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Third-Generation Cephalosporin Resistance in Enterobacter Species: Health and Economic Outcomes

ABSTRACT & COMMENTARY

Synopsis: *The emergence of resistance to third-generation cephalosporins by Enterobacter spp. is a common phenomenon in infected patients treated with these agents and is associated with adverse outcomes.*

Source: Cosgrove SE, et al. *Arch Intern Med*. 2002;162:185-190.

EMERGENCE OF CEPHALOSPORIN RESISTANCE BY *Enterobacter* species during therapy is a well-recognized phenomenon. Cosgrove and colleagues examined a cohort of 477 patients with initial cultures yielding *Enterobacter* species susceptible to third-generation cephalosporins by microbroth dilution assay. In 46 of these patients (10%), subsequent cultures yielded an *Enterobacter* isolate resistant to third-generation cephalosporins. These case patients were matched to 113 control patients by anatomic site of isolation and duration of prior hospitalization. The outcomes of interest were mortality, length of hospital stay, and hospital charges.

The crude mortality rate among cases was 26% compared with 13% among controls ($P = .06$). The median hospital stay for cases was 29.5 days and 19 days for controls ($P < .001$). Median hospital charge for cases was $79,323, compared with $40,406 for controls ($P < .001$). After adjusting for confounding by multivariable analysis, the emergence of resistance had a significant association with mortality (relative risk, 5.02; $P = .01$). Hospital stay for cases was significantly prolonged (1.5 fold; $P < .001$) and hospital charges were significantly higher (1.5 fold; $P < .001$). The increased length of stay attributable to emergence of resistance was 9 days, and the attributable increase in hospital charges was $29,379.

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INSIDE

COMMENT BY ROBERT MUDER, MD

Beta-lactam resistance by *Enterobacter* species is typically mediated by beta-lactamases of the AmpC type.[1] These enzymes are chromosomally encoded and are widely present in *Enterobacter* spp., *Serratia* spp., *Citrobacter freundii*, and *Morganella morganii*. While they are normally produced in minute quantities, increased production can be induced by exposure to some beta-lactam antibiotics, including third-generation cephalosporins. High levels of enzyme production after such exposure lead to dramatic increases in MIC, a marked inoculum effect, and in vitro resistance of previously susceptible strains. More important, however, is the selection of preexisting mutants, usually present at a frequency of approximately 10^{-7}, with mutations in their *AmpD* regulatory genes causing constitutive high level production of the AmpC enzyme. These strains are typically resistant to third-generation cephalosporins, extended-spectrum penicillins, and aztreonam. AmpC beta-lactamases are not subject to inhibition by beta-lactamase inhibitors such as clavulanate, sulbactam, or tazobactam. AmpC producing Enterobacteriaceae are nearly always susceptible to imipenem and meropenem.

The clinical importance of selection of mutant clones consistantly expressing large amounts of the AmpC enzyme of resistance by exposure to beta-lactamase was demonstrated by Chow and colleagues in a study of *Enterobacter* bacteremia.[2] Of those patients treated with a third-generation cephalosporin, 19% had subsequent isolation of a third-generation cephalosporin resistant to Entertobacter. In contrast, only 1% of patients treated with aminoglycosides had subsequent isolation of an aminoglycoside-resistant *Enterobacter*. Emergence of resistance was not encountered among patients receiving other classes of beta-lactam antibiotics.

The study by Cosgrove et al shows convincingly that emergence of in vitro cephalosporin resistance is associated with adverse clinical outcomes and increased costs. They did not report details of antimicrobial therapy, and thus did not relate emergence of resistance or outcome to use of cephalosporins. This might have provided additional useful information had they done so.

However, based on the data available from this report and Chow et al's prior study, it is clear that third-generation cephalosporins are poor choices in the treatment of serious infections due to *Enterobacter* spp., and by extension, *Serratia* spp. If they are used at all, a second agent to which the isolate is susceptible, such as a quinolone or aminoglycoside, should be added.

Finally, indiscriminate use of third-generation cephalosporins increases the likelihood of emergence of resistant strains. Although originally chromosomally mediated, AmpC beta-lactamases are now encoded on a number of plasmids that can be transferred to species that don't normally carry these enzymes, such as *E coli* and *Klebsiella*. Thus, the widespread dissemination of these enzymes, with major adverse clinical and economic consequences, is a real possibility. ■

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Defining the Susceptibility of *Streptococcus pneumoniae* to ß-lactam Antibiotics: Putting the Cat Among the Pigeons

ABSTRACT & COMMENTARY

Synopsis: *The MIC breakpoints for beta lactams against S pneumoniae have been revised, taking into account the different demands of therapy in meningeal and nonmeningeal infections.*

Source: Musher DM, et al. *Arch Intern Med*. 2001;161: 2538-2544.

Until the 1970s, it had been assumed that all strains of *Streptococcus pneumoniae* were universally susceptible to penicillin and would remain so. The appearance of resistant strains in South Africa was an unwelcome surprise. The definition of *Pneumococcal* resistance was based primarily on the laboratory and clinical data arising from meningitis, but not the more common manifestations of pneumococcal disease such as sinusitis, otitis media or pneumonia. Now, almost a quarter of a century later, this has been rectified with a change in the definition of susceptibility (*see Table 1*).

The choice of a low concentration of 0.06 mg/L was based on the fact that CSF levels of penicillin among children treated for meningitis 4 hours after the dose are around 1 mg/L and those of ceftriaxone are 3-4 fold higher. Hence, MICs that exceed this are unlikely to prove successful for treatment. However, it is plasma or serum levels that are more important in other forms of pneumococcal disease and these are higher than those obtained in CSF. For instance, in pneumonia an MIC of 2 mg/L of penicillin or 4 of ceftriaxone would be 2-4 fold lower than the peak serum concentrations and, hence, should prove amenable to treatment. Similar considerations apply to sinusitis and otitis media (*see Table 2*). While the *S pneumoniae* was eradicated after treatment with amoxicillin in 10 of the 14 cases with infection caused by a penicillin-resistant strain, only 6 of the 17 cases treated with cefaclor and none of the 6 cases treated with azithromycin responded. These results provide further motivation for setting different breakpoints for amoxicillin between meningeal and nonmeningeal disease or, rather, central nervous system disease and other diseases. The observation that the risk of dying within 4 days of starting treatment for bacteremia due to *S pneumoniae* was only increased for strains with an MIC of 4 mg/L or higher provides yet more evidence to support a change.

Importantly, it is now explicitly acknowledged that, besides the MIC of the strain, the site of infection and tissue levels of the drug (which, in turn, depends upon the dosage of antibiotic and the route of administration) need to be considered when defining susceptibility or resistance of *S pneumoniae*.

COMMENT BY J. PETER DONNELLY, PhD

A change in the breakpoint MICs for *S pneumoniae* is a move in the right direction but reminds me of a discussion that surfaces from time to time—namely, how are these breakpoints actually arrived at and do they make any real sense. There are increasingly more exceptions to the rule which tacitly acknowledges the simple fact that the one-fits-all principle does not actually apply as often as was hoped and that perhaps the approach advanced by Ericsson and Sherris 30 years ago namely, that each genus should have its own breakpoint to any given antibiotic, was correct after all.[1] Moreover, the susceptibility of bacteria to an antibiotic is bound to differ for infections in different body systems simply because bacterial growth in vivo is radically different from that found in a test tube. Microbiologists worry that complex rules for defining breakpoints might create

Table 1

Laboratory Definitions for the Susceptibility of *Streptococcus pneumoniae*

	Susceptible	Intermediate	Resistant
Penicillin			
Meningeal	≤ 0.06	0.12-1	≥ 2
Nonmeningeal	≤1	2	≥ 4
Amoxicillin			
Meningeal	—	—	—
Nonmeningeal	≤ 2	4	≥ 8
Cefotaxime, ceftriaxone			
Meningeal	≤ 0.5	1	≥ 2
Non-meningeal	≤ 4	—	≥ 8

Table 2

Microbiological Cure Rates for Otitis Media

	Dose (mg/kg)	Penicillin susceptible (MIC < 0.1 mg/L)	Penicillin resistant (MIC = 0.1 mg/L)
Amoxicillin	16.5 q8h	10/10	10/14
Cefaclor	13.5 q8h	16/19	6/17
Azithromycin	10 q 24h	10/10	0/6

confusion among clinicians, but my impression is that although a clear and unequivocal answer is usually demanded from the laboratory by clinicians, few actually expect a single breakpoint for the same bacterium under all circumstances. Indeed, some may argue that susceptibility testing is usually done after the fact because antibiotics are more often than not given empirically and the results only become of interest when treatment is considered to be failing. Perhaps it is time for clinicians to state directly whether they have a given drug in mind or whether they have already started treatment with the drug and only ask to be informed when the strain is found to be resistant with the microbiologist advising alternative drugs that might prove effective. The laboratory would still be able to use the result to refine the rates of susceptibility in order to judge whether the first-line treatment for a given indication needs to be reconsidered or not. For instance, if the incidence of *S pneumoniae* with MICs of penicillin exceeding 0.1 mg/L is low (as is still the case here in Nijmegen) knowing the susceptibility of a particular strain will not materially alter the odds of success or failure of treatment with a ß-lactam antibiotic. Conversely, high or rising rates of resistance would raise the alarm and necessitate changing the empirical regimen or at least adopting an approach whereby the initial regimen was changed accordingly should the offending strain prove less than fully susceptible given the site of infection. This seems to offer the best balance between meeting the needs of clinicians and allowing laboratories to exercise their expertise efficiently and economically. ■

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Clinical Trials

Voriconazole

By Stan Deresinski, MD, FACP

VORICONAZOLE WAS RECENTLY RECOMMENDED for FDA approval for use in the treatment of invasive aspergillosis. This approval was largely based on the pooled analysis of 2 multicenter clinical trials, one performed in Europe and one in the United States, in which a total of 392 patients were randomized to treatment with either voriconazole or amphotericin B deoxycholate.[1] In these studies, the global response rate at 12 weeks was 52.8% (95% CI for the difference, 9.6-33.6%) in the voriconazole recipients and only 31.6% in those randomized to amphotericin B. Furthermore, survival rates at 84 weeks were, respectively, 71.8% and 57.9% (P = 0.015). The few cases of *A flavus* infection did not respond to therapy. The results of an open, noncomparative experience in the treatment of invasive aspergillosis also appear generally favorable.

Separately, voriconazole was compared to liposomal amphotericin B in a randomized trial of empiric therapy of febrile neutropenic patients with hematological malignancy who remained febrile despite at least 96 hours of empiric broad spectrum antibacterial therapy.[1-3] Voriconazole (barely) failed to meet the predetermined criterion for noninferiority and, as a consequence, has not received FDA approval for this indication.[4] Nonetheless, there was no difference between the treatment arms with regard to breakthrough fungal infections or mortality. In fact, the apparent failure of voriconazole was solely due to less frequent resolution of fever during neutropenia.[5] Thus, despite the lack of FDA approval, and taking into account the lesser infusion related and renal toxicity relative to liposomal amphotericin B, many clinicians will come to the conclusion that voriconazole is an effective option in this setting.

In addition to its activity against *Aspergillus* spp., this bistriazole congener of fluconazole has antifungal activity in vitro against *Candida* spp., including many resistant to fluconazole, with MICs against these organisms similar to those of itraconazole. Thus, voriconazole has also been compared, in randomized trials, to both fluconazole and amphotericin B deoxycholate in the treatment of esophageal candidiasis. In each case, outcomes between patients receiving voriconazole and those receiving the comparator were similar. Reports of case series of open noncomparative administration indicate that voriconazole may also be effective in some cases of infection due to less commonly encountered fungi, such as *Scedosporium apiospermum,* for which previously available therapies have frequently ineffective.

Fungicidal or Fungistatic?

Voriconazole, like other azoles, does not have fungicidal activity against *Candida* spp. It has been claimed that, in contrast to itraconazole, voriconazole is fungicidal against *Aspergillus* spp. One study found that the concentration of voriconazole required to achieve a 95% reduction in colony forming units of *A fumigatus* was

0.5 µg/mL, compared to 1.0 µg/mL for itraconazole. Another study found a 95-99% reduction at a concentration of 5 µg/mL when read at 24 hours.[6] It is likely, however, that delay of the evaluation until 48 hours would sharply reduce the apparent efficacy of this drug. Furthermore, while these studies were performed using a conidial inoculum, reported experiments indicate that hyphae are significantly more resistant to the fungicidal activity of this agent.[6] Nonetheless, while the fungicidal activity of voriconazole against *A fumigatus* remains subject to debate, the clinical trial data discussed above leave little room for doubt about the efficacy of voriconazole in the treatment of patients with neutropenia and invasive aspergillosis.

Tolerability

Voriconazole has, in general, been well tolerated, although transient visual disturbance has been reported in every clinical trial with incidences that ranged from approximately 11-52%. In the empiric therapy in febrile neutropenia, the incidence was 22% in the voriconazole recipients and 1% in those given liposomal amphotericin. This adverse event appears to be plasma concentration-related, with an approximately 5% increase in risk for each 1.0 µg/mL increase in plasma voriconazole concentration. At plasma concentrations ≥ 3.0 µg/mL, the incidence of visual complaints was ≥ 25%. In addition, 4.3% of voriconazole recipients in the *Aspergillus* studies developed visual hallucinations, thought to be distinct from the more common visual disturbances.

The incidence of transaminase elevations was low and was similar in the recipients of voriconazole and of liposomal amphotericin. Data from compiled clinical trials suggest that serum ALT and AST elevations are associated with plasma concentrations of voriconazole in excess of 5 µg/mL. However, a threshold concentration for hepatotoxicity could not be discerned on examination of data from early Phase I/II trials. Nonetheless, reversible hepatotoxicity was observed in 3 of 7 subjects given 400 mg b.i.d. in a Phase I study.

Cardiac toxicity has not been reported in the clinical trials. However, in preclinical studies, QT interval prolongation was observed in dogs with peak serum concentrations of 24 µg/mL. The reported association of itraconazole and the development of congestive heart failure must also be kept in mind.

Voriconazole, like other azoles, is teratogenic.

Pharmacokinetics

In the absence of a loading dose, steady state trough concentrations are achieved after 5 days of dosing. The plasma kinetics of voriconazole are nonlinear as the consequence of saturable metabolism. Thus, a 2-fold increase in dose from 200 mg to 400 mg results in a 2.8-fold increase in C_{max} and a 3.9-fold increase in AUC, together with an increase in T1/2 from 6 hours to 12

Table 1

Dosing and Other Implications of Drug Interactions

Coadministered Drug	**Result and/or Action**
Rifampin	Contraindicated combination
Rifabutin	If rifabutin necessary, increase voriconazole maintenance dose to 5 mg/kg b.i.d. or to 400 mg po b.i.d. (from 200 mg po b.i.d.); Monitor CBC and rifabutin-associated adverse events, esp. uveitis
Phenytoin	Increase voriconazole maintenance dose to 5 mg/kg b.i.d. or to 400 mg po b.i.d. (from 200 mg po b.i.d.); Monitor phenytoin concentrations and adjust its dose
Warfarin	Monitor INR with warfarin adjustments
Omeprazole	Reduce omeprazole dose by one half
Tacrolimus	Reduce tacrolimus dose by one third & frequently measure tacrolimus levels
Sirolimus	Contraindicated
Cyclosporin	Reduce cyclosporin dose by one half & frequently monitor cyclosporin levels
Not Studied	**Likely Effect**
Carbamazepine	Significant decrease in voriconazole exposure
Long-acting barbiturates	Significant decrease in voriconazole exposure
Ergot alkaloids	Increased ergot concentrations ⇒ ergotism
Sulfonylureas	Increased sulfonylurea levels ⇒ hypoglycemia
Statins	Increased statin levels ⇒ myositis, hepatitis
Benzodiazepines	Increased benzodiazepine levels ⇒ somnolence
Vinca alkaloids	Increased vinca alkaloid levels ⇒ vinca toxicity

Table 2

Usual Dosing in Adults

	Intravenous	Oral	
		Weight > 40 kg	Weight < 40 kg
Loading Dose: 1st 24 hours	2 doses of 6 mg/kg 12 hours apart	2 doses of 400 mg 12 hours apart	2 doses of 200 mg 12 hours apart
Maintenance Dose			
*Candida**	3 mg/kg q 12 hours	200 mg q 12 hours	100 mg q 12 hours
Aspergillus *Scedosporium* *Fusarium*	4 mg/kg q 12 hours	200 mg q 12 hours	100 mg q 12 hours

* In the absence of an adequate clinical response, the IV maintenance dose may be increased to 4 mg/kg q 12 hours and the oral maintenance dose to 300 mg q 12 hours for those > 40 kg in weight and to 150 mg q 12 hours for those < 40 kg in weight.

Adult Dosing in Special Circumstances

Circumstance	Recommended Dose
Weight < 40 kg	One half the usual dose
Renal insufficiency	No change
Hepatic insufficiency	
Childs-Pugh Class A and B	Reduce maintenance dose by one half
Childs-Pugh Class C	No data

hours. The saturable metabolism also leads to plasma accumulation with significant increases in C_{max} and AUC with repetitive dosing. Females have significantly higher drug exposure and greater drug accumulation than males. Only 1.5% of the drug is excreted unchanged in the urine. Its major metabolite, N-oxide voriconazole, has minimal antifungal activity.

Voriconazole is a substrate, as well as an inhibitor of the CYP450 enzymes, CYP2C19, 2C9, and 3A4 and at least 30% of the variability in its pharmacokinetics is accounted for by widespread human polymorphisms in CYP2C19. Approximately 5% of Caucasians and 10-20% of Asians are deficient in this enzyme and, thus, are poor metabolizers of voriconazole. Analysis of the genotypes of the patients participating in the Phase I trials of this drug, 28% of whom were Japanese, found that 9% were PM and 29% were heterozygotes. Despite this reported variability, patients in the *Aspergillus* trials maintained mean plasma voriconazole levels between 2 and 4 µg/mL throughout the 12-hour dosing interval during which approximately 75% of individually measured levels were between 1 and 7 µg/mL. These results are not inconsistent with data compiled from Phase I studies in which, with repetitive dosing, 22% of patients had a voriconazole C_{max} = 1.0 µg/mL, while in 12% the C_{max} was = 6.0 µg/mL.

The voriconazole AUC is increased more than threefold in the presence of mild-to-moderate hepatic impairment (Child-Pugh Class A and B). As a consequence, after administration of the usual initial dose, subsequent doses of voriconazole should be reduced by one-half. There are no data in patients with Child-Pugh Class C liver disease. Voriconazole kinetics are not altered in the presence of renal insufficiency. However, voriconazole for IV administration is formulated with sulpho-butyl-ether-cyclodextrin and this solubilizing excipient is renally excreted and, in addition, is associated with nephrotoxicity in experimental animals. As a consequence, the IV formulation of voriconazole should not be administered to patients whose creatinine clearance is ≤ 50 mL/min. ■

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Meningococcal Disease in Pilgrims

DISEASE UPDATE

Synopsis: *Since the outbreak of Neisseria meningitides infections that occurred in Hajj pilgrims in 1987, Saudi Arabia has required pilgrims to be vaccinated with the bivalent meningococcal A/C vaccine. In recent years, outbreaks of meningococcal disease associated with pilgrims to the Hajj have shifted from serogroup A to W135. Saudi Arabia has changed the policy for the 2002 Hajj season to require that all pilgrims be vaccinated with the quadrivalent meningococcal vaccine.*

Source: Memish ZA. *Clin Infect Dis*. 2002;34:84-90.

A LARGE AND SERIOUS OUTBREAK OF SEROGROUP A meningococcal disease associated with the Hajj occurred in 1987. The outbreak led to a requirement that pilgrims traveling to Saudi Arabia be vaccinated with the meningococcal vaccine. After the institution of this

requirement, small outbreaks of meningococcal diseases still occurred in Mecca and Jidda, mainly in unvaccinated persons. Following the Hajj in 2000, an outbreak involving predominantly W135 was identified. It affected at least 330 pilgrims and their *contacts* in numerous countries.[1,2] In 2001, more than 150 cases of meningococcal disease were identified in the period following the Hajj, with greater than 50% attributed to serogroup W135.[3]

As a result of the shift to serogroup W135 predominance, the Ministry of Health of Saudi Arabia is instituting a change of policy for the Hajj in 2002. All local population at risk will be vaccinated with the quadrivalent vaccine. Moreover, all pilgrims must be vaccinated with the quadrivalent meningococcal vaccines. The vaccine needs to be administered at least 10 days before and not greater than 3 years prior to arrival in Saudi Arabia. Children 3 months to 2 years old should receive 2 doses of the vaccine separated by a 3-month interval.[4]

The transmission of meningococcal disease to contacts by vaccinated pilgrims demonstrates the failure of the polysaccharide vaccine to eliminate *N meningitides* carriage in vaccinees. Furthermore, while the serogroup A and C polysaccharide vaccines have a clinical efficacy of 85-100% in older children and adults, the serogroup C polysaccharide is ineffective in children younger than 2 years of age.[5] The efficacy of serogroup Y and W135 polysaccharides is less clear. Newer vaccines such as the meningococcal conjugate vaccines hold promise for improved protection and should become available within the next few years.

To assess pharyngeal colonization in pilgrims after returning from Saudi Arabia, the Centers for Disease Control and Prevention (CDC) performed a study in 2001. The carriage of W135 was found to be similar between pilgrims and nonpilgrims.[6] Therefore, the CDC does not recommend prophylactic antibiotics for returning pilgrims.

On the other hand, prophylactic medication after close-case contact (household, day care center, exposure to patients' oral secretions) should be given within the first 24 hours of exposure. For adults, the recommended antibiotic is one oral dose of ciprofloxacin 500 mg or ofloxacin 400 mg or azithromycin 500 mg. For postexposure prophylaxis in children, rifampin can be given at 5 mg/kg every 12 hours for 2 days in those younger than 1 month old, and 10 mg/kg every 12 hours for 2 days in those older than 1 month old. In children younger than 15 years of age, a single dose of ceftriaxone 125 mg IM is an alternative prophylaxis.

There is one meningococcal vaccine available in the United States, and that is the quadrivalent vaccine containing polysaccharide to serogroups A, C, Y, and W135 (Menomune). A serogroup A/C polysaccharide vaccine has been used outside of the United States, and a conjugate serogroup C vaccine has been available in the United Kingdom. Because of the change requiring the quadrivalent vaccine for pilgrims to Saudi Arabia, the immunization records of travelers should clearly reflect the administration of the quadrivalent A, C, Y, W135 vaccine. In addition to providing the immunization, a discussion of postexposure prophylaxis would benefit the travelers. ■

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CME Questions

11. Which of the following is correct with regard to the emergence of resistance to third-generation cephalosporins in *Enterobacter* spp.?

a. The lack of associated mortality suggests loss of virulence.
b. There is no increase in associated health care costs.
c. The frequency of occurrence during treatment with a third-generation cephalosporin has previously been reported to be approximately one-in-five.
d. *Enterobacter* spp. all constitutively produce AmpC beta lactamase in high concentration.

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UPDATES

By Carol A. Kemper, MD, FACP

A New Flu Peptide with a Purpose?

Source: Chen W, et al. *Nat Med*. 2001;7:1306-1312.

A novel peptide found in certain influenza viruses, which may be derived from strains of avian influenza, may explain the significant morbidity associated with certain outbreaks of influenza. For years, influenza was thought to have just 8 genes, which encoded 10 different proteins. Chen and associates discovered that the translation of an alternate reading frame for one of these genes, PB-1, resulted in a completely different 87-residue protein, PB1-F2. This new peptide is uniquely capable of being recognized by CD8+T cells, and induces apoptosis of human monocytes. Interestingly, the gene product could not be isolated from certain animal influenza viruses (eg, swine), but could be found in certain avian viruses. Chen et al theorize that PB1-F2 may function to promote killing of influenza virus-infected host immune cells, resulting in a rapid inability to fight off infection and higher frequency of morbidity and mortality. ■

D4T and Neuromuscular Weakness

Source: Stevens MR. Drug Warning, BMS Virology, February 2002.

The long-term administration of nucleoside analogue therapy, especially the agents zidovudine (AZT), didanosine (ddI), and stavudine (d4T), has been linked to the development of lactic acidosis and mitochondrial toxicity in patients with HIV (Kemper CA. *Infectious Disease Alert*. 2001;20(8)59-60). While some patients receiving NRTIs develop asymptomatic elevations of lactic acid, the significance of which is not known, such patients may rarely develop a rapidly progressive and sometimes fatal syndrome of lactic acidosis, often associated with pancreatitis, hepatic steatosis, and myopathy.

In addition, several cases of rapidly progressive neuromuscular weakness, resembling Guillain Barré syndrome, have been described in patients receiving d4T in combination with other antiretrovirals. Progression to frank paralysis and respiratory failure has occurred. Most of the cases occurred in patients with symptomatic elevations in lactic acid or more severe lactic acidosis. The manufacturer recommends immediate discontinuation of d4T in any patient with motor weakness, sudden neurologic symptoms, or lactic acidosis. Immediate hospitalization with close observation, administration of fluids, bicarbonate, and carnitine may be of benefit. ■

Congenital Malaria—Revisited

Source: *MMWR Morb Mortal Wkly Rep.* 2002;51:164-165.

Congenitally acquired malaria is unusual, but vertical transmission of *Plasmodium malariae* is almost unheard of. In September 2000, a 10-week-old infant presented with fever, anemia, and thrombocytopenia. The child had been born in North Carolina and had never been out of the country, although both parents were from the Democratic Republic of Congo (the mother in 1996). Multiple cultures of blood, urine, and CSF were negative, but blood smears obtained 2 days after admission were positive for *P malariae*. The mother reported a history of malaria and received chloroquine shortly before immigrating to the United States. However, multiple specimens from the mother, including smears and PCR for all 4 malaria species were negative, although antimalarial antibody titers were high.

Unlike *P vivax* and *P ovale*, which may remain dormant in the liver for years, *P malariae* has no dormant hepatic phase and can only persist in erythrocytes. Cases of asymptomatic, low-level parasitemia have been described, and recrudescence of infection has occurred as many as 70 years after primary infection! Vertical transmission in this case can only have resulted from inadequate treatment with residual low-level parasitemia in the mother prior to delivery, despite her negative studies at the later date.

This case is a reminder of the single case of congenital transmission of malaria that I've seen, which occurred many years ago at the county hospital.[1] A 4-week-old infant presented with fever and irritability to the Pediatric Clinic. Fortunately, while doing a manual differential, the laboratory detected ring forms of *P vivax*—a finding that would have been missed with an automated differential. Mom was newly immigrated to California from Mexico, and was unaware of any history of malaria, was asymptomatic, and had negative smears. Although unusual, clinicians should consider congenital malaria in any infant with persistent fever, anemia, and unremarkable cultures whose mother has risk factors for malaria. ■

Reference

1. Kemper CA, et al. Efficiency of diagnosis and adequacy of antimalarial therapy in patients hospitalized with malaria. In: Lobel H, Steffen R, Kozarsky P, eds. *Travel Medicine 2: Proceedings of the Second Conference on International Travel Medicine*. 1991; 109-111.

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Infectious Disease

Editor's Note: *In this feature, brief items, primarily gleaned from abstracts or articles in journals and other resources not commonly perused by most US Infectious Disease physicians, will be presented, usually without comment. —Stan Deresinki, MD, FACP*

Respiratory Infections

Aspiration Pneumonia and the Elderly

Examination of Medicare discharge data for elderly patients from 1991 through 1998 found that annual hospitalizations for aspiration pneumonia almost doubled, increasing by 93.5% (Baine WB, et al. *Am J Public Health*. 2001;91:1121-1123).

Does Sputum Induction Improve the Quality of Sputum Specimens for Routine Bacteriology? Answer: Not if They Have a Productive Cough

One hundred twenty hospitalized patients with productive cough and a diagnosis of lower respiratory tract infection were randomized to provide a sputum specimen either spontaneously or after induction by untrained nurses with hypertonic saline. The quality of the specimens, as judged by the cellular content seen after Gram staining, did not differ between the 2 groups. It should be noted, however, that an earlier study (*Respiration.* 2000;67:173) in patients with a nonproductive cough found sputum induction to be of value (Chuard C, et al. *Diagn Microbiol Infect Dis*. 2001;39:211-214).

Plasma D Dimer, Pneumonia, and Pulmonary Embolism

Plasma D dimer levels were elevated in patients with community-acquired pneumonia, although not to levels associated with high probability of pulmonary embolism. Nonetheless, it is concluded that measurement of D dimer levels are "useless in the differential diagnosis" between pulmonary embolism and pneumonia (Castro DJ, et al. *Respiration*. 2001;68:371-375).

Unsustained Benefit of Macrolide Therapy in Patients with Asthma and Past *Chlamydia pneumoniae* Infection

In this study, 232 patients with asthma and serological evidence of *C pneumoniae* infection (IgG ≥ 1:64 and/or IgA ≥ 16) were randomized to receive either roxithromycin (150 mg qd) or placebo for 6 weeks. The roxithromycin group had a significantly greater improvement in their peak expiratory flow rate, but this benefit was not sustained, being nonsignificant at 3-month and 6-month examinations (Black PN, et al. *Am J Resp Crit Care Med.* 2001;164:536-541).

Fluoroquinolones and Legionella

In vitro susceptibility testing of 140 *Legionella* spp. isolates using BYE alpha broth found that trovafloxacin, levofloxacin, moxifloxacin, and ciprofloxacin had MIC90s ranging from

0.008 µg/mL to 0.06 µg/mL, while those of erythromycin and azithromycin were 0.5 µg/mL for each. The MIC90 for rifampin was 0.004 mcg/mL. The MBCs of the fluoroquinolones and rifampin were ≤ 4 × MIC, while for the macrolides it was ≤ 8 × MIC. The duration of the postantibiotic effect ranged from 2.25 hours for the fluoroquinolones and rifampin, while it was 1.54 hours for erythromycin, and 1.65 hours for azithromycin. The use of a cell-free system in studies of this intracellular pathogen raises questions, however, regarding its relevance (Gomez-Lus R, et al. *Int J Antimicrob Agents.* 2001;18:49-54).

Pneumococcal Vaccination

A meta-analysis of 14 randomized trials involving 48,837 subjects found that pneumococcal polysaccharide vaccination is associated with a reduction in the incidence of definite and presumptive pneumococcal pneumonia of, respectively, 71% and 40%, while reducing mortality due to pneumonia by 32%. However, "no preventive effect was seen in the subgroup of patients 55 years or more, possibly due to a lack of statistical power." (Cornu C, et al. *Vaccine.* 2001;19:4780-4790.)

Zanamivir and Response to Influenza Vaccination

Zanamivir administration to healthy adults did not interfere with the antibody response to the H3N2 influenza A and the influenza B component of a trivalent vaccine, while the placebo group developed higher antibody titers to H1N1. Cox and colleagues suggest that, during an outbreak, zanamivir need be only administered for 12 days after vaccination (Cox RJ, et al. *Vaccine.* 2001;19:4743-4749).

Gastrointestinal Infections

Ophthalomoplegia and Campylobacter

An association between *Campylobacter jejuni* infection and the development of Guillian-Barré and Miller-Fisher syndromes has been described. Kuroki and associates report 3 patients with idiopathic cranial polyneuropathy with predominant ocular involvement from whose stool *C jejuni* was isolated. Each had elevated serum anti-GQ1 antibodies that decreased rapidly at the time of clinical recovery (Kuroki S, et al. *Pediatr Neurol*. 2001;25:71-74).

Helicobacter pylori Infection is Associated with a Decreased Incidence of Erosive Reflux Esophagitis, While its Association with Gastric Cancer is Confirmed

H pylori infection may prevent reflux esophagitis by inducing hypoacidity. This appears to be especially true with regard to strains that have the cytotoxin associated gene (*cagA*). *CagA+* strains have previously been associated with a reduced risk of esophageal adenocarcinoma. A meta-analysis found an estimated 5.9-fold relative risk of noncardia gastric cancer in association with *H pylori* infection (Koike T, et al. *Gut*. 2001;49:330-334; Yamaji Y, et al. *Gut*. 2001;49:335-340; Warburton-Timms VJ, et al. *Gut.* 2001;49:341-346; Webb PM, et al. *Gut*. 2001;49:347-353).

Endocarditis

Predictors of Recurrent Endocarditis After Valve Replacement Surgery

A retrospective review in Naples found that endocarditis recurred in 58 of 271 (22.5%) patients who had undergone replacement of a cardiac valve that had been or was infected. Variables associated with recurrence were surgery for prosthetic valve endocarditis, positive culture of the removed valve, and postoperative fever persisting for at least 7 days (Renzulli A, et al. *Ann Thorac Surg.* 2001;72:39-43).

Coagulase-Negative Staphylococci and Native Valve Endocarditis

Seven cases with histologically proven native valve endocarditis were seen at one institution over 10 years; all required valve replacement. While 4 patients had had central venous catheters and one had recently undergone surgery, 2 had no identifiable risk factors (Miele PS, et al. *Am Heart J*. 2001;142:571-576).

Nosocomial Bloodstream Infections (BSI) in Patients with Implantable Left Ventricular Assist Devices (LVAD)

In this study, 49% of 214 patients had BSI with an incidence of 7.9 per 1000 LVAD-days and 38% of the infections involved the device. Coagulase-negative staphylococci, *S aureus*, and *Candida* spp. were the most commonly identified pathogens (Gordon SM, et al. *Ann Thorac Surg.* 2001;72:725-730).

Central Nervous System Infection

Rapidity of CSF Sterilization After a First Parenteral Dose of Antibiotic

The rapidity with which empiric antibiotic therapy may render CSF culture-negative was analyzed in 128 children with bacterial meningitis—30% of whom had their first LP after the initiation of parenteral antibiotics. Another 43% had LPs both before and after the initia-

tion of therapy. Among 9 patients with meningococcal infection who received > 50 mg/kg of a third-generation cephalosporin, CSF was sterile in 3 within 1 hour, and all 9 were sterile within 2 hours (1 was sterile within 15 minutes). Among patients with pneumococcal infection, the first negative-CSF culture occurred at 4.3 hours and 5 of 7 were negative from 4 to 10 hours after initiation of parenteral antibiotics (Kanegaye JT, et al. *Pediatrics.* 2001;108:1169-1174).

Pyogenic Ventriculitis

The presence of ventricular debris, usually irregular in distribution and size, was present on CT and/or MRI of the brain in 16 of 17 (94%) of patients with pyogenic ventriculitis. Periventricular hyperintense signal and ependymal enhancement were also frequently observed (Fukui MB, et al. *Am J Neuroradiol*. 2001;22:1510-1516).

Cranial Subdural Empyema: Craniotomy is Better than a Burr Hole

Stepwise discriminant analysis of a retrospective cohort of patients with cranial subdural empyema found that craniotomy, rather than more limited surgical procedures, such as burr hole placement, found a significantly improved outcome when the former was performed (Nathoo N, et al. *Neurosurgery*. 2001;49:872-877).

Parvovirus B19 and Encephalitis

In what the authors indicate is a first, a previously healthy woman with clinical and serological evidence of parvovirus B19 infection developed encephalitis (Skaff PT, Labiner DM. *Neurology.* 2001;57:1336-1337).

Skin and Soft Tissue Infection

S aureus of Nose and Skin in Recurrent Skin Infections

Pairs of *S aureus* isolates obtained from the infection site and from the nares of 12 patients with chronic and recurrent skin infections were identical, both phenotypically (hemolytic activity, antibiotic resistance pattern, enterotoxin production, phage type) and genotypically (number of repeats in the X region of the *spa* gene, *coa* gene polymorphisms, PFGE macrorestriction analysis of chromosomal DNA) (Toshkova K, et al. *FEMS Microbiol Lett.* 2001;202:17-24).

Breast Abscess Management—Needle Aspiration

Thirty patients with 33 breast abscesses were treated with orally administered antibiotics and, instead of incision and drainage (I & D), by needle aspiration without ultrasound guidance. While 18 patients required only a single aspiration, 9 required multiple aspirations, and 6 (18%) required I & D (Schwarz RJ, Shrestha R. *Am J Surg.* 2001;182:117-119).

Imaging of Acute Deep Neck Infections

Forty-seven patients with proven neck infections underwent both CT and MRI with contrast. MRI was significantly better than CT in lesion conspicuity, determination of the number of anatomic spaces involved and extension, and determination of the source of infection. CT was somewhat better in the detection of intralesional gas and calcium (Munoz A, et al. *J Comput Assist Tomogr.* 2001;25:733-741).

Viral Hepatitis

Havrix vs. VAQTQ

Volunteers were randomized to receive 2 doses of inactivated HAV vaccine: Havrix-Havrix, Havrix-VAQTA, VAQTA-Havrix, or VAQTA-VAQTA. All 4 regimens were immunogenic, but VAQTA-VAQTA yielded significantly higher antibody concentrations than Havrix-Havrix (Bryan JP, et al. *Vaccine*. 2001;19: 743-750).

Delayed Booster Dose of HAV Vaccine Works

Healthy adults were given their 2nd dose of VAQTA 6, 12, or 18 months after the initial dose with comparable results in each case (Hornick R, et al. *Vaccine*. 2001; 19:4727-4731).

HAV Vaccination in Liver Transplant Recipients—Not so Hot

Although HAV vaccination appeared safe in liver transplant recipients, only approximately one fourth of patients seroconverted (Arslan M, et al. *Transplantation*. 2001;72:272-276).

HCV Infection with Normal LFTs

Only 94 of 135 (69%) of 135 consecutive HCV antibody positive patients with persistently normal ALT had detectable HCV RNA in serum. Serum ALT was lower and liver histology was less severe in patients without detectable serum HCV-RNA. None of 12 serum HCV RNA-negative patients had detectable HCV RNA in liver biopsy specimens. During a mean follow-up of 3.6 years, serum HCV RNA remained undetectable and ALT remained normal in all who were so initially while all others remained HCV RNA

positive and 21% of these had occasional slight increases in ALT. Liver histology remained stable in all who underwent rebiopsy (Martinot-Peignoux M, et al. *Hepatology*. 2001;34:1000-1005).

Hepatic HCV RNA

There was no correlation between the amount of hepatic HCV RNA in pretreatment liver biopsy samples and the severity of liver disease. Higher levels were found in patients infected with HCV genotype 1 and lower levels were seen in patients who proved to be sustained responders than in those without such a response. HCV RNA could not be detected in post-treatment liver biopsy samples of sustained responders (Gervais A, et al. *J Hepatol*. 2001;35:399-405).

HCV and Risk of Cirrhosis

A systematic literature review led to the conclusion that, for persons who acquire HCV infection in early adulthood, fewer than 10% are estimated to develop cirrhosis within 20 years. It was also concluded that previous higher estimates of risk (usually, approximately 20%) were the result of selection bias (Freeman AJ, et al. *Hepatology*. 2001;34:809-816).

Interferon Alpha Induction Followed by Combined Therapy for Infection with HCV Genotype 1

In a randomized trial examining higher dose interferon α for the first 14 weeks of therapy, and a combination treatment with ribavirin, no benefit was found for the participants as a whole. However, among patients infected with HCV genotype 1 treated with the highest induction dose (10 MU IntronA daily for 2 weeks followed by 10 MU qd for 10 weeks), sustained responses were almost twice as high as in those receiving lower induction doses (44.2% vs 28.6%, and 27.0%, $P < 0.05$). (Ferenci P, et al. *Hepatology*. 2001;34:1006-1001).

Retinopathy During Interferon α Therapy

Eight of 19 prospectively observed patients with chronic HCV infection receiving interferon α therapy developed transient asymptomatic retinopathy (Jain K, et al. *Br J Ophthalmol*. 2001;85:1171-1173).

Amantadine for HCV infection?

Two multicenter randomized trials failed to find any sustained benefit from the addition of amantadine to interferon α in the treatment of chronic HCV infection (Murray-Lyon L, et al. *J Hepatol*. 2001;35:512-516; Tabone M, et al. *J Hepatol*. 2001;35:517-521).

IL-12 for HBV/HCV Infection?

In 2 open-label multicenter trials, patients with chronic HCV infection (n = 60) and chronic HBV infection (n = 46) received recombinant human interleukin-12 (rHuIL-12) with minimal antiviral effect (Zeuzem S, Cerreno V. *Antiviral Res*. 2001;52:181-188).

Occult HBV Infection

Examination of 2565 Chinese patients, including patients with chronic hepatitis, cryptogenic cirrhosis, chronic renal failure on hemodialysis, and blood donors, found 51 (2.0%) with occult HBV infection (HbsAg-negative, HBV DNA-positive). Sequencing of the gene coding for the surface antigen found that 20 of 46 (43%) had one or more mutations in the major hydrophilic region of HbsAg. These results have important implications for blood screening (Hou JL, et al. *Hepatology*. 2001;34:1027-1034).

Combination Therapy for HBV Infection

In this study, 153 patients with chronic HBV infection were radomized to receive lamivudine with or without interferon α2b for 52 weeks with an additional 48 weeks follow-up. Sustained combination therapy was associated with improved HbeAg seroconversion (33% vs 15%; $P = 0.014$) and frequency of a 2 point or greater reduction in the hepatic inflammation score (46% vs 27%; $P = 0.021$) (Barbaro G, et al. *J Hepatol*. 2001; 35:406-411).

HBV, Interferon, and ALT Flares

A retrospective analysis of 121 patients and 42 untreated controls found that those who experienced an "ALT flare" during interferon alpha therapy were significantly more likely than those without a flare to have undetectable serum HBV DNA, as well as loss of serum HbeAg at the end of follow-up. Among those with high baseline serum HBV DNA, a severe flare was associated with an improved virological response. Multivariate analysis found that high baseline HBV DNA, high pretreatment ALT, and both moderate and severe ALT flare were independent predictors of a virological response (Nair S, Perrilo RP. *Hepatology*. 2001;34:1021-1026).

Triple Infection: HCV/HBV/HDV

Concurrent hepatitis D virus (HDV) infection suppresses hepatitis B virus (HBV) replication in dually infected individuals, sometimes to the extent that HBV surface antigen may become undetectable despite active disease. A study of patients dually infected with hepatitis C virus (HCV) and HBV has found that HCV has a similar effect. In triply infected (HCV/HBV/HDV) patients, HDV is the

dominant virus with HCV and HBV replication inhibited (Jardi R, et al. *Hepatology*. 2001;34:404-410).

Acute Non-A-E Hepatitis

In this trial, 45 (85%) of 53 adult patients admitted to a Taiwan hospital with acute non-A-E hepatitis had severe disease (albumin < 3 g/dL, bilirubin > 15 mg/dL, or prothrombin time prolongation > 3 seconds) with 3% having fulminant hepatitis and 7% having developed chronic disease (Chu CM, et al. *J Med Virol*. 2001;65:296-300).

Mycobacterial Infections

BCG and PPD Boosting

Repeat tuberculin skin testing at 1 week in BCG-vaccinated hospital employees caused a booster effect that was maximal (mean, ± 7.8 mm induration) at 48 hours and then waned (Singh D, et al. *Am J Resp Crit Care Med.* 2001;164:962-964).

Diagnosis of TB by Direct Application of Gen-Probe

Six hundred sixty-three respiratory and 238 nonrespiratory specimens from 464 patients, 56 of whom had pulmonary and 19 extrapulmonary tuberculosis were examined directly using the upgraded Amplified Mycobacterium Tuberculosis Test kt (AMTD; Gen-Probe, Inc.) with the results compared to clinical and culture data. Using the traditional cutoff for a positive test, the sensitivity was 96.7% with smear-positive and 81.0% with smear-negative specimens, with an overall specificity of 93.0%. It was possible to adjust the cutoff, improving specificity without impairing the sensitivity of the test (Alcala L, et al. *Diagn Microbiol Infect Dis*. 2001;41:51-56).

Tuberculous Pleural Effusion

Measurement of the concentration of adenosine deaminase levels in pleural effusions has been touted as a means of diagnosis of a tuberculous etiology. In this study of 106 pleural fluid samples with a predominance of lymphocytes, but of nontuberculous etiology, only 3 (2.8%) false-positive results were found (Lee YGC, et al. *Chest*. 2001;120:356-361).

Cavitary Bronchiolitis Obliterans Mimicking Tuberculosis ("TB or not TB")

Two cases are described (Heller I, et al. *Chest*. 2001; 120:674-678).

Sea Urchin Granuloma and *Mycobacterium marinum*

Sea urchin granuloma is a chronic granulomatous reaction, histologically resembling sarcoid, occurring after injury by sea urchin spines, generally thought to be an allergic-type foreign body reaction. A group of Spanish investigators detected *M marinum* DNA in biopsy specimens from 7 of 35 (20%) patients. (Something learned along the way: the word urchin is derived from "ekhinos," the Greek word for hedgehog). (De La Torre C, et al. *Br J Dermatol*. 2001;145:114-116).

Antibiotic Therapy and Antibiotic Resistance

Antibiotic Therapy—Some People Just Can't Make Up Their Minds

In this study, 427 antibiotic regimens were administered to 119 patients with suspected serious infections during the first 72 hours after admission to a university affiliated municipal teaching hospital. Multiple antibiotic changes were made without apparent clinical or microbiological indications. By 72 hours, each patient had received a mean of 3.1 ± 1.3 different antibiotics; 40 patients had received from 4 to 7 different antibiotics (Lawrence C, et al. *Am J Med Sci*. 2001;322:61-67).

Macrolide Therapy and Resistance in Oral Flora

Azithromycin therapy in children with respiratory tract infections was associated with a significantly greater number (85%) harboring resistant oral aerobic bacterial flora persisting 6 weeks after therapy than was seen with erythromycin, clarithromycin, roxithromycin, or josamycin (Kastner U, Guggenbichler JP. *Infection*. 2001;29:251-256).

Fluoroquinolone Pharmacodynamics and *S pneumoniae*

Serum concentration-time profiles were simulated for qd administration of levofloxacin 500 mg & 750 mg, gatifloxacin 500 mg, moxifloxacin 500 mg, and femifloxacin 320 mg. Using the free (nonprotein bound) serum concentrations and the MICs of 307 clinical isolates of *S pneumoniae*, the proportion of pneumococcal isolates for which an AUIC (AUC_{24}/MIC) > 30-50 was achieved was significantly inferior with levofloxacin 500 mg daily than with the other regimes (Kays MB, Denys GS. *Diagn Microbiol Infect Dis*. 2001;40:193-198).

Selection of Oxacillin Resistant *S aureus* by Fluoroquinolones

In vitro studies found that fluoroquinolones, especially ciprofloxacin (moxifloxacin, gatifloxacin, and lev-

ofloxacin were also studied) select out *mec(A)*-positive clones of *S aureus* from among a heteroresistant population (Venezia RA, et al. *J Antimicrob Chemother*. 2001; 48:375-381).

Flushing Fluoroquinolones

A Swiss study of urban wastewater effluents collected at treatment plants detected ciprofloxacin and norfloxacin in concentrations of 249 ng/L to 405 ng/mL in primary wastewater effluent and 45 to 102 ng/L in tertiary effluents (Golet EM, et al. *Analytical Chem*. 2001; 73:3632-3638).

Fluoroquinolones and Tendon Rupture

Although a population study found a 28% increase in nontraumatic tendon ruptures between 1991 and 1996, only 0.5% to 7% of the increase could be attributed to increased fluoroquinolone use (van der linden PD, et al. *Pharm World Sci*. 2001;23:89-92).

Colistin + Rifampin for Resistant Acinetobacter

Of 39 isolates of multidrug resistant *Acinetobacter baumanii*, 100% were inhibited by colistin (polymyxin E), synergy with rifampin was observed with some isolates (Giamarellos-Bourboulis EJ, et al. *Diagn Microbiol Infect Dis*. 2001;40:117-120).

The Immunocompromised Host (NonAIDS)

IL-2 and Common Variable Immunodeficiency

While common variable immunodeficiency is characterized by the presence of hypogammaglobulinemia and the lack of antibody response after antigen exposure, a variety of T cell defects, including reduced IL-2 production, have also been described in patients with this disorder. This paper reports that the administration of pegylated IL-2 for 12-18 months was associated with improved T cell proliferative responses and in vivo antibody production in response to a neoantigen (Cunningham-Rundles C, et al. *Clin Immunol.* 2001;100:181-190).

PCR Quantitation of EBV Genome

Semiquantitative PCR analysis found that EBV genome copy numbers per 10^5 PBMC ranged from 1000 to 40,000 in patients with infectious mononucleosis while it was < 100 in latently infected individuals and in asymptomatic renal transplant patients. Two bone marrow transplant patients had plasma levels of 16,000 and 50,000/mL as well as levels of 100,000 and 6.5 million copies 10^5 PBMC (Meerbach A, et al. *J Med Virol*. 2001;65:348-357).

BK and BMT

BK viruria is quantitatively related to the occurrence of hemorrhagic cystitis after bone marrow transplantation (Leung AYH, et al. *Blood*. 2001;98:1971-1978).

HIV/AIDS

Occult Antiretroviral Resistance in Treatment-Naïve Patients

While neither direct sequencing of HIV DNA from peripheral blood mononuclear cells (PBMC) nor HIV RNA from plasma isolates demonstrated the presence of drug resistance-associated mutations in the reverse transcriptase or protease genes, such mutations were detected by analysis of cloned HIV RNA and PBMC DNA at low frequencies in 4 of 5 treatment-naïve patients (Paolucci S, et al. *J Med Virol*. 2001;65:207-217).

RT, Protease Mutations, and Viral Replicative Fitness

Analysis of drug-resistant virus from 11 patients found that reduced replicative fitness was associated with the RT mutation M184I/V (11.6% decrease) and the PR mutations D30N (12.4% decrease) and M46I/L (21% decrease) (Devereux HL, et al. *J Med Virol.* 2001; 65:218-224).

HIV Protease Inhibitors— Direct Immunological Effects

Some recipients of HIV protease inhibitor therapy have persisting immunologic benefit despite virological failure. One reason for this discordant response may be a loss of viral fitness in the face of continued exposure protease inhibitor (PI) therapy (*see above*). Another proposed mechanism is a direct immunologic effect of PIs. Previous studies have reported that various PIs inhibit lymphocyte apoptosis, thus slowing the loss of lymphocytes. One group has now demonstrated that indinavir arrests lymphocyte cell cycling in G0/G1 phase in cells obtained from healthy volunteers as well as HIV-infected children. Such an effect may inhibit immune activation, thus preventing a state associated with disease progression (Chavan S, et al. *Blood*. 2001;98:383-389).

PI Concentration in Semen

Analysis of 45 paired serum and semen samples from 23 patients receiving antiretroviral therapy found that, while seminal plasma concentration of ritonavir and saquinavir were below their respective IC95s against wild type HIV-1, that of indinavir exceeded its IC95 (Taylor S,

et al. *J Antimicrob Chemother*. 2001;48:351-354.)

HIV Protease Inhibitors Unstick *Candida*

HIV protease inhibitors, whose retroviral target is an aspartyl protease, have been reported to inhibit production of secreted aspartic proteases (saps), which are important virulence factors of *Candida albicans*, at least in part as a result of the role of saps in allowing adhesion to human epithelial cells. This study found that ritonavir, indinavir, and saquinavir inhibit adhesion of *C albicans* to epithelial cells (Bektic J, et al. *FEMS Immunol Med Microbiol.* 2001;31:65-71).

Indinavir and Bilirubin Conjugation

Indinavir causes unconjugated hyperbilirubinemia by competitively inhibiting bilirubin UDP glucuronosyltransferase activity, thus inhibiting bilirubin conjugation. The increase in bilirubin is greater in subjects with Gilbert's syndrome—in which hepatic levels of this enzyme are already reduced (Zucker SD, et al. *Proc Natl Acad Sci USA*. 2001;98:12671-12676).

Gynecomastia and HAART

The incidence of gynecomastia in HIV-infected patients receiving HAART was 0.8 per 100 patient years; the prevalence among those who had received therapy from 2 years or more was 2.8%. Four patients with this condition were successfully treated with topical dihydrotestosterone gel (Piroth L, et al. *Scand J Infect Dis.* 2001;33:559-560; Beneniste O, et al. *Clin Infect Dis.* 2001;33:891-893).

Indinavir and Nephrolithiasis

Among 781 indinavir recipients with a median exposure to indinavir of 53 weeks, 7.3% developed renal complications; this represented an incidence of 6.7 per 100 person-years of indinavir exposure. Multivariate analysis found that treatment beyond 74 weeks was protective, while concomitant treatment with acyclovir increased the risk (Herman JS, et al. *J Antimicrob Chemother*. 2001;48:355-360).

Adefovir Nephrotoxicity and Renal Tubular Mitochondria

Adefovir, a nucleotide analog with activity against both HBV and HIV, was associated with significant nephrotoxicity in HIV infected patients and is being superseded by a similar drug, tenofovir. A study of renal biopsy material from a single patient suggests that the mechanism was reduction of mitochondrial DNA as a consequence of inhibition of mtDNA replication. The study is confounded by the fact that the patient was also receiving other antiretrovirals including stavudine and hydroxyurea (Tanji N, et al. *Human Pathol.* 2001;32:734-740).

DHEA in HIV Infection

In a randomized, double-blind, placebo-controlled trial involving 32 HIV-infected patients (mean CD4 count = 33 cells/mm^3), administration of dehydroepiandrosterone sulphate (DHEA-S) was associated with a significant improvement in the Mental Health Distress dimension of the Medical Outcomes Study HIV Health Survey (MOS-HIV), but no change in CD4 count (Debuire B, et al. *Clin Endocrinol*. 2001;55:325-330).

Reversible ALS-Like Disorder in HIV Infection

Six HIV-infected patients (mean CD4 count = 86/mm^3) developed distal motor weakness mimicking monomelic amyotrophy that rapidly progressed regionally or that developed a symmetric distribution involving more than one region. EMG was consistent with motor neuron disease. The neurological disease improved coincident with administration of antiretroviral therapy (Moulignier A, et al. *Neurology*. 2001;57:995-1001).

Geographic and Travel Medicine

DEET in Pregnancy

The safety of DEET use in the second and third trimesters of pregnancy was assessed in the context of a randomized trial involving 897 women. A median total dose of 214 g of DEET was applied with no evidence of adverse effects. Although DEET was detected in 8% of cord blood samples from a random subgroup, no adverse effects on the infant were found at 1 year follow-up (McGready R, et al. *Am J Trop Med Hyg*. 2001;65:285-289).

Chloroquine-Resistant *Plasmodium vivax* in Colombia

P vivax resistant to chloroquine are an emerging cause of infection in Asia and Oceania, with only rare case reports from other regions. This study reports that 3 of 27 (11%) patients with *P vivax* infection acquired in Colombia failed to respond to therapy with chloroquine (1500 mg base over 3 days). All responded to a second course of chloroquine given together with primaquine (Soto J, et al. *Am J Trop Med Hyg*. 2001;65:90-93).

QBC and Borreliosis

Relapsing fever, both the louse- and tick-borne varieties, are diagnosed by the relatively insensitive method of visual examination of Giemsa-stained blood smears. This study found that the use of fluorescence

microscopy and acridine orange-coated quantitative buffy coat (QBC) tubes was an effective and sensitive diagnostic techniques. In fact, in vitro studies using *B burgdorferi* as a model found that the method could detect spirochetes at a concentration as low as 10 organisms/mm^3 (Cobayae FC, et al. *Am J Trop Med Hyg*. 2001;65:164-165).

Strongyloidiasis on the Spanish Mediterranean Coast

One hundred fifty-two patients with strongyloidiasis were admitted to a single hospital in Valencia over an 8-year period. Sanchez and colleagues point out that this infestation is endemic on the Spanish Mediterranean coast, an area frequently visited by tourists (Sanchez PR, et al. *QJM*. 2001;94:357-363).

Liposomal Amphotericin B for Kala Azar

Nintey-one patients with Indian visceral leishmaniasis in India were randomized to receive 5 mg/kg liposomal amphotericin B to be given either as a single dose or as once daily infusions of 1 mg/kg with cure rates of, respectively, 92% and 93% (Sundar S, et al. *BMJ*. 2001;323:419-422).

Topical Cidofovir for Recalcitrant Orf

A renal transplant recipient receiving immunosuppressive therapy developed orf after contact with a freshly slaughtered sheep. The lesion progressed to massive size, failing to resolve despite a number of interventions. Complete and apparently permanent resolution of the lesion occurred in response to topical treatment with cidofovir (Geerinck K, et al. *J Med Virol*. 2001;64:543-549).

Miscellaneous

Measles Virus in Asymptomatic Individuals

Measles virus genome was detected by PCR in asymptomatic infants previously exposed to wild measles virus and vaccine strain genome was detected in PBMCs of 10 (71.4%) of 14 infants sampled within 2 months of vaccination. Wild type measles genome was detected in PBMC of 6 (46.2%) of 13 individuals who had been naturally infected in the distant past. Measles genome was not detected in nasopharyngeal secretions (Eishubinger AM, et al. *J Med Virol*. 2001;65:395-401).

Immunologic Correlates of Protection from Anthrax

In rabbits who received Anthrax Vaccine Adsorbed, subsequent antibody levels to "Protective Antigen" at both 6 and 10 weeks were highly significant predictors of survival after an aerosol challenge with a lethal dose of *Bacillus anthracis* spores (Pitt ML, et al. *Vaccine*. 2001; 19:4768-4773).

Reduced Mortality in Childhood Meningococcal Disease

The overall mortality of 123 children admitted to the pediatric ICU at the Royal Liverpool Childrens Hospital between 1995 and 1998 was only 8.9% which may be compared with a predicted mortality of 24.9% and also lower than previously published studies. Similarly, in a review of 331 children seen at St. Mary's Hospital in Norfolk, UK, from 1992-1997, the case fatality rate from fell from 23% to 2% over that time (Thorburn K, et al. *Arch Dis Child*. 2001;85:382-385; Booy R, et al. *Arch Dis Child*. 2001;85:386-390).

Doxycycline Therapy in Rheumatoid Arthritis?

Patients with erosive RA were randomized to receive IV doxycycline, po azithromycin, or placebo; no benefit was observed (St. Clair EW, et al. *Arthritis Rheum*. 2001; 44:1043-1047). ■