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The essential monthly primary care update

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Sulfonamide Antibiotics and Sulfonamide Nonantibiotics

Source: Strom BL, et al. *N Engl J Med*. 2003;349:1628-1635.

SULFONAMIDE ANTIBIOTICS (SULF-a) are the drugs most commonly associated with both the dread consequences of Stevens-Johnson syndrome and agranulocystosis. More commonly, clinicians see modest allergic dermatitis in SULF-a allergic patients. The allergen responsible for inducing allergic reactions is common both to SULF-a and nonantibiotic sulfonamides, such as thiazide diuretics (SULF-na).

Strom and colleagues used the General Practice Research Database from the United Kingdom, to scrutinize the relationship between SULF-a allergic reactions and subsequent SULF-na allergic reactions. Because Strom et al entertained the possibility that reactions to SUFL-na reflect a patient with an allergic diathesis, rather than specific intolerance to sulfonamides, they also examined adverse experiences in persons who had been prescribed a nonsulfonamide antibiotic, penicillin.

Approximately 10% of persons receiving SULF-na after an adverse SULF-a experience developed an allergic reaction (compared with a background incidence of 1.6% allergic reactions to a SULF-na in persons without a prior allergic sulfonamide reaction). Surprisingly, the likelihood of an adverse reaction to penicillin after an experience of SULF-a allergy was actually greater than that of an adverse reaction to SULF-na! These data support the concept that it may be allergic diathesis, rather than sulfonamide crossreactivity, which is responsible for the substantial degree of dermatologic intolerance manifestations to SULF-na among persons with demonstrated SULF-a allergy. ■

Autoantibodies Before Onset of SLE

Source: Arbuckle MR, et al. *N Engl J Med*. 2003;349:1526-1533.

THE DIAGNOSIS OF SYSTEMIC LUPUS erythematosus (SLE) is based, in part, upon laboratory findings, including measurement of autoantibodies (AAB) such as antinuclear antibody (ANA), anti-double-stranded DNA (aDS-DNA). Indeed, such AAB are contributors to the pathology of SLE. The timing of presentation of SLE AAB is not yet clearly established, since clinicians seek AAB status usually at the time of clinical presentation and are rewarded almost universally with positive AAB findings in persons with SLE diagnosis confirmation.

Among 130 patients with SLE, one or more AAB was present a mean of 3.3 years prior to diagnosis (range up to 9.4 years earlier). The most commonly detected AAB was ANA (78% at 1:120 or greater dilution), and the least common was antiphospholipid antibody (18%). Matched controls were positive 3.8% of the time.

The appearance of SLE AAB years prior to symptomatic presentation is established by these data to be commonplace and occurs in a predictable pattern much of the time. It appears that the number of different AAB increases over time until clinical presentation, after which the number remains constant, as if there is some self-limited aspect to AAB development. ■

Prevention of VTE with Ximelagatran

Source: Schulman S, et al. *N Engl J Med*. 2003;349:1713-1721.

TYPICALLY, AFTER A FIRST EPISODE OF DVT, prophylaxis will be advised for 3-6 months, although recent data show no diminution of benefit when warfarin prophylaxis for recurrent DVT is continued for as long as 24 months. The rationale for 3-6 months of DVT prophylaxis is based upon a risk-benefit analysis that includes expense, adverse effects (primarily bleeding), and need for repeated long-term monitoring on the downside of the equation.

Ximelagatran (XIM) is an orally administered direct thrombin inhibitor that has already demonstrated efficacy equal or superior to well-titrated warfarin prophylaxis in settings of DVT or atrial fibrillation. The remarkable difference between XIM and warfarin is that consistent anticoagulation responsivity seen with XIM results in no need for coagulation monitoring; that is, once patients are started on the twice-daily drug, no further INR testing or other coagulation monitoring is required.

In this trial, persons who had successfully completed 6 months of warfarin (n = 1223) were randomized to either placebo or XIM twice daily for an additional 18 months. Confirmed symptomatic venous thromboembolism was seen in 12/612 XIM patients vs 71/611 placebo recipients. There was no significant difference in all-cause mortality or bleeding between XIM and

placebo. XIM may be available as an oral anticoagulant in the very near future. ■

Combined Levothyroxine Plus Liothyronine Compared to Levothyroxine Alone in Primary Hypothyroidism

Source: Clyde PW, et al. *JAMA*. 2003;290:2952-2958

Prior to sophisticated development of drug therapy, thyroid hormone was administered as a derivative of animal thyroid glands, with varying amounts of T3 and T4. Currently, although solitary levothyroxine (T4) is the preparation provided to more than 90% of patients with hypothyroidism (hTHY), there has been some enthusiasm for use of combination products (T3 and T4) or T3 alone. However, it remains controversial whether T3 provides additional benefit over simply using T4 and anticipating adequate T3 derivation from that. A 1999 study had suggested that dual treatment enhanced cognitive function.

Clyde and colleagues randomized 46 stable hTHY patients to T4 alone vs T4 + T3. T3 was provided in a dose of 7.5 mg b.i.d. to replace 50 mg of T4 (ie, if a patient had been previously well controlled on 150 mg/d T4, they were switched to 100 mg T4 + 7.5 mg T3 b.i.d).

Both regimens provided appropriate suppression of TSH and adequate levels of T4 and T3, indicative of accurate therapeutic replacement. As might be anticipated, T3 supplementation resulted in higher serum T3, accompanied by compensatory reduced T4, although neither measurement exceeded boundaries of normal. No discernible benefit for symptoms, cognitive performance, or mood was demonstrated for dual treatment. The accompanying editorial reflects upon 2 additional recently published trials with similar results. Though the idea of combination thyroid replacement is appealing for patients who report hypothyroid symptoms despite laboratory documentation of adequate replacement, these recent data questions the viability of such an approach, which also entails greater complexity and expense. ■

Specific Site Involvement in Fixed Drug Eruption

Source: Ozkaya-Bayazit E. *J Am Acad Derm*. 2003;49:1003-1007.

Fixed drug eruption (FDE) is the recurrent presentation of cutaneous drug allergy manifest at the same local site. In the United States, the glans penis is one of the most common sites of FDE, often precipitated by tetracycline or trimethoprim-sulfamethoxazole (TMP-SMX).

This study provides details on 105 FDE patients seen in the Istanbul Medical Faculty Department of Dermatology Clinic 1996-2000. To confirm the FDE diagnosis and precipitating agent, oral provocation testing was performed.

TMP-SMX and naproxen were the most common causes of FDE (63.8% and 23.8%, respectively). Less common causes were oxicams such as piroxicam [Feldene] (4.8%), acetaminophen (0.95%), and dimenhydrinate (0.95%).

The most commonly involved sites for FDE were the genital mucosa (50.5%), trunk (38.1%), lips (37.1%), and hands (32.4%). Drug-specific differences were noted, in that TMP-SMX most often produced genital FDE, whereas NSAIDs most commonly affected the lips. Site-specific associations between drugs and FDE may help clinicians confirm diagnostic hypotheses. ■

Anticoagulation Therapy for Stroke Prevention in Patients with Atrial Fibrillation

Source: Go AS, et al *JAMA*. 2003; 290:2685-2692.

There is little challenge to the credibility of anticoagulation for stroke prevention in atrial fibrillation (SPAF) as demonstrated in numerous large clinical trials. Nonetheless, clinicians may not apply the same sanguine approbation when considering the options in "real life" settings, perhaps wondering whether clinical trial results reflect a more pristine patient population and whether the risk benefit-ratio will be similar in their particular local setting.

The cohort study reported by Go and colleagues assessed nonvalvular atrial fibrillation patients (n = 11,526) from an integrated health care system in Northern California, which might more accurately represent nonacademic practice milieu. The effect of warfarin treatment was very salutary (compared to no antithrombotic therapy), providing a 64% reduction in odds of thromboembolism. Similarly, warfarin treatment was associated with reduced all-cause mortality (31%). Although the risk of intracranial hemorrhage in persons on warfarin was increased (hazard ratio = 1.97), the absolute number of events was very small (0.46 per 100 person-years) and far outweighed by the other beneficial effects, including stroke reductions of 61%.

Clinicians should be heartened that application of literature-proven interventions may yield similar positive effect in traditional ambulatory settings. ■

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