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Norovirus Infection

ABSTRACT & COMMENTARY

Synopsis: Noroviruses are a frequent cause of acute gastroenteritis. During the last 2 months of 2002 in a single health district in Washington state, 10 outbreaks of acute gastroenteritis attributable to norovirus were investigated. These events affected 354 patients in 6 long-term care facilities, a community hospital, an outpatient clinic, and the county jail.

Source: CDC. Norovirus activity—United States, 2002. *MMWR Morb Mortal Wkly Rep*. 2003;52:41-45.

In new hampshire in 2002, 29 outbreaks of norovirus gastroenteritis in long-term care facilities (28 in a single month) and 2 outbreaks each in restaurants, schools, and residential summer camps were investigated. These investigations implicated person-to-person, food-borne, and water-borne transmission in 32, 2, and 1 outbreak, respectively.

Investigation of 66 outbreaks affecting approximately 1700 people in New York City occurring during 2 winter months of 2002-2003 implicated norovirus infection. Fifty-one percent occurred in nursing homes, long-term care facilities, and rehabilitation facilities; 10 in hospitals; 3 in restaurants; and 1 each in a school and a homeless shelter.

Of 27 norovirus outbreaks investigated by the CDC, 11 (41%) were caused by a single strain, the Farmington Hill strain. Although not epidemiologically related, 6 of the Farmington Hill strain outbreaks occurred on land and 5 on cruise ships.

COMMENT BY STAN DERESINSKI, MD, FACP

In 1972, viral particles were detected by immune electron microscopy in the stools of volunteers at the NIH who had ingested filtrates of stool obtained during an outbreak of diarrheal illness.[1] The virus was named after the site of that 1968 outbreak in Norwalk, Ohio.[2] Many subsequent outbreaks of what was called winter vomiting disease were found to be caused by Norwalk-like viruses, now called noroviruses. This small, positive-sense, single-stranded RNA

Volume 22 • Number 11 • March 1, 2003 • Pages 81-88

INSIDE

virus belongs to the family *Calciviridae*. Noroviruses have resisted cultivation, and there are no animal models. The development of an RT-PCR assay on stool has facilitated our understanding of the epidemiology of norovirus infection.

Noroviruses are the most common cause of gastroenteritis in the United States, accounting for approximately 23 million cases annually. While outbreaks of norovirus infection on cruise ships have been in the news lately,[3] the majority of outbreaks occur in settings on land such as nursing homes, restaurants, schools, and day care centers. Noroviruses may also account for more than 10% of sporadic cases of gastroenteritis in both children and adults. In 1996-1997, 86 of 90 outbreaks (96%) of nonbacterial gastroenteritis in the United States were due to Norwalk-like viruses.[4] The incidence of norovirus infections appears to be increasing for reasons that are not understood.

The illness caused by Norovirus often presents, after an incubation period of 24-48 hours, with vomiting, diarrhea, nausea, and abdominal pain. Fever occurs in no more than one-half of cases and is low grade and transient. The illness generally lasts 1-3 days. The features that identify an outbreak of gastroenteritis as possibly due to Norovirus are listed in the Table.[5]

Table

Features of Gastroenteritis Outbreaks Consistent with Norovirus

Etiology

- failure to detect a bacterial or parasitic pathogen in stool specimens
- vomiting in > 50% of patients
- mean duration of illness of 12-60 hours
- mean incubation period of 24-48 hours

Cases result from ingestion of contaminated food or water or from direct person-to-person transmission. Implicated food is characteristically served cold such as salads and sandwiches. Norovirus is probably also transmitted by droplet formation from vomitus. Persistent environmental contamination may be important in the epidemiology of the disease. Environmental contamination and person-to-person transmission account for secondary cases occurring in outbreaks, a feature characteristic of norovirus disease.

The infectious dose is as few as 10 viral particles. Asymptomatic shedding may persist for up to 2 weeks, and the virus is stable in the environment, being capable of surviving freezing, heating to 60°C, and as much as 10 ppm of chlorine. These factors, together with its multiple modes of transmission, wide strain diversity, and the transient nature of immunity to infection, account for the frequent outbreaks due to norovirus.[6]

Vaccine development may be problematic, given the existence of multiple strains of norovirus, as well as the transient nature of immunity after infection. In the meantime, the only means of control is prevention by maintenance of good food, environmental, and personal hygiene. ■

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Infectious Disease Alert, ISSN 0739-7348, is published twice monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

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GST Registration Number: R128870672. Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***Infectious Disease Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $20.
Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

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1 year *with* free AMA Category 1 credits: $289
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In order to reveal any potential bias in this publication, we disclose that Dr. Deresinski serves on the speaker's bureau of Merck, Glaxo-SmithKline, Ortho, Bayer, and Pfizer. Dr. John is a consultant for Cubist, Roche, and Bio-Merieux, is on the speaker's bureau of Merck, Pharmacia, GlaxoSmithKline, Bayer, and Wyeth, and does research for Merck. Dr. Kemper serves on the speaker's bureau of Virologic, GlaxoSmithKline, Pfizer, and Agouron and is involved in research with Chiron, Merck, Agouron, and Virologic. Dr. Schleis is on the speaker's bureau for Aventis and Bayer and is a consultant for FFF Enterprises, Aventis, and Bayer. Dr. Muder does research for Aventis, and Pharmacia. Dr. Tice is a consultant for Roche, Merck, and ZLB and is on the speaker's bureau of Roche, Ortho, GlaxoSmithKline, and Pharmacia, and does research for Elan, Roche, Merck, Pharmacia, and Becton-Dickinson. Dr. Jenson is on the speaker's bureau of Merck. Dr. Donnelly is a consultant for OrthBioTech, and does research for Janssen, Merck, Novartis, Numico, Pharmacia, and Pfizer. Dr. Smilack reports no speaker's bureau, research, stockholder, or consulting relationships having ties to this field of study.

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Vancomycin TDM: Therapeutic Drug Monitoring or Just Fooling Ourselves?

ABSTRACT & COMMENTARY

Synopsis: Despite many years of practice, a recent questionnaire about therapeutic drug monitoring of vancomycin revealed marked variability and a lack of consensus regarding postdose assay sampling times, target ranges, and what constituted a toxic level.

Source: Tobin CM, et al. Vancomycin therapeutic drug monitoring: Is there a consensus view? The results of a UK National External Quality Assessment Scheme (UK NEQAS) for Antibiotic Assays questionnaire. *J Antimicrob Chemother*. 2002;50:713-718.

A questionnaire about vancomycin therapeutic drug monitoring (TDM) was sent to 310 subscribers of the United Kingdom National External Quality Assessment Scheme (UK NEQAS) for antibiotic assays inquiring about the methodology, dosage regimen, and toxicity. Just more than half (178) responded, and, of these, 49% provided a 24-hour, 7-days-a-week service. A quarter of the laboratories received fewer than 100 requests annually, 38% received 100-500 requests, 13% received 500-1000, and 24% received more than 1000. Four in 5 had guidelines for vancomycin use based mostly on the manufacturer's labeling or the British National Formulary. Only 11% deviated from a twice-daily dosage regimen. Assays after 2-3 days of treatment were recommended by 71% of respondents. Trough samples were taken within 10 minutes of the dose by 92% of respondents. By contrast, postdose samples (ie, "peak samples") were taken 1 hour after the dose by 44% and 2 hours after the dose by 28%, with the remainder not mentioning any specific time at all. Only 11% of respondents stated that the sample time for a peak concentration referred to that observed after the end of the infusion. Anticipated trough levels ranged from 3 mg/L to 15 mg/L while corresponding peak levels ranged from 15 mg/L to 50 mg/L. Three out of 4 regarded trough levels ≥ 10 mg/L to be toxic, whereas 20%, 40%, and 13% considered postdose levels of 30 mg/L, ≥ 40 mg/L, and ≥ 50 mg/L, respectively, to constitute a toxic concentration (*see Table 2*). A dose reduction would be advised by 35%, omitting the next dose by 30% and extending the dosing interval by 25%. Microbiologists reported 47% of results, biomedical scientists 46%, and biochemists or pharmacists the remainder. All but 5% found the assays appropriate, with a quarter of respondents believing them to be useful and a further 25% regarding them as essential for patients given dialysis.

■ COMMENT BY J. PETER DONNELLY, PhD

Any newcomer to this field might well be quite taken aback by the fact that after more than 20 years of widespread use there seems to be no standard of TDM for vancomycin or even a consensus. Aside from the shortcomings of such surveys, which never elicit responses from all concerned, these results demonstrate a clear need for developing practice guidelines based on evidence. A cursory glance at the Table is enough to convince. While most (92%) used trough levels of < 10 mg/L, the best that can be said of anticipated peak levels

Table
Reported Peak and Trough Vancomycin Targets

peak conc [mg/L]	N = 111 n	%	trough conc [mg/L]	N = 115 n	%
50	1	1	15	1	1
40	1	1	12	1	1
35 to 45	3	3	10	54	47
35	1	1	8	2	2
30 to 50	1	1	5 to 15	1	1
30 to 40	2	2	5 to 12	1	1
30	8	7	5 to 10	52	45
26	1	1	5	1	1
25 to 40	12	11	3 to 10	2	2
25 to 35	3	3			
25 to 30	4	4			
25	1	1			
20 to 50	1	1			
20 to 45	1	1			
20 to 40	31	28			
20 to 25	1	1			
20 to 30	17	15			
20	1	1			
18 to 30	3	3			
18 to 26	13	12			
18 to 25	2	2			
18 to 24	1	1			
15 to 25	2	2			

is "somewhere between 15 mg/L and 50 mg/L." Hardly a good result. We do not know if the larger providers were more in agreement than the intermittent ones nor if the microbiologists had less-divergent practices than the biomedical scientists, but if TDM was a product there would be very few customers indeed. Imagine taking your car to several garages for its mandatory annual check-up with all offering the same service but with markedly different ways of interpreting this. Some are open all hours, while others are open only during office hours. Some tell you to run the engine for at least 2 hours before coming in, while others tell you to park it outside overnight so that it can be tested cold. All use the same diagnostic equipment, but some feel the idle speed should be 750 rpm, others 1000 rpm, and some even 1500 rpm. Different ones feel that the rpm should be 2500 rpm at a steady 50 mph, others 3000 rpm, and again a few 3500 rpm. Then each one interprets the same report differently. At the very least, you would be confused. You might even be sufficiently motivated to submit a complaint along with thousands of others to your local consumer watchdog, which would be up in arms and demand immediate legislation.

It would be unfair and naïve to assume that only microbiology suffers from a lack of standards. But the example is revealing especially at a time when standards are being demanded and good laboratory practice is accepted as a goal worth pursuing. Clearly a standard for vancomycin TDM is needed but that is only the beginning. Once drawn up, it has to be implemented and tested on a regular basis to ensure compliance. Achieving this within the United Kingdom is a tall order even for the most dedicated but still feasible with commensurate funding and support. Adopting it throughout the European Union may be asking for nothing short of a miracle. ■

Need for Susceptibility Testing of Linezolid

ABSTRACT & COMMENTARY

Synopsis: The study established a policy of routine susceptibility testing of linezolid and quinupristin/dalfopristin isolates of VRE from any sterile site.

Source: Potoski BA, et al. Clinical failures of linezolid and implications for the clinical microbiology laboratory. *Emerg Infect Dis*. 2002;8:1519-1520.

Linezolid is the first in a new class of antimicrobials known as the oxazolidinones. It is especially useful in treatment of Gram-positive infections caused by vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA). However, as reported in this article, 2 patients exhibited strains of linezolid-resistant and possibly linezolid-non-susceptible bacteria, suggesting the need to routinely perform susceptibility testing of linezolid and even quinupristin/dalfopristin (Synercid) before using.

The first patient was a 47-year-old male who underwent right ankle fusion with nail placement. Six months later the nail was replaced, and a month later the patient developed an ankle hematoma that was drained; the infection was treated with 7 days of cephalexin. Over the following several weeks the infection worsened, the area irrigated and debrided, and the patient discharged with amoxicillin/clavulanate. Gross pus that was obtained at this time was cultured and grew *S aureus* that was susceptible to vancomycin, trimethoprim/sulfamethoxazole (TMP-SMX) and gentamicin but resistant to all beta-lactams and clindamycin. Susceptibility testing to linezolid was not performed.

The patient was switched from amoxicillin/clavulanate to oral linezolid, 600 mg twice daily. The patient did well after completing a 7-week course of therapy, but 2 days after the linezolid was stopped, nausea, fever, and chills developed, necessitating a resumption of linezolid. The patient soon ended up in the emergency room with a temperature of 103°F and his ankle warm and tender to palpation. Linezolid was stopped and intravenous vancomycin started. The nail was removed, and cultures from the area grew MRSA with the same sensitivities as the previous MRSA isolate. This time susceptibility testing to linezolid was performed and the isolate was susceptible (MIC = 4 ug/mL). After 4 weeks of vancomycin, the patient was placed on oral TMP-SMX for an additional 12 weeks. Six months after therapy he remained asymptomatic.

The second patient was a 41-year-old woman with refractory acute lymphocytic leukemia admitted for an allogeneic bone marrow transplant. Her hospital course was complicated by *Klebsiella pneumoniae* sepsis, neutropenia, mental status changes, acute renal failure, and respiratory distress. Antibiotics received included imipenem, amikacin, piperacillin/tazobactam, vancomycin, amphotericin B lipid complex, fluconazole, ciprofloxacin, and tobramycin. While on vancomycin, peripheral and central venous catheter blood cultures grew vancomycin-resistant *Enterococcus faecium* that was also resistant to both ampicillin and penicillin. The vancomycin was stopped and linezolid, 600 mg intravenously every 12 hours, was started. Although linezolid susceptibility testing was ordered, linezolid was started before the results were available. Three days later, the patient died. The sus-

ceptibility results showed the isolate was resistant to linezolid by E-test (MIC = 32 ug/mL), and further testing also showed that the isolate exhibited intermediate susceptibility to quinupristin/dalfopristin (MIC = 2 ug/mL).

As a result of the above, Potoski and colleagues established a policy of routine susceptibility testing of linezolid and quinupristin/dalfopristin isolates of VRE from any sterile site. In the case of MRSA, linezolid and quinupristin/dalfopristin testing is only done upon request, due to the high number of isolates and the fact that nonsusceptibility of linezolid to MRSA has been reported only once.

■ COMMENT BY THOMAS G. SCHLEIS, MS, RPh

In an ideal world, no antimicrobial would be initiated until complete culture and sensitivity data were available. Obviously, that is impossible given the laboratory procedural constraints and the need for empirical antimicrobial coverage when there is nothing to culture. The choice of antimicrobial is often made on professional judgment and modified, if necessary, when laboratory data become available.

Linezolid and quinupristin/dalfopristin have given us ammunition in the fight against resistant organisms. Despite this, these 2 case reports demonstrate the need for accurate susceptibility testing before relying upon these agents to treat VRE or MRSA. This is especially true when these agents are used after other agents have failed or in an already-compromised or severely ill patient. Given the continuing development of antimicrobial-resistant organisms, we can never assume that an agent is going to be effective and must always be aware of, and concerned of, resistant bacteria.

What is especially disconcerting is the lack of effectiveness of linezolid in the first patient, even when susceptibility testing appeared to support its use. While only a single case, it raises a number of questions. Was there a sufficient level of antimicrobial at the site of infection? Should the linezolid have been dosed differently based upon individual patient pharmacokinetics? Do we need to collect more pharmacokinetic and pharmacodynamic data regarding linezolid? Certainly, if other case reports were to surface, these concerns would need to be addressed.

While these newer agents can be extremely effective, it appears that we need to be more cautious in how we use them and monitor their effectiveness. The culture and sensitivity testing policy suggested by Potoski et al appears to be a rational first step in improving the process.

Editor's note—The first case described was one of clinical resistance in the absence of in vitro resistance and was unsurprising given the presence of a foreign body. In the second case, de novo resistance of *E faecium* caused a lethal infection.

Resistance to linezolid may be induced by serial in vitro passage and is associated with mutation (characteristaly, G2576U in the closed loop of domain V of the 23S ribosomal RNA of the 50S ribosomal subunit). Such resistance occurs at a very low frequency (10-9 to 10-10 in *S aureus*). Since multiple copies of the encoding gene exist, resistance increases with accumulation of mutations in individual copies. For instance, in a study of serial isolates of *S aureus* developing resistance during linezolid therapy, an isolate with an MIC of 8 µg/mL had the G2576T mutation in 2 of 6 alleles, while a later isolate with mutations in 5 alleles had an MIC of 32 µg/mL.[1]

The emergence of resistance in *S aureus, E faecalis* and *E faecium* during linezolid therapy has been reported.[2-4] Enterococcal resistance to linezolid developed in 9 of 501 (1.8%) during the manufacturer's compassionate-use program. A protracted course of linezolid therapy has been associated with an increased risk of emergence of resistance in *E faecium*.[5]

In addition, the apparent emergence of resistance in *E faecium* in the absence of prior oxazolidinone exposure has previously been reported.[6] This may be the result of nosocomial spread. In one instance, *E faecium* that was first recovered from a liver transplant recipient was subsequently transmitted to 6 other patients who had not received linezolid.[7]

While the frequency is low, hospital laboratories must provide timely susceptibility testing of linezolid against relevant bacteria. ■

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Better Targeting of Antibiotic Therapy Against the Gram-Positive Coccal Infections of Neutropenic Patients

ABSTRACT & COMMENTARY

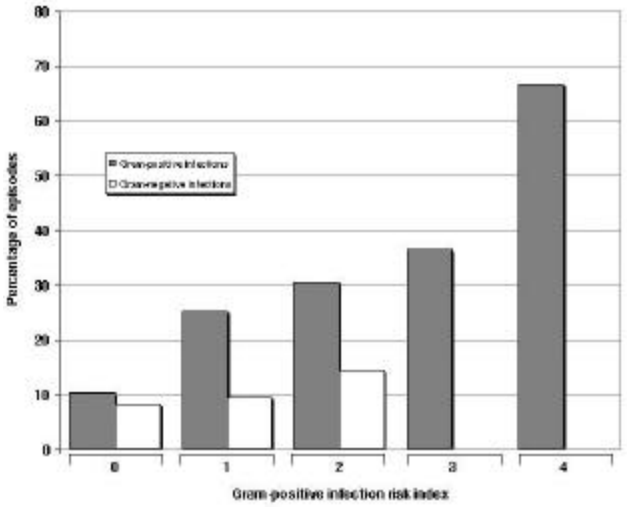
Synopsis: Indices have been developed to help assess the risk of neutropenic patients developing Gram-positive infections when they become febrile that might allow strategies to be developed for managing these infections.

Source: Cordonnier C, et al. Epidemiology and risk factors for Gram-positive coccal infections in neutropenia: Toward a more targeted antibiotic strategy. *Clin Infect Dis*. 2003; 36: 149-158.

Gram-positive cocci continue to harass neutropenic patients and perplex physicians because detection of these bacteria need not necessarily represent true infection. It is, however, often a direct consequence of the treatment or supportive care given to the patient as a result of mucositis and the widespread use of central venous catheters. These bacteria also account for more infections than do the Gram-negative bacilli. Moreover, we are seldom dealing with professional pathogens such as *Staphylococcus aureus* or *Streptococci pyogenes* in this patient population but rather their less pathogenic relatives, namely the *viridans* streptococci (mainly *Streptococcus mitis* and *Streptococcus oralis*) and the coagulase-negative staphylococci (mainly *Staphylococcus epidermidis*) that form a conspicuous part of the normal commensal flora of the oral cavity and skin, respectively. Infections due to Gram-positive cocci are usually indolent, but some *viridans* streptococci, particularly *S mitis*, are associated with sepsis and adult respiratory distress syndrome, which can prove fatal. The objective of this particular study was to determine the prevalence of Gram-positive coccal infections among febrile neutropenic patients and to develop a risk index to allow physicians to identify patients at risk for Gram-positive coccal infections and choose the most appropriate therapy. This last aspect is important given the predominance of the Gram-positive cocci and the fact that most empirical regimens are not optimal in this regard, being primarily intended to treat infections caused by Gram-negative bacilli, such as *Escherichia coli*, *Pseudomonas aeruginosa*, and the like.

Figure

Rate of Gram-Positive Infections and Gram-Negative Infections in Relation to the Gram-Positive Infection Risk Index



The study was conducted over a 2-month period in 36 French hospitals. The first episode of fever during neutropenia was registered for 513 patients. The presence of microbiologically defined infections were established in 168 (33%) and clinically defined infections in 40 (8%) episodes. No infection was identified in the remaining 305 (59%) episodes. Gram-positive cocci were involved in 108 (21%) episodes altogether and Gram-negative bacilli accounted for 55 (11%) of all episodes of fever. Twenty-eight patients died within a month of becoming febrile, and the primary infection contributed to 9 of these deaths. A wide range of factors that might influence infection were recorded, including age, hematology (diagnosis and status), the cause of neutropenia (conditioning regimen for transplantation when applicable, chemotherapy received during the month before enrollment), location during the week before the onset of fever (laminar air-flow room, single room, 2-bed room, or outpatient), any drugs used (growth factors and any anti-infective drugs including antifungal agents and drugs used for selective decontamination of the gut, antiulcer drugs, and antacids), and the site of the intravenous catheter (central or peripheral). The signs and symptoms likely to be associated with infection were recorded on the day of fever, and at least 2 samples of blood were obtained for aerobic and anaerobic culture before antibiotic therapy was started. The regimen for empirical therapy consisted of a ß-lactam antibiotic in 466 (91%) cases in combination with an aminoglycoside in 338 (66%) cases and/or a glycopeptide in 159 (31%) cases.

After conducting a multivariate analysis, the occurrence of Gram-positive coccal infections was found to be signifi-

cantly associated with 4 factors: high-dose cytarabine therapy; treatment with proton pump inhibitors; oral treatment with colimycin (colistin, polymyxin E) without a glycopeptide for gut decontamination; and the presence of chills.

Each episode was scored for each of these factors (0 = absent, 1 = present) to assign a Gram-positive infection risk index (GPRI), which was the sum of all the factors ranging from 0 to 4. The risk for Gram-positive infection increased 3, 3.9, 7, and 17.5 times when the GPRI was 1, 2, 3, and 4, respectively. A score of 3 or 4 effectively excluded a Gram-negative infection (*see Figure*). Further analysis showed that streptococcal infections were significantly associated with high-dose cytarabine therapy; oral treatment with nonabsorbable antifungal agents (nystatin, amphotericin B); oral treatment with colimycin; and diarrhea.

The only identified association with staphylococcal infections was the use of the polymyxin.

Each episode was subjected to a streptococcal infection risk index constructed in a similar way to the GPRI from these 4 factors. While the odds ratio increased from 3 to almost 20 with an increasing index, so, too, did the odds ratio for staphylococcal infection. Cordonnier and associates are now conducting a prospective study of neutropenic patients to evaluate these indices with a view toward addressing the question of which is the best strategy for managing Gram-positive infections in this vulnerable patient population.

■ COMMENT BY J. PETER DONNELLY, PhD

This study represents a novel approach to solving a perennial problem, namely how to recognize Gram-positive infections in neutropenic patients ahead of time. A risk index such as described heightens the awareness of the specific risk factors involved and might even help determine which antibiotic regimen is best suited to dealing with the problem. As Cordonnier et al realize, it is not just important to recognize the patient at risk for Gram-positive infections but more specifically to distinguish those likely to have streptococcal infection from those who have staphylococcal infections, as the treatment options differ. Managing a staphylococcal infection may require treatment with a glycopeptide, removal of the central venous catheter, or the application of an antibiotic block to tide the patient over until the device can be removed. By contrast, early recognition of an incipient streptococcal infection would allow treatment with penicillin or even therapy with corticosteroids to prevent ARDS.[1] The indices presented seem unlikely to be able to achieve latter objective on the basis of the evidence presented so far, although it is clearly worthy of further investigation. Some other aspects of this report have to be set in context. First, it remains standard practice to assume that every episode of fever that occurs is due to a Gram-negative bacillus and to start treatment promptly with a regimen consisting of a broad-spectrum ß-lactam such as ceftazidime or meropenem. Even if the fever remains unexplained or another etiology has been established, it is still common practice to continue the initial core regimen and to complement it with other antimicrobial agents as circumstances dictate. Second, many physicians feel compelled to complement the core regimen with one of the glycopeptides, vancomycin or teicoplanin, regardless, as occurred in almost a third of patients in this study. Given the risks attached, it is clearly desirable to establish objective criteria by which patients who need these drugs get them while others are spared. Third, and importantly, 3 of the 4 factors identified will vary from center to center since oral treatment with nonabsorbable antifungal agents like nystatin or amphotericin B has largely been supplanted by other drugs such as fluconazole for prophylaxis against fungal infections. Similarly, oral treatment with colimycin has been all but abandoned in many countries and was never used in other regions such as the United States. It is biologically plausible that each of the factors incorporated into the risk indices actually does increase the risk of infection in some way; however, the use of the indices will very much depend upon the practices of one's own hospital. ■

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CME Question

12. Which of the following is true?

a. There has never been a case of MRSA resistant to linezolid.
b. All cases of VRE are susceptible to linezolid and quinupristin/dalfopristin.
c. VRE and MRSA organisms can be resistant to linezolid and quinupristin/dalfopristin.
d. It is necessary to perform susceptibility testing of linezolid and quinupristin/dalfopristin to all VRE and MRSA isolates.

Answer: 12(c)

In Future Issues:

Tenofovir in HIV/HBV Coinfected Patients

UPDATES

By Carol A. Kemper, MD, FACP

Acyclovir & Renal Dysfunction

Source: Vomiero G, et al. *Pediatr Nephrol*. 2002;17:633-637.

Historically, acyclovir has been reported to precipitate renal impairment in up to 16% of patients, although more recent clinical experience suggests that, with adequate hydration, this problem occurs far less frequently. Investigators at the Children's Hospital of Eastern Ontario had an unusually negative experience in 17 pediatric patients (aged 1-14) who received a combination of high-dose ceftriaxone and acyclovir for meningoencephalitis. In retrospective analysis, 12 patients (70%) developed renal insufficiency, 3 of whom (17.6%) developed acute renal failure. The degree of renal impairment was associated with the higher acyclovir dosages. Urinalyses were consistent with a tubular proteinuria pattern, and renal biopsy in a single patient showed a tubular toxic picture. Vomiero and associates speculate that the combination of the 2 agents may somehow potentiate the renal toxicity of acyclovir. ■

What Makes BCG Less Virulent than MTb?

Source: Lewis KN, et al. *J Infect Dis*. 2003;187:117-123.

The genetic mutational basis of TB vaccine bacille Calmette-Guerin (BCG) has remained a mystery for years. Ever since Calmette described the organism, which is naturally attenuated, researchers have attempted to determine the difference between it and MTb.

Attention has focused on RD1, a single 9.5-kb region of DNA, which is present in all MTb strains but absent in all BCG strains. After deletion of this region from a strain of MTb (MTb:ΔRD1), bacterial growth and cytotoxicity was assessed in human peripheral blood monocyte-derived macrophages. The growth of MTb:ΔRD1 in cell monolayers over a 7-day period was similar to BCG controls, in contrast with intact MTb strains, which destroyed > 80% of the cell monolayer. In addition, MTb:ΔRD1 and BCG grew similarly slowly in mice receiving aerosol challenge.

Interestingly, although the bacterial burden in mice was ultimately similar for both attenuated and virulent strains, the degree of inflammation and granuloma formation in lung tissue was significantly less with the attenuated strains. Despite similar bacterial burdens, only 2 of 15 mice challenged with virulent MTb were still alive at week 39, compared with all 18 mice challenged with MTb:ΔRD1. These data suggest that RD1—either directly or indirectly by controlling other genes—is essential to MTb virulence. What RD1 actually does is now the mystery. ■

Broad-Range Bacterial PCR in Meningitis

Source: Saravolatz LD, et al. *Clin Infect Dis*. 2003;36:40-45.

Dna amplification techniques may significantly enhance our ability to quickly diagnosis bacterial meningitis. Using a broad-range primer sequence for bacterial 16s RNA, which is highly conserved, Saravolatz and colleagues examined the specificity and sensitivity of a polymerase chain reaction (PCR) assay for the diagnosis of meningitis in 74 cerebrospinal fluid specimens obtained from 70 patients.

Fifteen patients had positive culture results, and 2 patients had positive Gram staining but negative cultures. Positive CSF cultures included a broad range of organisms, including S epidermidis (5), S pneumoniae, Group B strep (2), Neisseria meningitidis (1), and Gram-negative bacilli (5). PCR was positive in all 17 cases with direct microbial findings, as well as 1 of 57 of the remaining cases with negative cultures and negative Gram stains.

These results yield a sensitivity of 100% and specificity of 98.2%; the positive predictive value is 94.4% and the negative predictive value is 100%. Based on these results, Saravolatz et al suggest that the administration of antibiotic therapy could be safely avoided or discontinued more quickly in patients with negative PCRs. More clinical experience would be needed before this stategy can be used. Also, while the results of this assay could theoretically be available in hours and could improve clinical decision-making, few hospitals have the capability to perform PCRs in-house. Unfortunately, send-out tests always take longer and, in my experience, often delay clinical decisions. ■

PHARMACOLOGY WATCH

Smallpox Vaccination Guidelines Published by CDC

The CDC published "Smallpox Vaccination and Adverse Reactions—Guidance for Clinicians" in the Jan. 24th edition of *Morbidity and Mortality Weekly Report.* The guidance is a thorough review of the smallpox vaccine with a well-illustrated compendium of complications. Some of the highlights include:

Inoculation is administered using a multiple-puncture technique with the bifurcated needle. The inoculation site progresses from papule to vesicle, eventually becoming a pustule within 10 days. The pustule scabs over within 2-3 weeks usually leaving a pitted scar. Development of a pustular lesion is considered a major reaction and a successful vaccine take. Lesser reactions are considered equivocal and are nontakes. Large vaccination reactions may occur in 10% of first-time vaccinees. Systemic reactions are common in all vaccinees and include fatigue, headache, myalgias, chills, nausea, and fever. The vaccine is made from live vaccinia virus (it does not contain variola virus) and transmission is possible from the vaccination site up to 3 weeks after vaccination. The shedding period may be less for revaccination. The inoculation site is generally considered infectious from the time just after vaccination until the scab separates from the skin. Vaccinia is transmitted by close contact and can lead to the same adverse events in an infected contact as in the vaccinee. The inoculation sites should remain covered and vaccinees should wash their hands immediately after touching vaccination sites or changing dressings. The smallpox vaccination is generally considered safe, but is contraindicated in patients who have, or are in close contact with, those who have atopic dermatitis (eczema) regardless of the severity, skin diseases that disrupt the epidermis, pregnant women or women who plan on becoming pregnant within 1 month after vaccination, and immunocompromised patients. Others who should not receive the vaccine include those who have an allergy to a component of the vaccine, are breast-feeding, are using ocular steroids, have moderate-to-severe intercurrent illness, or are younger than 18 years of age.

The CDC has an excellent web site for health-care providers who wish to learn more about the smallpox vaccine: www.bt.cdc.gov/training/smallpox-vaccine/reactions/default.htm

Nurses: Delay Vaccination Program

Meanwhile, not everyone is happy with the national smallpox vaccination program. Recently the American Nurses Association (ANA) requested that the Bush administration delay the smallpox vaccination program until certain safety issues can be addressed. Specifically, the ANA is seeking information regarding potential transmission of vaccinia virus to family members of vaccinated nurses, coverage of medical costs related to vaccination, safety of the vaccination materials, adequate educational materials and staffing issues, and job security issues related to the vaccination program. Others such as Thomas Mack, MD, MPH, argue in the Jan. 30 edition of the *New England Journal of Medicine* that

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smallpox is overrated as a bioterrorist weapon. His view is that the current vaccination policy would provide little protection and the cost from vaccine complications would outweigh any benefit (*N Engl J Med*. 2003;348:460-463). However, a special article in the same issue developed scenarios of smallpox attacks and reviewed possible outcomes of control policies. Their analysis favors a program of prior vaccination of health care workers but favors vaccination of the public only in the likelihood of a national attack, or multiple attacks is very high (*N Engl J Med*. 2003;348:416-425).

Viagra Effective for Depression Treatment

Sildenafil (Viagra) is an effective treatment for antidepressant-associated sexual dysfunction in men. The drug was tested in a multicenter randomized double-blind placebo-controlled trial. Ninety men with major depression in remission on SSRI antidepressants were randomly assigned to take sildenafil (50 to 100 mg) or placebo for 6 weeks. Men who were most affected by antidepressant-associated sexual dysfunction were significantly more likely to improve with sildenafil (24/44, 54.5% response rate) vs placebo (2/45, 4.4% response rate) ($P < .001$). Erectile function, arousal, ejaculation, orgasm, and overall satisfaction measures improved significantly with sildenafil compared with placebo (*JAMA*. 2003;289:56-64). This study is important because sexual dysfunction is a common cause of noncompliance with serotonin reuptake inhibitors, and use of sildenafil may improve compliance with antidepressant treatment.

Finisteride/Doxazosin no Better than Placebo for Urinary Obstruction

Finisteride (Proscar) is no better than placebo when used in combination with doxazosin for the treatment of urinary obstruction due to benign prostatic hypertrophy, according to the recently published Prospective European Doxazosin and Combination Therapy (PREDICT) trial. These findings come in contradiction to the Medical Therapy of Prostatic Symptoms (MTOPS) trial published in May 2002, which showed a benefit of the combination of finasteride and doxazosin. In the current study, more than 1000 men were randomized to doxazocin, finisteride 5 mg per day, the combination of both, or placebo. The groups receiving doxazocin alone or in combination with finisteride had significant improvements in total maximal urinary flow rates and International Prostate Symptoms Score compared to the finisteride alone group and placebo group ($P < .05$). There was no significant difference between treatment with finisteride and placebo. Doxazosin was initiated at 1 mg per day and titrated to a maximum of 8 mg per day. All treatments were well tolerated (*Urology*. 2003;61:119-126).

Sildenafil, however, may be effective of relieving obstructive urinary symptoms in men who use the drug on a regular basis. British researchers looked at 112 men with erectile dysfunction at 1 and 3 months after taking sildenafil as needed before sexual intercourse. Only 20 of the 112 men complained of lowered urinary tract symptoms, but of those men, improved urinary scores at 3 months strongly correlated with improvement in sexual function. The authors suggest that an increase in nitric oxide associated with the resumption of normal sexual activity may be responsible for the improvement in urinary symptoms (*Br J Urol Int*. 2002;90: 836-839).

Serevent Receives 'Dear Doctor' Letter

GlaxoSmithKline has issued a "Dear Doctor" letter regarding its asthma bronchodilator salmeterol (Serevent). The warning is based on interim results from a large study of salmeterol that was initiated in 1996. The Salmeterol Multi-center Asthma Research Trial (SMART) was a postmarketing study designed to investigate reports of several asthma deaths associated with use of salmeterol. Analysis of the interim results showed a trend "toward a greater increase in asthma deaths and serious asthma episodes" with the largest increase in African-American patients. Data on almost 26,000 patients were available for analysis. While there was no significant difference for the primary end point of combined respiratory related deaths and respiratory related life-threatening experiences including incubation and mechanical ventilation between salmeterol and placebo, a higher, but not statistically significant number of asthma related life-threatening experiences including deaths occurred in the salmeterol group. The number of adverse events reached statistical significance in African-Americans who represented 17% of the study. No other ethnic group drew any conclusions. The use of inhaled corticosteroids reached only 47% in the entire population of the SMART study. Because of these findings, GlaxoSmithKline has decided to discontinue the study and continue reviewing data from the interim analysis. The FDA is involved in this process and will likely require label changes for Serevent that will reinforce guidance on appropriate and safe prescribing. ■

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Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports,* and *Sports Medicine Reports.*

VOLUME 8, NUMBER 3 PAGES 5-6 MARCH 2003

The Metabolic Syndrome and Total and Cardiovascular Disease Mortality in Middle-Aged Men

Source: Lakka HM, et al. *JAMA*. 2002;288:2709-2716.

THE METABOLIC SYNDROME (MBS) HAS 2 currently popular definitions. According to the National Cholesterol Education Program, MBS exists when a patient has at least 3 of the following characteristics: fasting glucose (FPG) > 110 mg/dL, abdominal obesity, triglycerides > 150, HDL < 40 mg/dL, and elevated blood pressure (> 130/85). The World Health Organization (WHO) definition stratifies things just a bit differently, defining MBS as either hyperinsulinemia (upper quartile of the adult, nondiabetic population) or FPG, and any 2 or more of abdominal obesity, dyslipidemia (triglycerides > 150 mg/dL or HDL < 35), and BP > 140/90. Despite these modest differences, the criteria basically define the same group of individuals. Lakka and associates prospectively studied for a mean of 11.6 years a random, age-stratified sample of men in Finland (n = 2682) aged 42 and older, to examine cardiovascular and overall mortality in relation to MBS.

MBS patients had reduced (79%) Kaplan-Meier estimates of overall survival when compared with patients without MBS. Similarly, CHD mortality was 2.4-3.4 times higher in persons with MBS. The prevalence of MBS at baseline was 9-14%. The public health impact of MBS is substantial. Whether specific treatment of MBS will reduce mortality has not been determined. ■

Amlodipine Fosinopril Combination on Microalbuminuria in Hypertensive Type 2 Diabetic Patients

Source: Fogari R, et al. *Am J Hypertens*. 2002;15:1042-1049.

NUMEROUS STUDIES HAVE CONfirmed the role of ACE inhibitors in modulation of microalbuminuria. The data on effects of calcium channel blockers (CCB) have been conflicting, especially as concerns dihydropyridine CCB (eg, amlodipine, felodipine, nifedipine). Fogari and associates addressed the effects of fosinopril (FOS) and amlodipine (AML), alone or in combination (COM), in an open-labeled, randomized, prospective, parallel group study for 4 years (n = 309).

By 3 months' time, the FOS group had demonstrated a decline in urinary albumin excretion (UAE), which decreased slightly further in the first year, and then stabilized. The AML group also demonstrated a decline in UAE, but not until 18 months into the study, after which point the UAE stabilized. COM therapy produced an impact at 3 months, which increased at 12 months and again at 36 months, and was statistically significantly greater than either monotherapy.

The mechanism by which COM therapy is superior to either monotherapy is uncertain, but the greater reduction in BP achieved (approximately 12/5 greater reduction by the former) is thought to have figured prominently. ■

Relation Between Alcohol Consumption and C-Reactive Protein Levels in the Adult United States Population

Source: Stewart SH, et al. *J Am Board Fam Pract*. 2002;15:437-442.

EPIDEMIOLOGIC DATA CONSISTENTLY indicate that moderate intake of alcohol (ETOH) is associated with reductions in cardiovascular mortality. Though the mechanism by which this effect is achieved is uncertain, increases in HDL by alcohol may explain as much as 50% of the protective effect.

C-reactive protein (CRP) is increasingly recognized as an independent risk factor for cardiovascular endpoints, suggesting an important role of inflammation in promoting atherosclerotic events. To evaluate the relationship between CRP and ETOH, Mainous and associates analyzed data from the National Health and Nutrition Evaluation Survey (NHANES III), which included complete information on 11,572 US adults.

Almost half of the NHANES population were alcohol abstainers; CRP levels in abstainers were significantly greater than in those who drink alcohol, regardless of level of alcohol ingestion. The mechanism by which ETOH might reduce CRP (or inflammation) remains unknown. A small trial of ETOH in healthy volunteers has shown a reduction in CRP and is stimulus for follow-up evaluation in larger studies. ■

Prostate Cancer Screening

Source: Ransohoff DF, et al. *Am J Med*. 2002;113:663-667.

In contrast to screening for breast and colon cancer, both of which have been demonstrated to reduce mortality, prostate cancer screening (PCS) has not yet been proven to favorably affect overall mortality, although some trials have found that PCS screening reduces prostate cancer-related mortality. Hence PCS has not met the same standard as other commonly used screening tools. Because of the discordance between the relative lack of supportive data to provide justification for PCS and the very high frequency of PCS testing, Ransohoff and colleagues sought to evaluate what factors promote PCS. That PCS can result in harm (eg, postsurgical impotence, incontinence) is clear; whether PCS can provide benefit (ie, reduction in mortality) remains to be demonstrated.

Ransohoff et al describe the PCS model as "lacking negative feedback:" a patient who undergoes PCS and has no cancer-suggestive findings feels reassured by these findings and is happy to have participated; a patient who has an elevated PSA often undergoes medical or surgical intervention. Even in the face of postintervention sequelae, the screened patient may feel that, ultimately, the intervention has spared his life, and he too may be grateful for the PCS.

Currently, whether PCS is mortality-effective is uncertain. Nonetheless, public satisfaction and enthusiasm for PCS remains high. It is conceivable that, in the long run, harm from PCS-stimulated intervention may outweigh benefit. Until the relative risks and benefits of PCS are more clearly defined, clinicians are well advised to review the decision path of PCS with patients before the process is embarked upon, in order that fully informed consent, dispassionately, may be attained. ■

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Can We Trust Home BP Measurement?

Source: Bachmann LM, et al. *J Clin Hypertens*. 2002;4:405-407,412.

The window of observation of blood pressure as obtained in the typical office setting has important limitations, with both exaggerations (ie, "white-coat" hypertension), and underestimates (ie, "masked hypertension") of hypertension burden being well documented. Abnormal circadian BP patterns, such as failure to experience the normal nocturnal decline in blood pressure, predict higher cardiovascular risk yet are not discerned by simple office measurement. Twenty-four-hour Ambulatory Blood Pressure Monitoring (ABPM) can resolve all 3 of these issues but is not without significant expense, and despite the endorsement of ABPM by the JNC VI report and the WHO guidelines, this technique remains only rarely used. Whether home blood pressure measurement, perhaps an intermediate step between office measurement and ABPM, is reliable is the subject of this report.

Bachmann and colleagues included 48 hypertensive patients from a single practice, who had been referred for 24-Hour ABPM. Subjects were randomly assigned to either a group which was asked to keep a personal log of the BP measurements recorded by the ABPM, and advised that their log would be checked for accuracy against that registered by the ABPM device, or a group who were also advised to periodically record BP measurements as registered by the ABPM device, but who were unaware that the ABPM automatically records and stores BP measurements. Discrepant results occurred when patient-recorded records either had an incorrect time, an incorrect BP value, or a BP was entered as recorded when the ABPM device had not performed such a measurement. Although patients unaware of the ABPM recording capacity were found to have more "fictional" registrations than the "informed" group (10/728 vs 29/616), ultimately these discrepant recordings did not confound the overall mean accuracy of averaged home blood pressure readings. ■

Systolic and Diastolic Dysfunction

Source: Redfield MM, et al. *JAMA*. 2003;289:194-202.

Congestive heart failure (CHF) is typically classified as systolic (ie, reduced ejection fraction), diastolic (normal ejection fraction, with impaired ventricular filling), or both. Indeed, though CHF may have been generally conceptualized solely as "inadequate pumping," some degree of diastolic dysfunction accompanies almost all patients suffering systolic dysfunction. Additionally, isolated diastolic dysfunction, which may present with identical clinical symptoms as systolic dysfunction, has recently been recognized to be approximately as common as systolic dysfunction in patients with manifest CHF. Redfield and associates evaluated with doppler echocardiography adults older than 45 years of age participating in the Rochester (Minnesota) Epidemiology Project (n = 2042), none of whom entered the study with a diagnosis of CHF.

In this asymptomatic (for CHF) group, validated CHF prevalence was 2.2%, approximately equally divided between systolic and diastolic dysfunction. Diastolic dysfunction, whether mild, moderate, or severe, was found by multivariate analysis to be predictive of all-cause mortality. This trial indicates that diastolic dysfunction, previously regarded as more "benign" than systolic dysfunction, portends significant adverse health outcomes. ■