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PEDIATRIC & ADOLESCENT MEDICINE REPORTS™

The essential guide to developments in primary care for infants, children, and adolescents

Vaccines Against Lyme Disease are Near

ABSTRACTS & COMMENTARY

Synopsis: *Two large studies of similar recombinant vaccines against Lyme disease showed efficacies of 76-92% after three doses (at 0,1, and 12 months). An FDA advisory panel has recommended RDA approval. One or more of these Lyme disease vaccines will probably be licensed soon, but many questions remain.*

Sources: Steere AC, et al. Vaccination against Lyme disease with a recombinant *Borrelia burgdorferi* outer-surface lipoprotein A with adjuvant. *N Engl J Med* 1998;339:209-215; Sigal LH, et al. A vaccine consisting of recombinant *Borrelia burgdorferi* outer-membrane surface protein A to prevent Lyme disease. *N Engl J Med* 1998;339:216-222.

Two multicenter, double-blind, randomized trials over two years of 10,936 and 10,305 subjects living in areas in the United States endemic for Lyme disease were conducted using two different recombinant preparations of *Borrelia burgdorferi* outer surface protein A (OspA). Two vaccine doses were administered one-month apart, with a booster at 12 months. Vaccine efficacies for prevention of infection with *B. burgdorferi* after two doses were 49% (95% CI, 15-69%) and 68% (36-85%), and after three doses were 76% (58-86%) and 92% (69-97%). Vaccination was associated with mild, self-limited symptoms including soreness at the injection site (24% and 2%), myalgia (3% and 6%), and low-grade fever (up to 2%) during the first seven days after vaccination. There was no evidence of vaccine-associated arthritis, even in persons with prior self-reported Lyme disease, or exacerbation of neurologic conditions during 24 months of follow-up.

COMMENT BY HAL B. JENSON, MD, FAAP

Lyme disease is the most common vector-borne disease in the United States, with 16,461 cases reported in 1996, clustered in the Northeastern coast (Massachusetts, Connecticut, Rhode Island) to the mid-Atlantic region (New York, New Jersey, Delaware, Pennsylvania, Maryland), the upper Midwest (Wisconsin and Minneso-

INSIDE

ta), and northern California and Oregon. Lyme disease vaccines have been developed that induce antibodies of OspA that are lethal to *B. burgdorferi* in the gut of the carrier Ixodes tick while it is taking blood from a human through a bite—effectively blocking transmission of the bacterium from the tick. Antibodies of OspA are minimal or absent in persons with natural Lyme disease. The vaccine protects against the most common strains of *B. burgdorferi* in the United States but does not protect against all strains.

An FDA advisory panel recently recommended that the vaccine used in the first study (LYMErix, by SmithKline Beecham) be approved for use in persons 15-70 years of age in a 0, 1, and 12-month regimen with the doses given February-April, immediately preceding the peak Lyme disease season during the spring and summer.

Licensure and use of a vaccine for Lyme disease will be novel in several respects. It would be the first licensed vaccine for a vector-borne infection. It will also likely be licensed for regional use in the United States, for persons who live in endemic regions or who work in occupations that expose them to ticks. This will create many dilemmas. Persons traveling within the United States to endemic areas will be vaccine candidates, but a minimum of two doses, and preferably three doses over 12 months, are necessary to provide optimal protection.

Several concerns remain as to whether individuals with undiagnosed Lyme disease or those already suffering from chronic arthritis should receive the vaccine. It was reassuring that neither study found evidence of vaccine-associated arthritis. Neither study included persons younger than 15 years of age, despite the occurrence of one-fourth of cases of Lyme disease in children. Also, the duration of immunity is unknown. It appears that there is not long-term protection and booster doses are likely to be required, although the optimal booster regimen is unknown. Studies of the vaccine in children 4-18 years of age, and to determine the need for booster doses, are underway.

Whether an individual has received Lyme disease vaccine, it is important, especially in children, to check for ticks after outdoor activities in endemic areas. Transmission of *B. burgdorferi* requires more than 24 hours of tick-feeding, providing ample opportunity to interrupt transmission by frequent inspection, and removal of ticks. ❖

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Antibiotic Treatment vs. Placebo for Adenitis from Cat Scratch Disease

ABSTRACT & COMMENTARY

Synopsis: *Five days of oral azithromycin was more effective than placebo in reducing the size of adenitis associated with cat scratch disease in this well-designed study with a small number of patients. The difference was most significant at 30 days post-treatment.*

Source: Bass JW, et al. Prospective randomized double blind placebo-controlled evaluation of azithromycin for treatment of Cat-Scratch Disease. *Pediatr Infect Dis J* 1998;17:447-452.

The article by bass and colleagues describes a prospective, randomized, double-blind, placebo controlled clinical trial that compares azithromycin to placebo in treating adenitis secondary to *Bartonella henselae* infection or cat-scratch disease.

Patients aged 6-65 years old were enrolled when suspected of having a *B. henselae* infection if there was: 1) regional lymphadenopathy and a cat-scratch, bite, or papule in the area of the involved node; 2) regional lymphadenopathy and no skin lesion but a

history of intimate cat exposure; and 3) a positive immunol fluorescent antibody (IFA) test of 1:64 or more. The number of days until an 80% reduction of the initial lymph node volume was noted using three-dimensional ultrasonography. The dose of azithromycin used was 500 mg initially then 250 mg for a total of five days in patients more than 45.5 kg, and 10 mg/kg on the first day and 5 mg/kg for the subsequent four days in children.

Seven of 14 patients in the azithromycin group and one of 15 in the placebo group had an 80% reduction of node size during the first 30 days following treatment. After 30 days, there was no difference between groups. At 30 days after treatment, the greatest statistical significance was noted (P = 0.02), with an odds ratio of approximately 17 but a wide 95% confidence interval (1.5-196).

COMMENT BY LOUIS M. BELL, MD, FAAP

Although cat-scratch disease (CSD) was described more than 45 years ago, only recently has a gram-negative coccobacillus, *B. henselae* (formerly the genus Rochalimaea) been isolated from the lymph node tissue of patients with adenitis. In addition, CSD can be associated with fever of unknown origin, seizures, encephalitis, micro abscesses in the liver or spleen, and aseptic meningitis.

Diagnosis of *B. henselae* infection by culture is difficult, requiring extended incubation (up to 1 month) on solid agar. PRCR amplification of Bartonella specific nucleic acid sequence is a research tool not routinely available.

Fortunately, an indirect fluorescent antibody (IFA) test is available. A positive result at titers of 1:64 or more occurs in 84-88% of patients with suspected CSD. Patients with adenitis and cat contact, especially in cats younger than 1 year of age, or actual cat scratch are more likely to be seropositive.

Unfortunately, therapy with antibiotics for cat scratch adenitis have not resulted in dramatic clinical improvement. In 1992, Margileth in an uncontrolled retrospective study, attempted to determine the effectiveness of antibiotic therapy. The results were not conclusive and, in immunocompetent patients with uncomplicated CSD adenitis conservative, symptomatic treatment was recommended. The infection is self limited, gradually resolving in 2-3 months.

The current study by Bass et al is well designed with a small number of enrolled subjects comparing treatment with azithromycin and placebo. Ultrasonography was performed at mean intervals of 9.7 (± 4.7) days in the azithromycin group and 8.7 (± 3.7) in the placebo group with no significant difference between the groups at these interval evaluations. However, at one month after treatment, the treatment group was 17 times more likely to have an 80% reduction in the size of the adenitis as compared to the placebo group. However, the 95% confidence interval reveals that the effect of treatment could be as low as 1.5 times that of placebo.

This is a good first step in determining the choice and duration of antibiotic therapy for CSD, but it remains to be seen whether patients with mild-to-moderate CSD adenitis will gain significant clinical benefit from antibiotic therapy. ❖

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Nebulized Budesonide, Intramuscular Dexamethasone, and Placebo for Moderately Severe Croup

ABSTRACT & COMMENTARY

Synopsis: *In children with moderately severe croup, treatment with intramuscular dexamethasone or nebulized budesonide resulted in more rapid clinical improvement than did administration of placebo with dexamethasone offering the greatest improvement. Treatment with either glucocorticoid resulted in fewer hospitalizations.*

Source: Johnson DW, et al. A comparison of nebulized budesonide, intramuscular dexamethasone, and placebo for moderately severe croup. *N Engl J Med* 1998;339:498-503.

Johnson and associates at the hospital for Sick Children in Toronto compared the effects of parenteral dexamethasone and nebulized budesonide on symptoms and need for hospitalization in children

with moderately severe croup. They conducted a double-blind, randomized study involving 144 children with croup who were seen in their ED during an eight-month period of time in the winter and spring of 1995-1996 because of the acute onset of stridor with a "seal-like" barking cough. Ages ranged between 3 months to 9 years of age.

The children were randomized to receive either nebulized budesonide (4 mg), intramuscular dexamethasone, (0.6 mg/kg), or placebo. They were assessed prior to therapy and then hourly for five hours. The characteristics of the three groups were similar at base line, including the types of viruses identified, the types of croup, and the assessed clinical severity of illness. The overall rates of hospitalization were 71% (35 of 49) in the placebo group, 38% (18 of 48) in the bedesonide group, and 23% (11 of 47) in the dexamethasone group. Children treated with budesonide or dexamethasone had a statistically, significantly greater improvement in croup scores than those receiving placebo, and those treated with dexamethasone had a greater improvement than those treated with budesonide.

COMMENT BY THOMAS F. DOLAN, MD, FAAP

Johnson et al have performed a careful study comparing the treatment of moderately severe croup with intramuscular dexamethasone, nebulized budesonide, or placebo. Patients in all three groups additionally received standard therapy including racemic epinephrine by inhalation and mist therapy.

Parainfluenza virus A, B, or C was isolated from approximately 30% of their patients. Another 10% grew influenza or RSV virus. Only six of 144 patients were diagnosed as spasmodic croup. Twenty-seven percent of patients had a history of previous croup, and 18% had a history of having prior treatment with racemic epinephrine. There was more rapid improvement clinically in patients treated with steroids than placebo and a marked decrease in hospitalization rate. The intramuscular dexamethasone (0.6 mg/kg) given once proved superior to inhaled budesonide. This is somewhat surprising to me, since, theoretically, more steroid should be delivered to the subglottic area more rapidly by inhalation. Perhaps in an ED setting, a frightened toddler might not do a good job inhaling steroids.

Historically, the management of croup has changed drastically over the past 30 years. Those of us with gray hair may remember the infamous "croup rooms" in many pediatric hospitals. One had to don a raincoat when entering these rooms and was barely able to see the patient through the fog. The mist was supposed to liquefy mucus. Cold mist rooms were replaced by mist tents, and it became fashionable to treat all children with respiratory tract disease with mist tents. Perhaps the good results people thought they were seeing were due to the fact that the mist was generated by oxygen rather than room air (this was before oximetry was available). Mist tent therapy was abandoned when Wolsdorf et al showed that mist therapy was only an expensive way to moisturize the nasal canal.[1] A more serious problem with mist tents was that one cannot easily see or evaluate the infant. A study comparing the effects of humidified air vs. non-humidified air showed no statistical benefits.[2]

Antibiotics were commonly used to treat croup for fear the patient had epiglottitis due to Haemophilus Influenzae type b. I never thought the presentation was similar, but the problem has become moot since virtually all patients receive Hib vaccine, and Hib epiglottis has essentially disappeared in the United States.

There were great arguments about the value of racemic or l-epinephrine. Many clinicians believed that any child receiving these drugs should be admitted to the hospital because of a concern that a late rebound of symptoms might occur.

The value of steroids in croup was the topic of violent (and mostly anecdotal) arguments until the article by Super et al definitively proved that steroids were beneficial.[3] Newer studies, such as the one conducted by Johnson et al, show that nebulized or parenteral steroids improve outcome.

I personally favor using intramuscular dexamethadose because oral steroids, both tablet and liquid preparations, are bitter and may be difficult to administer to an excited, frightened child with respiratory distress in the ED milleau. I suspect that a combination of an oral or IM steroid plus one or two doses of a nebulized steroid will be evaluated in the near future in an attempt to further decrease hospitalization rates. *(Dr. Dolan is Professor of Pediatrics at the Yale-New Haven Children's Hospital.)* ❖

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Little Leaguer's Shoulder

ABSTRACT & COMMENTARY

Synopsis: *Little Leaguer's Shoulder is throwing related pain in the proximal humerus and the radiologic finding of widening of the proximal humeral physis in young or adolescent baseball players. Twenty-three children with this syndrome were treated by rest from baseball throwing for an average of three months. Ninety-one percent became asymptomatic and were able to resume playing baseball.*

Source: Carson WG, Gasser SI. Little leaguer's shoulder: A report of 23 cases. *Am J Sports Med* l998;26:575-580.

Twenty-three cases of little leaguer's shoulder Syndrome were studied by Carson and Gasser at the Sports Medicine Clinic of Tampa. The average age of the patients was 14 years, and they were followed for an average of 9.6 months until they had either returned to baseball playing or their symptoms had resolved. The chief complaint of all patients was pain localized to the proximal humerus during the act of throwing. Physical examination revealed tenderness to palpation over the lateral aspect of the proximal humerus (87%). All patients had radiographic widening of the proximal humeral physis of the throwing arm on internal and external rotation radiographs of the affected shoulder. All patients were treated with rest from baseball for an average of three months. Twenty-one of 23 patients (91%) became asymptomatic and returned to baseball playing. Rest from throwing for at least three months followed by a gradual return to throwing when the shoulder is asymptomatic is recommended.

The report of 23 cases by Carson and Gasser is an excellent review of another overuse injury seen in children and reemphasizes the growing nature of this type of problem. As seen with other overuse injuries in children, mid-adolescence is the age of peak frequency and the symptoms are insidiously progressive. Focal tenderness is frequently present, but signs of active inflammation are not.

COMMENT BY BARRY GOLDBERG, MD, FAAP

Overuse problems are increasing in youth sports and pitching creates repetitive microtrauma on the shoulder and elbow as a result of the kinetic forces applied. Prevention is a critical component and incorporates a large number of issues. The most significant include total number (not innings) and type of pitches thrown, proper biomechanics, consistent supervised conditioning, control of "outside" pitching, and not ignoring early signs and symptoms, such as discomfort or dropping of the elbow in delivery. Of recent concern are young pitchers who participate in multiple leagues to pitch a greater number of innings. In many instances, overzealous parents are responsible for these excesses.

Treatment of Little League shoulder has no absolutes in terms of restricted pitching, but therapy ranges from 6-16 weeks, depending on such variables as the symptoms and x-ray findings. When the shoulder has been entirely asymptomatic for a week, a slow graduated program of long, light toss followed by increasing distance to 45 feet as well as increasing velocity can be introduced.

Eventually, the youthful pitcher should be able to move to regulation distance and pitch off the mound. This time of rehabilitation should not only be used to allow for epiphyseal healing but also for identification of risk factors, such as poor mechanics, excessive pitching, types of pitches thrown, etc., so that these factors can be reviewed and corrected. *(Dr. Goldberg is Director of Sports Medicine, Yale University Health Service, New Haven, CT.)* ❖

Exudative Pharyngitis: Do Steroids Help?

ABSTRACT & COMMENTARY

Synopsis: *Patients with painful, exudative pharyngitis who were given betamethasone as adjunctive therapy in addition to antibiotic therapy had more rapid relief of pain compared to patients who received a placebo.*

Source: Marvez-Valls EG, et al. The role of betamethasone in the treatment of acute exudative pharyngitis. *Acad Emerg Med* 1998;5:567-572.

This prospective, randomized, double-blinded, placebo-controlled study evaluated the efficacy of betamethasone as an adjunct to antibiotic therapy for patient with exudative pharyngitis. All patients with exudative pharyngitis were treated with antibiotics, either IM penicillin or oral erythromycin. Patients were randomized to receive either IM saline or betamethasone. Patients were asked to rate their pain on a visual analogue scale (VAS) at the time of treatment. Each patient was called periodically to rate their pain on the VAS compared to their initial rating. Marvez-Valls and colleagues did not ask about analgesic use, and not all patients had throat cultures performed.

Patients receiving betamethasone started to feel relief five hours earlier and had complete resolution of pain 14 hours earlier than the placebo group. However, the num-

ber of days or missed school or work was not significantly different between the two groups. In patients whom were cultured, those in the culture-negative group did not show any differences in pain scores comparing betamethasone to placebo. Marvez-Valls et al conclude that as an adjunct to antibiotic therapy, betamethasone appears to lessen the time to pain relief in patients with acute exudative pharyngitis, and that this treatment may be most effective in patients with streptococcal pharyngitis.

COMMENT BY GLENN C. FREAS, MD, JD, FACEP

In a previous study by O'Brien and associates, dexamethasone was shown to be an effective adjunct to antibiotic treatment for acute pharyngitis.[1] Since that study, many emergency physicians used steroids in the treatment of acute pharyngitis to more rapidly decrease the pain associated with this common disease. This study will undoubtedly be cited by many of our colleagues to further justify this practice. Nonetheless, there are persistent questions and concerns about the efficacy and cost effectiveness of this practice. Some of them are highlighted in the accompanying editorials in the same issue of *Academic Emergency Medicine*.

One area of concern is the validity of the visual analogue scale that was used in this study and its applicability to the pain of pharyngitis. Cydulka points out that even if we assume that the VAS can be applied to the setting of acute pharyngitis pain, the clinical differences between the placebo group and the betamethasone group described at 24 hours disappear at 48 hours.[2] Half of the patients had to be reminded of their initial rating on the VAS and did not have the actual visual scale in front of them at home. This is no longer a "visual" analogue scale.

Marvez-Valls et al acknowledge that the lack of control for analgesic use may also call their findings into question. Also, follow-up did not include questions about compliance in the group that was given erythromycin (9% of the patients who received betamethasone were given erythromycin). Finally, as with O'Brien's study, there was no attempt to document the cost-effectiveness of treatment with betamethasone. Do hours of less pain justify the use of an IM injection? The risk of needle stick to health care personnel must also be factored into any cost (risk)-benefit analysis.

For the above reasons, I have been show to jump on the steroid bandwagon for treatment of pharyngitis. While I am sensitive to the need to help our patients with the pain of acute pharyngitis, I am still not convinced that the routine use of steroids for all patients with this common disease is cost-effective and warranted. *(Dr. Freas is Associate Program Director, Emergency Medicine Residency, Allegheny University Hospitals, Philadelphia, PA.)* ❖

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Special Feature

Prophylaxis with Monoclonal Antibody for RSV Infections in High-Risk Infants

By Hal B. Jenson, MD, FAAP

A randomized, double-blind, placebo controlled trial was conducted at 139 centers in the United States, Canada, and the United Kingdom. During the 1996-1997 respiratory syncytial virus (RSV) season, 1502 children with prematurity (< 35 weeks) or bronchopulmonary dysplasia (BPD) were randomized to receive five injections every 30 days of either Palivizumab, a "humanized" monoclonal antibody against RSV, or placebo.[1] The children were followed for 150 days. Children who were hospitalized for RSV infections were evaluated for total hospital days, total days with severe or moderate lower respiratory illness, and total days of intensive care and mechanical ventilation.

Palivizumab prophylaxis resulted in a 55% reduction in hospitalizations for RSV; children with prematurity but no BPD had a 78% reduction; children with BPD had a 39% reduction. The treatment group had fewer hospital days, fewer RSV hospital days with increased oxygen, fewer RSV hospital days with a moderate or severe lower respiratory tract illness, and a lower incidence of ICU admissions. Palivizumab was safe and well tolerated.

RSV is the most important cause of lower respiratory tract infections in infants and young children, accounting for 90,000 pediatric hospitalizations and 4500 deaths annually during yearly outbreaks in winter and spring. Approximately half of all children become infected with RSV each winter season. The frequency and severity of repeat RSV infections diminish with advancing age. In the first 3-4 years of life, RSV infections are an important cause of significant mortality and morbidity in children who are born prematurely, especially those prematures who have suffered from bronchopulmonary dysplasia.

Aerosolized ribaviran treatment for RSV infection

has been controversial. The most recent study found that ribavirin was not effective in reducing severity of RSV and could have prolonged illness compared to placebo treated control patients.[2] The financial costs, logistical problems with the aerosol route of administration, concern for potential toxicity in exposed personnel (especially pregnant women), and uncertain clinical efficacy have diminished its use.[3]

RSV-IGIV (RespiGam) intravenous immune globulin prepared from individuals with high titers of anti-HSV antibodies was licensed in January 1996. It is administered as a series of five monthly injections of RSV-IGIV given during the RSV season and reduces the incidence of RSV infections by 41%, hospital days with moderate or severe RSV by 54%, and total RSV-associated hospital days by 53%. RSV-IGIV also reduces hospitalization for respiratory illness from any cause by 38% and also the incidence of otitis media.[4]

In a March 1997 comment on RSV-IGIV, I indicated that monoclonal antibody preparations against HSV were under development.[5] A "humanized" monoclonal antibody that is highly active against RSV has been prepared by inserting the antibody determining region of a murine monoclonal antibody directed to the RSV F protein into a human I.G. framework. The resulting humanized monoclonal antibody named palivizumab and marketed as Synagis, is composed of 95% human and 5% murine sequences. Since it is not prepared from human blood, there is no potential transmission of blood-borne pathogens. Palivizumab is 50-100 times more potent against RSV than an equivalent amount of RSV-IGIV. It is reconstituted with sterile water and is administered in monthly intramuscular doses of l5 mg/kg with up to 1 mL per injection site.

The IMpact-RSV Study Group showed a 55% reduction in RSV-associated hospitalizations (10.6 for placebo vs 4.8 for psalivizumab), which compares favorably to the 41% reduction reported earlier with the use of RSV-IGIV. The primary advantage of palivizumab is the ease of intramuscular administration compared to the intravenous administration of RSV-IVIG that requires intravenous access, sometimes difficult in these patients, and it may take 4-6 hours for the infusion. Another advantage is that there is no interaction that necessitates delay of live virus vaccination, such as the nine months that measles vaccine must be deferred after RSV-IVIG. One advantage of RSV-IVIG is the reduced incidence of respiratory infections other than RSV, including a reduced incidence of otitis media. Palivizumab and RSV-IVIG are only indicated for prophylaxis and not treatment of RSV disease.

Palivizumab will supplement most of the use of RSV-IVIG. The cost, using average wholesale pricing, which is higher than the actual cost for many hospitals of a five-month treatment of a 5 kg infant with RSV-IVIG is approximately $7600 compared to $4500 for Palivizumab. One cost consideration is that reconstituted Palivizumab must be used within six hours, so that the actual cost may be higher due to wastage. This can be minimized by seeing all patients receiving Palivizumab at the same time. Despite the high costs, savings from reduced hospitalizations and ICU care are cost effective for both Palivizumab and RSV-IVIG.

I have one final comment about this latest study. The use of a placebo control design for a serious disease that has an accepted and recommended, effective alternative available therapy is a little troubling. ❖

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CME Questions

18. A diagnosis of *Bartonella henselae* infection should be suspected in all of the following *except*:
a. a child with regional adenitis and a history of a cat scratch in the region of the node.
b. a child with generalized lymphadenopathy.
c. a child with regional adenopathy but no history of cat scratch, but a history of intimate exposure to cats.
d. a child with a positive indirect fluorescent test against *B. henselae*.

19. A vaccine for Lyme disease:
a. has been approved for human use by the FDA in children younger than 15 years of age.
b. requires a minimum of two doses for optimal protection.
c. evokes antibodies that are present in high levels in patients who have had Lyme disease.
d. is effective against all strains of *B. burgdorferi*.

20. True statements about "Little Leaguer's Shoulder" include all of the following *except*:
a. There are usually no radiologic abnormalities in the affected humerus.
b. Pain to palpation over the lateral, proximal humerus is often present.
c. The most important part of treatment is restriction of throwing.
d. Early symptoms and signs include shoulder discomfort and dropping of the elbow when throwing.

21. Childhood croup:
a. requires early administration of antibiotics.
b. requires mist therapy.
c. treatment with steroids improves outcome.
d. viruses can be isolated in most cases.

22. Prophylaxis of RSV infections in high-risk infants:
a. is not necessary because of an effective therapy—ribavirin.
b. is comparably effective with the use of either RSV-IVIG or Palivizumab.
c. is not cost effective because of the high costs of prophylactic medications.
d. does not reduce the severity of RSV infections.

In Future Issues:

Screening Adolescent Athletes for Cardiac Disease

Thyroid Dysfunction in Down's Syndrome: Relation to Age and Thyroid Autoimmunity