has been widely used for the treatment of congestive heart failure in hospitalized patients. On Scios' website, nesiritide is touted as the "best-selling IV cardiovascular drug ever brought to market." All that may change with the publication of a new study that suggests that patients with acutely decompensated heart failure (ADHF) treated with nesiritide have a higher death rate at 30 days compared with patients who are not treated with the drug. The study was a pooled analysis of 12 randomized, controlled trials, of which 3 met all inclusion criteria. In those 3 trials, 485 patients with ADHF were randomized to nesiritide and 377 to control therapy which was noninotrope-based treatment. Thirty-day death rate was higher among the nesiritide group (7.2% vs 4.0% for placebo, 1.74 risk ratio; 95% CI [0.97-3.12]; *P* = .059). The authors conclude that therapy with nesiritide may be associated with increased risk of death after treatment for acutely decompensated heart failure, and suggest that an adequately powered, controlled trial should be undertaken (*JAMA*. 2005;293:1900-1905). This follows an earlier study that suggested nesiritide may worsen in renal function in patients with ADHF. In that study, which was also a pool analysis from 5 randomized studies, 1269 patients with ADHF were reviewed. Nesiritide was associated with a significantly increased risk of worsening renal function, compared with noninotrope control therapy (RR, 1.52; 95% CI, 1.16-2.0; *P* = .003) or any control therapy, including noninotrope and inotrope based therapies (RR, 1.54; 95% CI, 1.19-1.98 ; *P* = .001). Even low-dose nesiritide was found to worsen renal function. The authors conclude that nesiritide significantly increases the risk of worsening renal function in patients with ADHF, but suggests further investigation to determine the prognostic importance of this finding (*Circulation*. 2005;111:1487-1491).

Stopping Aspirin Before Surgery

A new study suggests that stopping aspirin 5 days prior to surgery is optimal. Researchers from Ireland recruited 51 volunteers who were randomly assigned to 3 groups: placebo, aspirin 75 mg per day, or aspirin 300 mg per day. Utilizing template bleeding times and specific platelet function testing, all bleeding times normalized within 96 hours and all platelet function test normalized within 144 hours after discontinuing aspirin. By day 6, there was no demonstrable hemostatic defect in any of the volunteers. There was also no difference between the 75 mg or 300 mg dose of aspirin. The authors conclude the data sup-

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ports withholding aspirin for 5 days with elective surgery been performed on the sixth day (*J Am Coll Surg*. 2005;200:564-573). This study is important because of recent data that cardiovascular events are much more likely to occur in patients who had recently withdrawn from aspirin—with the peak of events occurring at 10 days (*Pharmacology Watch*. March, 2005). Safely stopping aspirin for 5 days prior surgery, with reinstitution as soon as possible after surgery, makes good clinical sense.

The Sponge Returns

The Today Sponge contraceptive device is returning to the US market this summer. Last marketed more than 10 years ago, the sponge was removed from the market because of manufacturing problems. It is being brought back by Allendale pharmaceuticals, whose manufacturing facility met FDA standards. The sponge, which was made infamous by a memorable *Seinfeld* episode, is an over-the-counter, round, disposable, soft sponge that is impregnated with spermicide. It is inserted vaginally, and can be kept in place for 24 hours and for multiple sexual encounters. When it was taken off the market in 1994, the sponge was the most popular over-the-counter female contraceptive available, with 250 million of them sold in the 11 years it was available.

Preventing Metabolic Syndrome

Metformin and intensive lifestyle intervention both help prevent metabolic syndrome in patients who have impaired glucose intolerance. In a study derived from the Diabetes Prevention Program, 1711 patients with impaired glucose tolerance (defined by World Health Organization criteria plus fasting glucose level < 95) were evaluated. More than half the participants (53%) had metabolic syndrome at the baseline. In patients who did not have metabolic syndrome, metformin 850 mg twice daily or intensive lifestyle intervention designed to achieve and maintain 7% weight loss and 150 minutes of exercise per week were both effective in preventing metabolic syndrome. Lifestyle intervention was the more effective intervention with a 41% reduction in the incidence of metabolic syndrome ($P < .001$) while metformin reduced the incidence by 17% ($P = .03$) compared to placebo. Three-year cumulative incidences of metabolic syndrome were 51%, 45%, and 34% in the placebo, metformin, and lifestyle groups, respectively. The authors conclude that both lifestyle intervention and metformin are effective in reducing the development of metabolic syndrome in patients with glucose intolerance, although the impact of lifestyle intervention was more marked than that of metformin (*Ann Intern Med*. 2005;142:611-619).

FDA Actions

The FDA has approved exenatide for the treatment of type 2 diabetes in patients who have not responded to other treatments. The drug was derived from lizard saliva, and represents a new class of antidiabetic agents known as incretin mimetics—which mimic the effect of GLP-1, a naturally occurring incretin hormone found in human gut. Exanatide normalizes postprandial physiology by stimulating beta cells to secrete insulin in glucose dependent fashion. In alpha cells, the drug normalizes the pathologic hypersecretion of glucagon in a glucose dependent fashion. It also slows gastric emptying and improves satiety, all which serve to reduce postprandial hyperglycemia. There is some evidence that the drug may also attenuates weight gain seen with other hypoglycemic agents and may even be associated with weight loss. The drug will be marketed by Eli Lilly and Amylin Pharmaceuticals under the trade name Byetta.

Ropinirole (Requip) has been approved for the treatment of moderate-to-severe restless leg syndrome (RLS), the first US medication to be approved for this indication. The drug has been available for the treatment of Parkinson's disease since 1997. The approval was based on 3 randomized, double-blind, placebo-controlled trials in adults diagnosed with moderate to severe RLS. All 3 studies demonstrated a statistically significant improvement in the treatment group receiving ropinirole. Side effects include nausea, extreme drowsiness, and dizziness, and the drug will be labeled to warning about the possibility of falling asleep while engaged in activities of daily living including driving. GlaxoSmithKline is enthusiastic about the prospect of treating the estimated 1 out of 10 adults in this country with restless leg syndrome, the most common cause of insomnia. ■