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A Spoonful of Sugar Helps the Negative Blood Culture Rate Down

ABSTRACT & COMMENTARY

Synopsis: *The number of episodes of bacteraemia detected was increased by one-third simply by inoculating blood into blood culture medium supplemented with 5% sucrose, creating a hypertonic environment with which cell-wall deficient bacteria could grow.*

Source: Woo PC, et al. *Lancet.* 2001;357:675-679.

About 4 of 5 episodes of neutropenic fevers are thought to be caused by infections, but an isolate is detected in fewer than half of these cases. One explanation might be that some of the bacteria involved might possess a deficient cell wall because of exposure to antibiotics—particularly the beta-lactam antibiotics. Woo and associates set out to investigate the role of cell-wall-deficient bacteria, if any, in causing infection in recipients of an haematopoietic stem cell transplant (HSCT). Recipients' blood cultures were obtained when patients developed fever and were inoculated into an aerobic bottle with resin, an anaerobic bottle, and a hypertonic bottle containing 5% sucrose to isolate cell-wall deficient bacteria. When growth was detected in this bottle, a small sample of the broth was subcultured onto solid media, and the isolate was identified by standard biochemical methods. While 55 episodes of bacteraemia due to normal bacteria were detected in 15 (17%) of 86 bone marrow transplant (BMT) recipients enrolled into the study, a further 20 episodes due to cell-wall deficient bacteria were detected in 12 (14%) patients. Antibiotic treatment was successful in 19 (95%) of these episodes. A beta-lactam antibiotic, a glycopeptide, or both had been administered in 16 cases within 10 days before blood cultures had been taken. The majority of isolates detected during neutropenia were Gram-positive bacteria—half of which were cell-wall deficient and only detected in the sucrose-enriched media (*see Table*).

These results indicate that bacteraemia due to cell-wall-deficient bacteria causes a significant proportion of so-called culture-negative febrile episodes in HSCT recipients.

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COMMENT BY J. PETER DONNELLY, PhD

Cell-wall deficient bacteria or L-forms are known to be induced by both in vitro and in vivo antibiotics that act specifically on cell-wall synthesis. These include the beta-lactam antibiotics, penicillins, cephalosporins, and carbapenems, as well as the glycopeptides, vancomycin and teicoplanin. That the majority of cell-wall deficient species were Gram-positive bacteria is also not a surprise since their cell wall is exposed to antibiotic action consisting as it does of a thick peptidoglycan layer. In contrast, the cell wall of the Gram-negative bacilli such as *Escherichia coli*, *Pseudomonas aeruginosa* and nonfermenting bacilli is enveloped by an outer membrane consisting of lipopolysaccharide (endotoxin), which acts as both a barrier and an osmotic stabilizer making the formation of cell-wall deficient forms less likely. Neither is prior exposure to cell-wall active antibiotics an unusual finding. However, the results of this study pose a few intriguing questions.

Table

Table of Isolates

Gram reaction	Isolate	Cell-wall deficient	Normal bacteria
Gram-positive		**11**	**11**
	Cocci	3	9
	Staphylococcus species	1	4
	Streptococcus species	1	3
	Micrococcus species	1	0
	Enterococcus species	0	2
	Bacilli	8	2
	Bacillus species	7	2
	Lactobacillus species	1	0
Gram-negative bacilli		**2**	**6**
	Enterobacteriaceae	0	2
	Non-fermentors	2	4
Total		**13**	**17**

First, if the bacteraemia rate can be almost doubled by simply including an extra bottle of broth with some sugar, why isn't everyone doing it? In fact, this is an old chestnut that has been roasted before. Twenty-five years ago, Washington and colleagues already investigated the value of using hypertonic medium for detecting bacteraemia and concluded "The addition of sucrose . . . did not significantly increase the rate of positivity or the time interval to detection of positivity of any group of bacteria."[1] Later, others came to a different conclusion reporting that hypertonic medium offers no advantage in the recovery of anaerobes but is of value in the recovery of facultative anaerobes (ie, the bacteria in question).[2] Later, another group demonstrated that the growth of both *Staphylococcus aureus* and *Enterobacteriaceae* occurred earlier or solely in hypertonic broth cultures collected during treatment of patients with beta-lactam antibiotics.[3] This was confirmed by another study in which the recovery not only of Gram-positive and Gram-negative facultatively anaerobic bacteria was improved using hypertonic broth but also that of yeasts.[4] Since then, the field has lain fallow.

Second, will it really make a difference, besides adding to the costs, if all haematology departments were to adopt a hypertonic medium? Frankly, I doubt it. Most, like Woo et al, already use broad-spectrum antibiotics, which, though not ideal for treating Gram-positive bacterial infections, do deal remarkably effectively with the vast majority of neutropenic fevers resulting in few deaths due to bacteria even without the addition of a glycopeptide—a fact that Woo et al readily admit.

Last, are these cell-wall deficient bacteria any other than an interesting curiosity? Probably not. Detecting them can be interpreted as either a sign that the antibi-

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otic regimen is failing or as an indication that although not optimum, the drugs are affecting the bacteria adversely in damaging their cell wall, rendering such cells osmostically unstable. Only if they were to cause excess mortality or lead to relapse need one draw any great significance from recovering them from blood cultures since the organisms involved were almost exclusively the indolent bacterial species that are least associated with complications. The only exception in the study reported was the case with bacteraemia due to the enteric bacillus *Serratia marcescens*, which were recovered only in a hypertonic medium and, despite being susceptible to the antibiotic regimen used for treatment, nonetheless went on to disseminate, fulminate, and result in death. This case defied explanation microbiologically and unfortunately probably would have proven fatal whichever medium was used to detect it. ❖

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Daptomycin Tested in an In Vitro Model of Endocarditis Due to MRSA, GISA, and VREF

ABSTRACT & COMMENTARY

Synopsis: *Daptomycin given at high doses has good bactericidal activity against glycopeptide-intermediate susceptible Staphylococcus aureus and vancomycin-resistant Enterococcus faecium in an in vitro model of endocarditis.*

Source: Akins RL, Rybak MJ. *Antimicrob Agents Chemother*. 2001;45:454-459.

The bactericidal activity of 2 daptomycin dosing regimens against strains of glycopeptide-intermediate susceptible *Staphylococcus aureus* (GISA), vancomycin-resistant *Enterococcus faecium* (VREF), and methicillin-resistant *Staphylococcus aureus* (MRSA) was evaluated in an experimental in vitro model of endocarditis.

Simulated endocarditis vegetations were prepared by mixing a suspension of the microorganism to be studied with human donor cryoprecipitate and platelet suspension, to which bovine thrombin in the presence of a monofilament was added. This is a process that results in the formation of bacteria embedded in platelet-fibrin matrix, the typical components of in vivo endocardial vegetations.

The simulated vegetations were subsequently placed in a 250-mL container containing nutrient broth. The antibiotics were added to the broth at regular intervals, and antibiotic-containing broth was removed from the container with a peristaltic pump and replaced with antibiotic-free broth at a rate designed to simulate the in vivo peak and trough concentrations, as well as the half-lives of the antibiotics at specific dosages. Experiments were performed by simulating endocarditis with GISA, VREF, and MRSA, and quantitative cultures of the simulated vegetations were performed at regular intervals for a period of 72 hours, simulating therapy with no antibiotic (growth control), daptomycin 6 mg/kg/d, daptomycin 10 mg/kg/d, and vancomycin 1 g every 12 hours.

The results of serial quantitative cultures of the simulated vegetations showed that daptomycin 10 mg/kg/d resulted in an undetectable bacterial content within 72 hours in all 3 sets of experiments (GISA, VREF, and MRSA). Undetectability was achieved most rapidly (within 8 hours) and most consistently (throughout the 72-hour period) in the GISA experiment. Daptomycin 6 mg/kg/d did not achieve undetectability in any of the 3 experiments; however, it resulted in significantly more bacterial killing than vancomycin in all experiments, including the MRSA (vancomycin-susceptible) experiment.

The above results indicate that daptomycin exhibits a significant dose-dependent killing of MRSA, GISA, and VREF in an experimental in vitro model of endocarditis.

COMMENT BY JOSEPH F. JOHN, MD, & IMAD H. DURRA, MD

The management and containment of antibiotic-resistant bacteria has become a major concern of health care professionals almost since the introduction of antibiotics several decades ago.[1] Historically, most of the efforts were made to contain the emergence of resistant Gram-negative organisms, and little efforts were made for the development of newer antimicrobial agents for use against resistant Gram-positive organisms. Although the emergence of MRSA had been at least partially controlled with the escalating use of vancomycin, the emergence of VREF[2] and GISA[3] left the

medical community facing potentially dreadful organisms with no adequate antibiotics available in their pharmacologic armamentarium.

There are currently 2 antibiotics available for the treatment of infection due to VREF or GISA: linezolid, an oxazolidinone, and quinupristin/dalfopristin (Q/D), a combination of 2 different streptogramins. There are no publications in the medical literature concerning the usefulness of linezolid in the treatment of endovascular infections. Most of the evidence for the use of Q/D in the treatment of endocarditis comes from isolated case reports[4] or from experimental endocarditis in animals. Animal model experiments showed that Q/D is adequately bactericidal against MRSA-infected vegetations and demonstrated an even penetration into the tissue of the vegetations.[5]

Daptomycin (Cubist Pharmaceuticals) is an investigational lipopeptide antibiotic in phase III trials. Trials with earlier lipopeptide agents were interrupted because of their side effects, but the interest in this class of antibiotics is now being renewed. Daptomycin was shown to be adequately effective in experimental VREF endocarditis, but only at extremely high dosages (12 mg/kg q 8 hours), especially when given in combination with an aminoglycoside.[6]

In the current article, Akins and Rybak showed that daptomycin may eventually prove to be an adequate antibiotic choice for GISA and VREF endocarditis at an even lower dose, 10 mg/kg/d. Several issues, however, limit the ability to draw conclusions from their findings. One issue is the dosage of daptomycin suggested: 10 mg/kg/d has never been a dose used in any of the human trials of the antibiotic, and the currently used dose of 6 mg/kg/d has already been associated with a significant amount of side effects, especially myositis, though to a lesser extent than earlier lipopeptides.

The second major issue is finding how close the in vitro endocarditis model is to the real human endocarditis, both in terms of the pathophysiology of the vegetation and the pharmacodynamics of the body, which rarely behaves like a test tube.

Although more experiments need to be done on the animal model of endocarditis using the higher dosing regimen of daptomycin before drawing any conclusions, it is probably encouraging to have a long-awaited and definitively bactericidal antibiotic that can be used for GISA and VREF endocarditis. We will have to wait to see if the use of daptomycin may be mitigated by unwelcome side effects, although reports from early clinical trials suggest that serious side effects are rare. (*Dr. Durra is an Infectious Diseases Fellow at Robert Wood Johnson Medical School, New Brunswick, NJ.*) ❖

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MIC, MBC, and Now—MPC!

ABSTRACT & COMMENTARY

Synopsis: *The mutant prevention concentration may be a useful predictor of the relative potential of antibiotics to select resistant mutants.*

Source: Blondeau JM, et al. *Antimicrob Agents Chemother.* 2001;45:433-438.

Blondeau and colleagues determined the mutant prevention concentration (MPC) of 4 fluoroquinolones and 1 naphthyridone against clinical isolates of *Streptococcus pneumoniae*. Serial concentrations of antibiotic in agar were seeded with 10^{10} or more of CFU. The MPC was recorded as the lowest antibiotic concentration that allowed no growth after incubation for 24 hours. After omitting data from 6 isolates deliberately included because of their fluoroquinolone resistance, the MIC90 and MPC90 (the concentration below which 90% of isolates had no growth with an inoculum of 10^{10} CFU) were determined. The MIC90 was 0.25 mg/mL for moxifloxacin and trovafloxacin, 0.5 mg/mL for gatifloxacin and grepafloxacin, and 1.0 mg/mL for levofloxacin. The MPC90 for these same strains was 2.0 mg/mL for moxifloxacin, 4.0 mg/mL for trovafloxacin and gatifloxacin, and 8.0 mg/mL for grepafloxacin and levofloxacin. The ratios of MPC90 to MIC90 was 8 to 16.

Thus, based on their potential for restricting the selection of mutants, as reflected in the MPC, the relative potencies of the drugs studied was moxifloxacin > trovafloxacin > gatifloxacin > grepafloxacin > levofloxacin. The MIC90 ranking was moxifloxacin = trovafloxacin > gatifloxacin > grepafloxacin > levofloxacin.

COMMENT BY STAN DERESINSKI, MD, FACP

After the recommended 400-mg dose of moxifloxacin the mean peak antibiotic concentration reached is approximately 4.5 mg/mL; the peak after a 400-mg dose of gatifloxacin is slightly lower. The mean peak serum concentration achieved after the recommended 500-mg dose of levofloxacin is approximately 5.7 mg/mL. Both moxifloxacin and gatifloxacin maintain serum concentrations above the *S pneumoniae* MIC90 for all or most of the 24-hour dosing interval, while levofloxacin may not. In addition, moxifloxacin maintains serum concentrations above the MPC90 for all or most of the dosing interval, while levofloxacin does not. Gatifloxacin has an intermediate level of activity.

An argument has been made that the use of less-active fluoroquinolones for treatment of respiratory tract infection may accelerate the inevitable march of resistance in *S pneumoniae* to these agents. While only a single *parC* topoisomerase mutation is necessary for the development of levofloxacin resistance, 2 mutations (*parC* and *gyrA*) are necessary for the development of clinically significant resistance to the newer fluoroquinolones. The de novo selection of double mutants from populations of wild-type bacteria occurs at an extremely low frequency—approximately 10^{14}—while a single-step mutation occurs at frequencies as high as 10^{7}. Thus, the widespread use of levofloxacin may lead to a large dispersed population of *S pneumoniae* that may require only a further single mutation to achieve resistance to moxifloxacin or gatifloxacin.

A pharmacodynamic argument reaching the same conclusion has also been made. It has been reported that, for fluoroquinolones, an AUIC (the ratio of the 24-hour area under the curve to the MIC) greater than 100-120 is associated with both improved outcome and reduced risk of selection of resistant mutants. During treatment of pneumococcal infection with a fluoroquinolone, the AUIC is most reliably above this threshold when the newer agents are used.

However, it must be recognized that the human data supporting these conclusions remain scanty. Furthermore, while the concept of the MPC is an attractive one, its validity and relevance remain to be determined. It is possible that it is too simplistic. These studies do not, for instance, take into account antibiotic protein binding, antibiotic tissue kinetics, or host response. ❖

Suggested Reading

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2. Turnidge J. *Drugs.* 1999;58(Suppl 2):29-36.

G-CSF in the Treatment of Diabetic Foot Ulcers

ABSTRACT & COMMENTARY

Synopsis: *In a randomized, controlled trial, patients with diabetic foot ulcers treated with a 21-day course of G-CSF (in addition to standard treatment) along with antibiotic therapy had a lower rate of bone amputation at 9 weeks than patients treated with antibiotics alone.*

Source: de Lalla F, et al. *Antimicrob Agents Chemother.* 2001;45:1094-1098.

Patients with severe diabetic foot infections were randomized to receive either standard treatment (local care and antibiotics) or standard treatment plus recombinant granulocyte-colony stimulating factor (G-CSF) at a dose of 263 µg subcutaneously each day for 21 days. Empiric antibiotic therapy consisted of ciprofloxacin and clindamycin; therapy was adjusted based on the results of deep ulcer cultures. Patients with severe limb ischemia (ankle/brachial blood pressure index < 0.5) were excluded. Twenty patients were enrolled in each group. The 2 groups were similar in terms of age, ulcer severity, laboratory parameters, and microbiology of lesions. Based on culture results, initial antibiotic therapy was adjusted in 60% of patients in each group. All patients had osteomyelitis as documented by bone exposure or probe. Ulcer assessment was carried out by a plastic surgeon who was blinded as to study group assignment. de Lalla and associates defined clinical failure as absence of clinical improvement, or as amputation (consisting of any excision of bone segment) performed after 15 days of appropriate antibiotic therapy.

At 9 weeks, 7 (35%) patients in each group were cured. Five patients receiving G-CSF demonstrated clinical failure compared with 9 control patients (25% vs 45%; $P = .19$). Amputation as a cause of failure occurred in 3 patients receiving G-CSF compared with 9 control patients (15% vs 45%; $P = .038$). No patients had adverse reactions to G-CSF.

COMMENT BY ROBERT MUDER, MD

Infection is a major contributor to limb loss in diabetic patients. In addition to vascular disease and peripheral neuropathy, diabetics demonstrate a number of defects in polymorphonuclear leukocyte function that impair the ability to contain and eradicate microorganisms. These include abnormalities in migration, chemotaxis, phagocytosis, and intracellular killing of bacteria.

G-CSF is an endogenous glycoprotein that stimulates proliferation and differentiation of granulocytic precursors into mature neutrophils. In addition, G-CSF enhances the phagocytic and bactericidal activity of both normal and abnormal neutrophils. G-CSF is often used in patients rendered neutropenic by cancer chemotherapy or marrow transplantation in order to decrease the duration of neutropenia. Studies in nonneutropenic animals have shown improved outcome after admistration of G-CSF in experimental infection. A previous randomized, placebo-controlled trial found that a 7-day course of G-CSF therapy was associated with earlier eradication of pathogens, quicker resolution of inflammation, and a shorter duration of antibiotic therapy than standard therapy.[1] Neutrophil superoxide production was significantly increased in G-CSF-treated patients, confirming its effect on neutrophil function in diabetic patients.

G-CSF appears to be a promising adjunctive agent in the treatment of diabetic foot infections. The clinical trials reported thus far have several limitations—the most notable being small numbers of patients. In the study of de Lalla et al, the decision to perform amputation was made by orthopedic surgeons who were not members of the study team and not blinded as to treatment assignment. Thus, it is not clear that uniform criteria for amputation were followed in all patients.

However, these preliminary studies are encouraging and should provide the impetus for larger, randomized trials of G-CSF in the treatment of diabetic foot infections. ❖

Reference

1. Gough A, et al. *Lancet*. 1997;350:855-859.

Does Reducing Antibiotic Use for Otitis Media Increase the Incidence of Mastoiditis?

ABSTRACT & COMMENTARY

Synopsis: *Discouraging the use of antibiotics may have a negative side, but the benefits outweigh it (please also see special supplement enclosed with this issue).*

Source: Van Zuijlen DA, et al. *Pediatr Infect Dis J*. 2001;20: 140-144.

In the 1980s, the dutch college of general Practioners published recommendations that children seen and diagnosed with acute otitis media (AOM) should be watched for a few days rather than treated empirically with antibiotics. The exceptions were children younger than 6 months of age, high-risk patients (recurrent otitis media, craniofacial malformations, immunodeficiencies), children 1-2 years of age with continued symptoms after 24 hours, and children up to 14 years with earache or fever for more than 3 days or otorrhea for more than 14 days. There was a remarkable reduction in antibiotic (usually amoxicillin) prescribing for AOM to 31% of cases, according to a report in 1990. This is considerably lower than any other country in Europe or North America, where empiric antibiotic use has been nearly universal.

Van Zuijlen and colleagues investigated the possible effect of this reduced antibiotic use by gathering information on the frequency of hospital discharges of children with a diagnosis of acute mastoiditis. They collected information from Norway, Denmark, the United Kingdom, Canada, the United States, and New York City. They also found population figures to derive an estimate of the incidence of acute mastoiditis of about 3-4 per 100,000 children in The Netherlands, Denmark, and Norway, but only 1 or 2 per 100,000 children in the other countries. They estimated antibiotic use for AOM was nearly 100% for other countries with the exceptions of Denmark, Norway, and The Netherlands, where it was estimated to be 80%, 70%, and 30%, respectively.

There was an inverse correlation between antibiotic use for AOM and acute mastoiditis, with the exception of Norway and Denmark where the mastoiditis frequency was high despite the high use of antimicrobials.

COMMENT BY ALAN D. TICE, MD, FACP

The compliance of the physicians with antimicrobial use guidelines in The Netherlands is remarkable, if true. Not only was physician behavior changed but dramatically so. What has happened since the survey reported in 1990 is not known. It would also be interesting to know the changes that have occurred in AOM prescribing there and in the other countries since then. The success of the campaigns to reduce antibiotic prescribing have had a limited effect in the United States.

The reduction in the use of antibiotics appears to carry some risk. It does appear that the incidence of acute mastoiditis is greater with reduced antibiotic use for AOM. The question then is what to do about it. It is not really feasible to do clinical trials to get better data on the risks and benefits of treating AOM because of the huge numbers that would be needed and the lack of available funding.

This investigation has numerous faults, and the data are getting old. Some of the shortcomings include vary-

ing rates of hospitalization for acute mastoiditis among countries, diagnosis coding variations, documentation of actual use of antibiotics for AOM, and consistent population figures. Antimicrobial resistance has also increased dramatically and the vaccine for *Hemophilus influenzae* has been introduced. The lack of correlation between antibiotic use and mastoiditis in Denmark and Norway is not consistent with the findings in other countries.

The case of an inverse correlation between the use of antibiotics for AOM and acute mastoiditis is not clearly proven, but it does make sense. Any approach to antimicrobial therapy has not only benefits, but risks as well. Mastoiditis would seem much less likely in patients with otitis media who are receiving an effective antibiotic.

This type of epidemiologic study may become more useful in the future as information systems about patient care develop and data are collected in a standardized format. This research may give us better answers to some of the age-old questions. On the other hand, the information on means, medians, and statistical analyses will never replace the need for physician evaluation of the next patient who presents in the office with otitis media. Guidelines and generalizations may not apply (as every individual is unique), and the variables to consider are limitless.

The possibility of reducing the risk of acute mastoiditis by 2 cases per 100,000 children through doubling or tripling the amount of antibiotics used for AOM in The Netherlands must also be weighed. From Van Zuijlen et al's figures, 2500 Dutch children with AOM would have to be treated with antibiotics to prevent 1 case of acute mastoiditis. They estimate it would take an additional 7800 antibiotic prescriptions per year to accomplish this. Aside from the added cost, this would likely cause amoxicillin-related side effects in 1600 patients and stimulate antibiotic resistance as well.

It seems each decision on antibiotic use has its pros and cons. It will be helpful to have better data and analyses to understand the effect of intervention. ❖

Attention Subscribers. . .

A special supplement to Infectious Disease Alert titled "Antibiotics Anonymous Redux" is included with this edition, as a bonus to our subscribers. This was originally published in the July 1, 2000, issue of Infectious Disease Alert, but because of the overwhelming response, we decided to publish the article as a supplement. It takes a tongue-in-cheek look at a problem facing many physicians: over-prescription of antibiotics. Here is an editorial note from Stan Deresinski, MD:

The problem of antibiotic resistance continues to worsen. An important contribution to this problem is the inappropriate prescription of antibiotics by physicians. For example, excess prescription of antibiotics for respiratory tract infections, particularly in children, has been identified as an important factor in the emergence of penicillin-resistant Streptococcus pneumoniae. Indeed, it has been suggested that some physicians have lost control over their antibiotic prescribing—that they have become, in effect, antibiotic dependent. I have, as a consequence, devised a questionnaire for the diagnosis of this dreaded addiction afflicting practicing physicians. If the answer to one or more of these questions is yes, you have a problem!. . .❖

CME Questions

29. How many children with acute otitis media would have to be treated with antibiotics to avoid one case of acute mastoiditis?
a. 50
b. 100
c. 500
d. 2500

30. The incidence of acute mastoidits in children in North America is approximately:
a. 1.5 per 100,000.
b. 2 per 100,000.
c. 3 per 100,000.
d. 4 per 100,000.
e. 5 per 100,000.

31. Which antibiotic does *not* lead to cell-wall deficient bacteria?
a. Ceftazidime
b. Gentamicin
c. Imipenem
d. Penicillin
e. Piperacillin

32. Which of the following is correct?
a. MPC stands for minimal prohibitory concentration.
b. The MPC of an antibiotic against an organism is ordinarily greater than its MIC.
c. Daptomycin is a member of the oxazolidinone class of antibiotics.
d. G-CSF inhibits phagocytic activity of neutrophils.

In Future Issues:

Herbal Medications—Not Harmless Anymore

UPDATES

By Carol A. Kemper, MD, FACP

Cases of Lyme Disease Remain Elevated

Sources: *MMWR Morb Mortal Wkly Rep.* 2001;50:181-185; Parola P, Raoult D. *Clin Infect Dis.* 2001;32:897-928.

As suburban sprawl pushes communities deeper into wooded areas, cases of Lyme disease in the United States have risen. Overall, 16,801 and 16,273 cases were reported to the CDC in 1998 and 1999, respectively, up 27-30% from 1997 and more than double the figures for 1990. Nine states accounted for 90% of cases, including (in descending order) Connecticut, Rhode Island, New York, Pennsylvania, Delaware, New Jersey, Maryland, Massachusetts, and Wisconsin. Disease incidence exceeded 100 cases per 100,000 population in 24 counties located in these states.

The highest disease incidence (950.7) was reported in Nantucket County, Mass. Only 139 cases were reported from California, one of which I know to have been imported from Wisconsin (Kemper CA. *Infectious Disease Alert* 2001;20:77-79). Five states reported no cases (Alaska, Georgia, Hawaii, Montana, and South Dakota). More than half of the cases were reported in June and July.

Lyme disease can generally be prevented with a few simple measures. Growing up in Minnesota, we were trained at an early age to observe good tick practices: 1) Avoid tick-prone areas, or if you must camp or hike in an area with ticks, wear long sleeved shirts and long pants with socks rolled up over the cuffs; 2) Use insect repellant; 3) Do a tick check every night before bed during peak season—check all hairlines, and around breasts and under arms where the skin is soft and warm; 4) Remove any tick within 24 hours of attachment in order to reduce the risk of transmission; and 5) check your pets before letting them back in the house.

People living in areas of greatest risk should consider vaccination. But vaccination is no substitute for good tick practices. Primary care physicians in endemic areas should consider posting recommendations for good tick practices in their waiting rooms, especially during spring and summer months. ■

Superinfection During Treatment of Otitis Media

Source: Dagan R, et al. *J Infect Dis.* 2001;183:880-886.

Dagan and associates prospectively examined whether cases of clinically refractory acute otitis media (AOM) are caused by superinfection with resistant organisms during antimicrobial therapy. Dagan et al examined 119 youngsters with AOM of ≤ 7 days duration with positive cultures of middle ear fluid (MEF) for ≥ 1 bacterial organism and ≥ 1 nasopharyngeal culture (NP) for *Streptococcus pneumonia* (SP) obtained prior to the administration of antibiotics. Patients were assigned to receive azithromycin, amoxacillin-clavulanate, or trimethoprim-sulfamethoxazole. Repeat tympanocentesis for culture was performed at 4-6 days of therapy and in the event of relapse.

About one-third of the children reported 3 or more episodes of AOM in the past year and 24% had received antibiotics within the preceding month. *H influenzae* was isolated from 58% of patients, SP from 36%, and both organisms were isolated from 24%. About two-thirds of SP isolates from MEF and NP were susceptible to the agent received. Patients with positive NP cultures for SP were more likely to have positive MEF cultures for SP. A resistant MEF strain of SP was obtained from 13 of 32 children (41%) with a resistant NP SP strain, in contrast to only 3 of 57 (5%) children with a sensitive NP strain and 3 of 30 (10%) of children with negative NP cultures for SP. In 19 of 119 (16%) cases, an organism susceptible to the agent received was isolated from the MEF but NP cultures yielded resistant SP.

Within a few days of treatment, repeat MEF cultures demonstrated that the resistant SP strain had replaced the previous organisms in the MEF in 9 of these 19 patients (47%). In two cases, resistant SP replaced sensitive strains of SP, as demonstrated by strain type and anabiograms. Several of these children had shown initial improvement but then later relapsed.

Pediatricians and primary care physicians should be aware that clinically unresponsive otitis or relapse may be due to acquisition of resistant strains that had previously colonized the nasopharynx. It may be interesting to examine whether attempts at decolonization of nasopharyngeal carriage of resistant SP is beneficial. ■

Rotavirus Vaccine and Intussusception

Source: Murphy TV, et al. *N Engl J Med.* 2001;344:564-572.

Following 9 reports of intussusception in infants possibly related to vaccine use, rotavirus vaccine was pulled from the market in 1999 (Kemper CA. *Infectious Disease Alert* 1999;21: 168). This investigation of vaccinated infants confirms that rotavirus vaccine, for reasons that are not clear, does indeed increase the risk of intussusception. Of 426 infants with intussusception, 74 (17.4%) had received rotavirus vaccine. Compared with infants who did not receive rotavirus vaccine, vaccinated infants were at 14 times greater risk of intussusception during the first week post-vaccination. Of note, during the initial clinical trials performed for licensing, only 5 cases of intussusception occurred in more than 10,000 infants. ■