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FOR

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This document is divided into two parts

1) The **HIGHLIGHTS AND *EDITORIAL COMMENTS* SECTION**

HIGHLIGHTS condenses the contents of studies, and allows a quick review of pertinent points of each article.

EDITORIAL COMMENTS *are the editor's assessments of the clinical practicality of articles based on his long-term review of the current literature and his 20-year publication of Practical Pointers.*

2) The main **ABSTRACTS** section is designed as a reference. It presents structured summaries of the contents of articles in much more detail.

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 6 years can be accessed at www.practicalpointers.org

Richard T. James Jr. M.D.
Editor/Publisher.

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HIGHLIGHTS AND *EDITORIAL COMMENTS* DECEMBER 2009

Aim for 5 Grams of NaCl Daily, or Less

12-1 THE CASE FOR POPULATION-WIDE SALT REDUCTION GETS STRONGER

Excess intake of sodium chloride has an important and probably predominant role in the pathogenesis of raised BP. On average, as salt intake increases, BP increases. The importance of this association cannot be overstated. The evidence is indisputable.

Several studies have estimated the societal benefits of population-wide salt reduction. One study estimated that across 23 countries with a high burden of chronic disease, 850 000 lives would be saved each year from a reduction in salt intake to 5 grams daily. This is the recommended limit set by the WHO.

A recent analysis reported that an average daily intake of 5.8 gram NaCl (2300 g sodium; the recommended upper limit in the US) would reduce the prevalence of hypertension by 11 million, save $18 billion in health care costs, and gain 312 000 quality adjusted life years. This line of reasoning, however, is indirect.

A meta-analysis in this issue of BMJ is a welcome addition to the medical literature.

The meta-analysis included 13 cohort studies and 19 independent samples, which demonstrated a higher salt intake is associated with increased incidence of stroke. A 5 gram increase in salt intake was associated with a 23% higher risk of stroke. And a 17% higher risk of CVD.

Of course, this is nothing new. I abstracted the article because I believe salt is the neglected aspect of the healthy diet. Few individuals calculate their salt intake. They pay less attention to salt than to fats and calories.

Additionally, those of us who eat commercially prepared foods face difficulties in reducing salt intake. Ideally, to reduce salt intake food must be prepared at home. And the salt shaker removed from the table.

Perfect Protection for 6 Years, And Likely Longer

12-2 SUSTAINED EFFICACY AND IMMUNOGENICITY OF THE HUMAN PAPILLOMA VIRUS (HPV)-16/18 AS0-4-ADJUVATED VACCINE

Infection with oncogenic human papilloma virus (**HPV**) is the necessary cause of cervical cancer (**CC**). Fifteen oncogenic types have been identified. Most (70%) CC is caused by types related to HPV 16 and 18. Other common types are 31, 33, 45, 52, and 58.

Vaccines for HPV have to provide long-term protection, since the risk of acquiring an infection begins with sexual debut and continues through life.

Women with a naturally acquired infection remain at risk for a new infection with the same HPV type possibly because antibody concentrations after natural infection are low and do not offer sufficient protection.

The HPV 16/18 ASO-4 vaccine used in this study is adjuvated by a system comprised of aluminum salt and the immunostimulatory molecule ASO4. This adjuvated vaccine produces consistently higher antibody titers, which are sustained over a longer period, together with a higher frequency of memory B cells than do the same antigens adjuvated with aluminum only.

This multicountry study (27 sites), begun in 2003 and continued through 2007, entered healthy young women (age 15-25; n = 776). All had normal cervical cytology, were HPV 16 and 18 seronegative, and were DNA negative by PCR for 14 oncogenic HPV types in their cervical cells.

Randomized, double-blind to:

1) Three doses of 16/18 adjuvated vaccine, or

2) Placebo

Mean follow-up = 5.9 years; maximum follow-up = 6.4 years.

Infection with 16/18:

	Vaccine (n = 401)	Placebo (n = 373)
Incident infection	4	70
6-month persistent infection	0	34
12-month persistent infection	0	20

(The vaccine was considered 100% effective against persistent infection with 16/18. This was despite recurrent exposure to the viruses over 6 years.)

Cytology: Associated with 16/18

	Vaccine (n = 481 to 505)	Placebo (n = 470 to 497)
CIN 1+	0	15
CIN 2+	0	9

(The vaccine was considered 100% effective against development of CIN.)

There was also some evidence of effectiveness against other types of HPV.

Incident infection (6 years)	16/18 Vaccine	Placebo
HPV type 31	13	30
HPV type 45	5	21

Immune response to vaccine: Neutralizing antibodies and IgG antibodies for 16 and 18

remained remarkably stable over 6 years at 5 to 13 times higher than the immunity produced by natural infections.

Safety: The vaccine was well tolerated. A similar number of women in both the vaccine group and the placebo group reported adverse events. No serious event was judged to be related or possibly related to vaccination. Over 130 pregnancies occurred in both groups without any difference in outcomes.

Although 16/18 cause roughly 50% of high grade squamous intraepithelial lesions, vaccine efficacy reached 72% against any CIN 2+, an indication that the vaccine is able to confer some protection beyond 16/18.

Because the incidence of CC peaks on average more than 30 years after adolescence, vaccine has to confer protection for many years. Six years of protection is the longest time span so far.

"We expect protection to continue for many more years."

An excellent study! Detailed and convincing. This is an important step forward.

Even though CIN is a substitute outcome for CC, I believe it is a strong one.

It appears that the adjuvated vaccine will produce long-lasting immunity. Perhaps a booster will be required in 20 years or so.

Now the problem is to make HPV vaccine available world wide, where it is most needed.

We continue to face the question about immunizing males as well as females.

The Advisory Committee on Immunization Practices (ACIP):

The FDA has approved both the bivalent (16, 18) and the quadrivalent vaccine (6, 11, 16, 18)

The latter also protects against genital warts.

There have been no published head-to-head studies between the two vaccines comparing effectiveness and duration of protection against cervical neoplasia and precancerous lesions

The vaccine is recommended for females at age 11 to 12 with catch up vaccination through ages 13 to 26.

Ideally, the vaccine should be administered before sexual debut but if not, women should still be vaccinated. Complete vaccination consists of three doses, the second at 1 month, the 3rd at 6 months.

Vaccine may be given to women with a history of an abnormal Pap smear, or a positive HPV DNA test, as these conditions are not evidence of prior infection with all HPV vaccine types.

The ACIP added a permissive use of the quadrivalent vaccine in males.

Annals Internal Medicine January 5,2010; 152: 36-38

"Cluster Headache Is Probably The Most Severe Pain Known To Humans."

12-3 HIGH-FLOW OXYGEN FOR TREATMENT OF CLUSTER HEADACHE

Cluster headache (**CH**) is a stereotypic primary headache syndrome characterized by attacks of unilateral excruciating pain, usually in the eye, periorbital region, and temple, with associated cranial autonomic symptoms such as conjunctival injection, lacrimation, nasal blockage, rhinorrhea, ptosis, and eyelid edema. During attacks, patients are often restless and agitated,

Untreated, attacks usually last for 15-180 minutes and have a frequency of 1 every other day to up to 8 attacks per day.

Attacks usually occur in bouts or clusters lasting for weeks or months, separated by remissions lasting months or years.

Treatment relies on therapy to abort the individual attack, and prophylactic therapy to prevent or suppress attacks when they occur. Therapy for attacks must be fast-acting.

Serotonin receptor agonists (sumatriptan; zolmitriptan) are the most effective treatment for acute CH.

Drawbacks for triptans include limitations of daily usage in order to prevent tachyphylaxis and rebound. Triptans are contraindicated in patients with cardiovascular disease.

This randomized, placebo-controlled, double-blind crossover study (2002-2007) compared;

1) 100% oxygen at 12 L/min delivered by a facemask for 15 minutes from the beginning of an attack, or
2) Air delivered the same way.

At end point:	O2	AIR
No of attacks treated	150	148
Pain free at 15 min	78%	20%

(By my calculation, the NNT with oxygen to render one patient pain-free at 15 minutes = 2 RTJ)

Reduction of pain (%)		
15 min	68	20
20 min	81	30
30 min	85	38
60 min	92	59
Need for rescue meds within 15 min (%)	28	53

At all time points, oxygen was superior to air in reducing secondary endpoints.

CONCLUSION

Treatment of patients with CH at symptom onset using inhaled high-flow oxygen compared with placebo was more likely to result in being pain-free at 15 minutes.

CH have been termed "suicide headache".

If you practice primary care medicine long enough, you will encounter a patient with CH. These patients are desperate. Any patient who gains relief of pain will be most grateful.

Oxygen therapy might be inconvenient, but may be made available most of the time.

Triptans increase BP, and are contraindicated in many patients.

Which therapeutic modality to use (or both) would be a matter of trial and error in the individual.

The article did not deal with prophylactic therapy.

12-4 MORE EVIDENCE ON LOW VITAMIN D LEVELS

Many studies report that D deficiency and insufficiency are tied to poor health outcomes from a variety of conditions in a large proportion of the U.S. population. Conditions cited include osteoporosis and bone fracture, muscle weakness, cancer, respiratory tract illnesses, auto-immune disease, diabetes, schizophrenia, depression, lung dysfunction, kidney disease, and cardiovascular disease.

The studies are mainly retrospective. This makes it difficult for regulatory bodies or specialty societies to develop specific recommendations for raising levels for minimum D intake. And leaves some physicians reluctant to aggressively diagnose and treat patients for deficiency.

The National Health and Nutrition Examination Survey (2001-2004) found that, among over 9700 children and young adults, 9% had deficiency in 25-OH-D (<15 ng/mL), and 61% had insufficiency (15-29 ng/mL).

"Vitamin D used to be all about rickets, and whatever the level you needed to prevent rickets was the accepted level. But as other risk factors have arisen, the recommended level should also be on the rise."

Other observers have cautioned that most of the evidence is epidemiological, in which D levels have been associated with various disease processes. This does not establish cause and effect. Randomized, controlled trials are needed.

The Institute of Medicine is scheduled to report regarding D intake in May 2010. It is expected that it will emphasize an increased intake of D and encourage its further use as a food additive. The IOM will look beyond bone health to consider other chronic diseases. Currently the IOM recommends that the upper intake should be limited to 1000 IU for infants up to age 1 and 2000 daily for all over age 1.

The benefit / harm -cost ratio of D is very high. Benefits seem to be high (although not likely as widespread as some have predicted); harms low; and costs very low (Three cents for 1000 IU in some pharmacies.)

Many primary care clinicians adhere to the traditional approach--testing for deficiency, and then prescribing. Most individuals in the U.S. do not consult physicians frequently, and when consulting, D levels may not be considered.

I believe the "polypill" principle would apply to D--ie, recommending almost universal use without pretesting and without follow-up.

A Problem Especially In Young Women With Aural Migraine Who Smoke And Use Oral Contraceptives

12-5 MIGRAINE WITH AURA AND INCREASED RISK OF ISCHEMIC STROKE

Roughly one quarter of people with migraine experience temporary neurological symptoms (aura) before onset of the headache. Aura is distinguished from other causes of brief recurrent neurological disturbance (e, TIA) by its gradual onset and disappearance, and its shorter duration.

Visual disturbances are the most common form of aura. Sensory and motor auras also occur. To identify patients with aura, it is necessary to detect only visual aura, since 99% of people with non -visual aura also have visual aura occasionally.

A recent study[1] clearly shows that the increased risk of ischemic stroke in patients with migraine is largely confined to those with aura. The risk of TIA and angina is also related to aura. Hemorrhagic stroke is not.

Patients with aura should be followed closely and treated aggressively for modifiable cardiovascular disease risk factors. But information to patients with aura should be put in context. The absolute risk of stroke is low, so a doubling of the risk is not cause for panic. At the population level, the risk deserves attention because the prevalence of migraines is so high.

The study also found the risk of ischemic stroke in patients with migraine is magnified by the combination of smoking and contraceptive use, mostly in women under age 45. Incidence of stroke is also increased in patients with frequent migraine.

Clinicians need to identify young women with aural migraine, particularly those who seek estrogen-containing contraception. Those without aura should not be denied the benefits of hormonal contraception.

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1 *See the full abstract*

An alert primary care clinician may be able to avert a tragedy.

"In particular, young women who have migraine with aura should be strongly advised to stop smoking, and methods of birth control other than oral contraceptives may be considered."

"Patients with migraine should be screened for traditional cardiovascular risk factors . . . and these risk factors should be modified."

During my active practice years, the only patient with migraine with ischemic stroke I can recall was a middle aged man.

Six of Every 100 Primary Care-Based Smokers Could Achieve Abstinence

12-6 COMPARATIVE EFFECTS OF 5 SMOKING CESSATION PHARMACOTHERAPIES IN PRIMARY CARE CLINICS

Primary care is the ideal environment in which to study comparative effectiveness of cessation treatments:

1) Many smokers report being receptive to advice from their primary care provider (**PCP**).
2) More than 70% of smokers visit their PCP annually.
3) Health considerations are especially salient in a clinical setting, making patient visits "teachable moments".
4) A majority of smokers express interest in cessation treatment. Many prefer more intensive treatment.
5) Primary care based cessation treatments are cost effective.

The Public Health Service guidelines recommend brief counseling and cessation medication for smokers. This will increase likelihood of successful quitting.

This study recruited over 1300 smokers in primary care clinics. All were motivated to quit. Mean age = 44; age at first cigarette 14; cigarettes smoked per day 20; previous quit attempts 6.

Randomized to 5 different pharmacotherapies (provided free of charge), in combination with telephone counseling provided through a state sponsored tobacco quit line. Participants were informed which drug(s) they were to receive.

The 5 pharmacotherapies (all drugs FDA approved): 1) Nicotine patch; 2) Nicotine lozenges 3) Bupropion SR; 4) Bupropion SR + nicotine lozenge; 5) Bupropion SR + nicotine patch.

Cessation counseling was provided by telephone, the Wisconsin Tobacco Quit Line. Among 7100 eligible smokers attending routine primary care medicine, 1300 (19%) enrolled in the study.

Sixty % of those enrolled did not use telephone counseling.

Participants who used fewer than 90 minutes of counseling had an abstinence rate of 20% (almost equal to that of non-users of counseling). Those that had more than 90 minutes of counseling time had an abstinence rate of 36%.

Abstinence rates at 6 months:	%
1) Nicotine patch	18
2) Nicotine lozenge	20
3) Bupropion SR	17
4) Bupropion SR + patch.	27
5) Bupropion SR + lozenge	30

The buproprion + lozenge combination was especially effective relative to the monotherapies, with approximately a doubling of abstinence rates at 6 months.

About 1 in 5 primary care smokers attending primary care are willing to undertake an unplanned quit attempt during a primary care visit that included the opportunity to receive free medication and telephone counseling.

"Assuming that 1 in 5 smokers visiting a primary care clinic for routine care will undertake an unplanned quit attempt and that up to 30 in every 100 of these smokers making a quit attempt could achieve long-term (6 month) cessation, the overall success (defined as long-term abstinence) of this intervention model corresponds to 6 of every 100 primary care-based smokers (ie, all smokers including those who are not motivated to make a quit attempt) achieving long-term abstinence."

Conclusion: Provision of free cessation medications plus quit line counseling arranged in the primary care setting holds promise for assisting large numbers of smokers to quit.

The trial concluded that counseling + drugs, not drugs alone, was essential to achieve abstinence.

Some of these smokers must have relapsed after the trial concluded. Try, try again.

Achieving a success rate of 6% is a major public health achievement.

"Suggesting A New Avenue For Therapeutic Exploration"

12-7 ANEMIA AND IRON DEFICIENCY--NEW THERAPEUTIC TARGETS IN HEART FAILURE?

Anemia in patients with heart failure (**HF**) ranges from 10% for patients with mild HF, to over 40% in patients with advanced HF

Anemia in HF has been associated with old age, diabetes, chronic renal dysfunction, more advanced HF, lower peak exercise capacity, and worse health-related quality-of-life metrics.

Anemia is a powerful predictor of hospitalization and survival in chronic HF.

A complex interaction between impaired cardiac performance, activation of neurohumoral and inflammatory responses, drug effects, renal dysfunction, and bone marrow hypo-responsiveness appears to contribute to the anemia.

Iron deficiency may also be due to the effect of HF on absorption of dietary iron. Gastrointestinal malabsorption, long-term aspirin, and uremic gastritis may add to iron deficiency.

Chronic iron deficiency may, by itself, cause ultrastructural alterations in cardiomyocytes.

Since anemia is closely associated with poor clinical outcomes among patients with HF, it is logical to consider whether correcting anemia may improve functional capacity and survival.

A study in this issue of NEJM (*see the full abstract for citation*) reported the effect of intravenous iron given to patients with mild to moderate HF.

The administration of iron convincingly improved self-reported Patient Global Assessment and NYHA functional class; 50% reported they were much or moderately improved as compared with 23% in the control group. The degree of improvement was similar in patients without anemia and those with anemia.

Patients receiving iron also improved their 6-minute walk distance by 30 m.

I abstracted this article because it presents an entirely new aspect of treatment of HF. Primary care clinicians, keep it in mind

"The Potential Devastation Of Lemierre Syndrome Deserves Our Consideration."

12-8 EXPAND THE PHARYNGITIS PARADIGM FOR ADOLESCENTS AND YOUNG ADULTS

Recent evidence suggests that *Fusobacterium necrobacterium* may cause as many as 10% of cases of pharyngitis in adolescents. *F necrophorum* can cause a severe complication of pharyngitis--Lemierre syndrome.

Lemierre described a clinical syndrome (1936) in adolescents whose illness started with tonsillitis. Although they improved initially, the adolescents developed clinical signs of bacteremia, including rigors, after about 4 days. They developed suppurative thrombophlebitis of the internal jugular vein and metastatic infections (most commonly pulmonary abscesses) due to *F necrobacterium*. The mortality rate was high.

Lemierre syndrome remains life threatening. Patients may require intensive care, intubation and drainage of abscesses. Convalescence may be long.

Most patients present with pharyngitis several days before the Lemierre syndrome develops. Thus treating *F necrobacterium* with appropriate antibiotics could prevent Lemierre syndrome.

It is estimated that *F necrobacterium* causes about 10% of acute pharyngitis in adolescents. The risk of Lemierre syndrome after *F necrobacterium* infection is likely higher than the risk of rheumatic fever after a streptococcus infection.

The diagnostic paradigm of pharyngitis in adolescents and young adults should include both group A beta-hemolytic streptococcal and *F necrobacterium* pharyngitis. (The current paradigm supports teaching students to look for streptococcus [with a rapid test] and otherwise avoid antibiotics.)

The author suggests that, until we have better data, we should treat adolescents and young adults who present with at least 3 of the following for *F necrobacterium*: 1) fever, 2) tonsillar exudates, 3) swollen tender anterior cervical adenopathy, and 4) lack of cough.

Macrolides (eg, erythromycin) are *not* effective against *F necrobacterium.* Penicillin-metronidazole or clindamycin should be used.

Lemierre syndrome has been termed a "forgotten disease".

F necrobacterium is a gram negative anaerobic non-spore forming bacterium well known to veterinarians. It is a common animal pathogen. It is a normal inhabitant of the human oropharynx.

Primary care clinicians should remember Lemierre syndrome. Early treatment may be life-saving.

Dr Robert Centor, the author of this article, proposed rapid clinical criteria for diagnosing group A streptococcal pharyngitis:

Fever

Tonsillar exudate

Tender anterior cervical adenopathy

Absence of cough.

The criteria must now include F necrobacterium infection.

"A Public Health Problem"

12-9 PERCEIVED INSUFFICIENT REST OR SLEEP AMONG ADULTS: United States, 2008

The importance of chronic sleep insufficiency is under-recognized as a public health problem. It is associated with numerous physical and mental health problems: injury, loss of productivity, and mortality.

About 29% of US adults report sleeping less than 7 hours per night. Millions have chronic sleep and wakefulness problems.

This report summarizes the results of a survey of 50 states and 3 territories in 2008. Among 403 981 respondents, 31% had no difficulty sleeping (reported no days of insufficient sleep or rest during the preceding 30 days), 41% reported 1 to 13 days of insufficient sleep, 17% reported 14-29 days, and 11% reported insufficient rest or sleep every day during the preceding 30 days

Health care providers should consider adding an assessment of chronic rest or sleep insufficiency to routine office visits so they can make needed interventions or referrals to sleep specialists.

According to the National Sleep Foundation, adults need 7 to 9 hours of sleep each night. Primary care clinicians should evaluate patients who report chronic insufficient sleep and advise them of effective behavioral strategies including keeping a regular sleep schedule, and avoiding stimulating activities within 2 hours of bedtime.

"Pharmacological intervention also might be warranted."

Primary care clinicians are very well aware of how common sleep problems are. I would guess that the major response to a complaint about sleep would be to reach for the prescription pad.

Is this the best response? Would not a try at improving sleep hygiene be the best first step?

I have had no experience with sleep specialists. They might help a minority of patients, but the burden remains on primary care.

Information about sleep hygiene and a print-out to give patients can be obtained at:

www.sleepfoundation.org/article/ask-the-expert/sleep-hygiene

ABSTRACTS DECEMBER 2009

Aim for 5 Grams of NaCl Daily, or Less

12-1 THE CASE FOR POPULATION-WIDE SALT REDUCTION GETS STRONGER

Excess intake of sodium chloride has an important and probably predominant role in the pathogenesis of raised BP.

On average, as salt intake increases, BP increases.

The importance of this association cannot be overstated. The evidence is indisputable.

Worldwide, raised BP accounts for 62% of strokes, and 49% of coronary heart disease events.

Treatment to reduce BP prevents stroke and CHD events.

This compelling evidence has led numerous authorities to conclude that salt reduction would prevent stroke and CHD. But direct evidence to support calls for salt reduction has been limited.

Several studies have estimated the societal benefits of population-wide salt reduction. One study estimated that across 23 countries with a high burden of chronic disease, 850 000 lives would be saved each year from a reduction in salt intake to 5 grams daily. This is the recommended limit set by the WHO.

A recent analysis reported that an average daily intake of 5.8 gram NaCl (2300 g sodium; the recommended upper limit in the US) would reduce the prevalence of hypertension by 11 million, save $18 billion in health care costs, and gain 312 000 quality adjusted life years. This line of reasoning, however, is indirect.

Direct evidence has come from clinical trials and prospective observational studies with cardiovascular disease (**CVD**) events as outcomes. To date, 3 trials have reported the effects of reduced sodium. Two trials tested lifestyle interventions that focused on reducing salt intake. One trial tested the effects of a reduced sodium salt that was high in potassium. In each instance, clinically important CVD events were reduced by 21-41% in people who received an intervention to reduce sodium intake. Direct evidence, albeit limited, is consistent with indirect evidence on the benefits of salt reduction.

However, because of large day-to-day variations in salt consumption, imprecise and inaccurate assessment of dietary intake, results from prospective observational studies have been inconsistent and occasionally paradoxical.

A meta-analysis in this issue of BMJ[1] is a welcome addition to the medical literature.

The meta-analysis included 13 cohort studies and 19 independent samples, which demonstrated a higher salt intake is associated with increased incidence of stroke. A 5 gram increase in salt intake was associated with a 23% higher risk of stroke. And a 17% higher risk of CVD.

The disparate and often poor quality of measurements of dietary salt intake contributes to the significant heterogeneity of study results. (The gold standard for salt intake is the 24-hour excretion of sodium assessed by multiple complete 24-hour urine collections. No studies included these measurements.) Some studies reported a substantial under-reporting of salt intake.

"The case for population-wide salt reduction is now stronger."

BMJ December 5, 2010; 339: 1266-67 Editorial by Lawrence J Appel, Johns Hopkins University, Baltimore MD

1 "Salt Intake, Stroke, and Cardiovascular Disease: Meta-analysis of Prospective Studies" BMJ December 5 , 2009: 339: 1296 doi.10.1136/bmj.b4567 Research article, first author Pasquale Stazzullo, Frederico II University of Naples, Italy.

The research article is published in full in the doi.

The study included 177 000 participants followed for 3.5 to 19 years.

The pooled relative risk indicated a 23% greater risk of stroke for an average difference in sodium intake equivalent to 5 grams of NaCl. RR of stroke = 1.23

And a RR of cardiovascular disease. of 1.17

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Perfect Protection for 6 Years, And Likely Longer

12-2 SUSTAINED EFFICACY AND IMMUNOGENICITY OF THE HUMAN PAPILLOMA VIRUS (HPV)-16/18 AS0-4-ADJUVATED VACCINE

Cervical cancer (**CC**) is the second most common malignant disease in women. It carries substantial societal effects since it affects women at a younger age.

Infection with oncogenic human papilloma virus (**HPV**) is the necessary cause of CC. Fifteen oncogenic types have been identified. Most (70%) CC is caused by types related to HPV 16 and 18. Other common types are 31, 33, 45, 52, and 58.

Vaccines for HPV have to provide long-term protection, since the risk of acquiring an infection begins with sexual debut and continues through life.

Serum neutralizing antibodies are believed to be a major basis of protection offered by HPV vaccines.

Women with a naturally acquired infection remain at risk for a new infection with the same HPV type possibly because antibody concentrations after natural infection are low and do not offer sufficient protection.

This HPV 16/18 ASO-4 vaccine is adjuvated by a system comprised of aluminum salt and the immunostimulatory molecule ASO4.[1] This adjuvated vaccine produces consistently higher antibody titers, which are sustained over a longer period, together with a higher frequency of memory B cells than do the same antigens adjuvated with aluminum only.

This study reports results of the 16/18 vaccine over 6.4 years.

STUDY

1, Multicountry study (27 sites), begun in 2003 and continued through 2007, entered healthy young women (age 15-25; n = 776). All had normal cervical cytology, were HPV 16 and 18 seronegative, and were DNA negative by PCR for 14 oncogenic HPV types in their cervical cells.

2. Randomized, double-blind to:

   1) Three doses of 16/18 adjuvated vaccine, or

   2) Placebo

3. Followed periodically up to 6.4 years after the first vaccine dose. Tested cervical samples for

   A. 14 oncogenic types by PCR

   B. Cervical cytology

   C. Total IgG antibodies for HPV 16 and 18

4. Primary objective = long-term vaccine efficacy in prevention of incident cervical infection with HPV 16 or 18 or both.

RESULTS

1. Ninety percent of subjects completed the trial.

2. Mean follow-up = 5.9 years; maximum follow-up = 6.4 years.

3. Infection with 16/18:

	Vaccine (n = 401)	Placebo (n = 373)
Incident infection	4	70
6-month persistent infection	0	34
12-month persistent infection	0	20

(The vaccine was considered 100% effective against persistent infection with 16/18. This was despite recurrent exposure to the viruses over 6 years.)

4. Cytology: Associated with 16/18

	Vaccine (n = 481 to 505)	Placebo (n - 470 to 497)
CIN 1+	0	15

CIN 2+	0	9

(The vaccine was considered 100% effective against development of CIN.)

5. There was also some evidence of effectiveness against other types of HPV:

Incident infection (6 years)	16/18 Vaccine	Placebo
HPV type 31	13	30
HPV type 45	5	21

6. Immune response to vaccine: Neutralizing antibodies and IgG antibodies for 16 and 18 remained remarkably stable over years at 5 to 13 times higher than the immunity produced by natural infections.
7. Safety: The vaccine was well tolerated. A similar number of women in both the vaccine group and the placebo group reported adverse events. No serious event was judged to be related or possibly related to vaccination. Over 130 pregnancies occurred in both groups without any difference in outcomes.

DISCUSSION

1, "The HPV-16/18 AS04-adjuvated vaccine in healthy women age 15-25 years provides high, sustained efficacy up to 6.4 years against HPV 16/18 infections and cytological endpoints, associated with high and persistent concentrations of total and neutralizing antibodies against HPV 16 and HPV 18."
2. There was 100% vaccine efficacy against CIN1+ and CIN 2+ associated with HPV 16. and 18.
3. The study population was continuously exposed to HPV infections.
4. There was also some cross protection against HPV-31 and HPV-45 incident infection.
5. There was a favorable safety profile.
6. Vaccine efficacy against cytological ASC-US or greater or would save many interventions with colposcopy and other follow-up, and reduce costs.
7. Although 16/18 cause roughly 50% of high grade squamous intraepithelial lesions, vaccine efficacy reached 72% against any CIN 2+, an indication that the vaccine is able to confer some protection beyond 16/18.
8. Because the incidence of CC peaks on average more than 30 years after adolescence, vaccine has to confer protection for many years. Six years of protection is the longest time span so far.
9. The sustained production of antibodies likely indicate both the generation of long-lived plasma cells and the induction of memory cells that replenish the plasma cell pool. The ASO4-adjuvant is likely a key factor. "We expect protection to continue for many more years."

CONCLUSION

The vaccine conferred a high level of protection against HPV 16/18 and associated cytohistological endpoints for 6.4 years.

It also offered some cross protection against HPV types 31 and 45.

Lancet December 12, 2009; 374: 1975-85 Original investigation by the GlaxcoSmithKline Vaccine HPV-007 Study group. Correspondence to Barbara Romanowski, University of Alberta, Canada. Funded by GlaxcoSmithKline

1 3-O-desacyl-4 monophosphoryl lipid A This was my introduction to this compound. I know nothing about it.

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"Cluster Headache Is Probably The Most Severe Pain Known To Humans."

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Cluster headache (**CH**) is a stereotypic primary headache syndrome characterized by attacks of unilateral excruciating pain, usually in the eye, periorbital region, and temple, with associated cranial autonomic symptoms such as conjunctival injection, lacrimation, nasal blockage, rhinorrhea, ptosis, and eyelid edema. During attacks, patients are often restless and agitated,

Untreated, attacks usually last for 15-180 minutes and have a frequency of 1 every other day to up to 8 attacks per day.

Attacks usually occur in bouts or clusters lasting for weeks or months, separated by remissions lasting months or years. There are two types of CH:

1) Episodic: bouts lasting up to 7 days or more with breaks of 1 month or more between bouts. Bouts usually occur once a year.
2) Chronic: occurring for more than a year without remission, or with remissions lasting less than one month.

CH attacks may occur with clocklike regularity during the day and may be precipitated by sleep, usually occurring 90 minutes after onset of sleep.

CH affects more men than women. Prevalence is estimated at 3 per 1000 in the general population.

"Cluster headache is probably the most severe pain known to humans."

Treatment relies on therapy to abort the individual attack, and prophylactic therapy to prevent or suppress attacks when they occur. Therapy for attacks must be fast-acting.

Serotonin receptor agonists are the most effective treatment for acute CH:

1) Sumatriptan, (*Imitrex*; GlaxoSmithKline) administered by injection or by nasal spray. It is effective within 15-30 minutes. (Subcutaneous currently licensed for acute attacks)

2) Zolmitriptan (*Zomig*; AstraZeneca) orally is effective at 30 minutes in episodic CH only. Intranasally, it is effective in both forms.

Drawbacks for triptans include limitations of daily usage in order to prevent tachyphylaxis and rebound. Triptans are contraindicated in patients with cardiovascular disease.

High-dose oxygen has been used in the past for episodic CH, alone or combined with other therapy This article presents a controlled trial of oxygen in treatment of acute attacks of CH.

STUDY

1. Randomized, placebo-controlled, double-blind crossover study (2002-2007) compared;
   1) 100% oxygen at 12 L/min delivered by a facemask for 15 minutes from the beginning of an attack, or
   2) Air delivered the same way.
2. Participants (n = 109; mean age 39) stayed in the study long enough to treat 4 attacks. They were treated in their homes.
3. Included patients with either episodic or chronic CH. All had experienced between one attack every other day to 5 a day. The duration of the attacks was between 45 minutes and 3 hours.
4. Patients with both migraine and CH were included if they could distinguish between the two.
5. Patients were required to record treatment effects on diary cards.
6. All patients crossed over after 2 treated attacks.
7. After 15 minutes, patients who experienced no relief could take any rescue medication they wished.
8. Primary endpoint for effectiveness of treatment: pain free in 15 minutes, or adequate relief at 15 minutes. (Pain was rated as 0, 1 for mild, 2 for moderate, 3 for severe, and 4 for very severe.)
9. Secondary endpoints: pain free at 30 minutes; reduction in pain scale at 15, 30, 45, and 60 minutes (ie, reduction in pain to at least one point less severe than the start of the headache), need for rescue medication at 15 minutes, overall response to treatment and overall disability, and effect on associated symptoms.
9. Global response to treatment was considered positive if the patient indicated “good” or “excellent”, and negative if “no effect” or moderate effect”.

RESULTS

1. Randomized 109 patients. 33 did not receive treatment because they came out of bout, were lost to follow-up, or withdrew, 76 actually received treatment: 57 with episodic CH and 19 with chronic CH were available for the intention-to-treat analysis. Most patients received 4 treatments.

2. Characteristics of patients	Randomized (n = 109)	Completed trial (n = 76)
Age	39	39
Male	82%	84%
Episodic	74%	75%
Chronic	26%	25%
Years with CH	12	11

3. At end point:	O2	AIR
No of attacks treated	50	148
Pain free at 15 min	78%	20%

(By my calculation, the NNT with oxygen to render one patient pain-free at 15 minutes = 2 RTJ)

Reduction of pain (%)		
15 min	68	20
20 min	81	30
30 min	85	38
60 min	92	59
Need for rescue meds within 15 min (%)	28	53

4. At all time points, oxygen was superior to air in reducing secondary endpoints.
5. No serious adverse effects.

DISCUSSION

1. A strength of this crossover study came from the extraordinary commitment of the patients. Only one patient withdrew who could have completed further treatments, and 2 stopped because their bout stopped.
2. Current data and clinical practice advises: the use of sumatriptan subcutaneously or by nasal spray, or zolmitriptan intranasally for treatment of an acute attack. Triptan agents have their drawbacks: contraindicated in ischemic heart disease and vascular disease. Use is limited to twice daily (subcutaneously) or 3 times daily (intranasally). Oxygen use is not limited.

3. A head-to-head comparison of triptans and oxygen is warranted.
4. Many patients with CH are smokers. Care in use of oxygen in these patients.

CONCLUSION

Treatment of patients with CH at symptom onset using inhaled high-flow oxygen compared with placebo was more likely to result in being pain-free at 15 minutes.

JAMA December 9, 2009: 302: 2451-57 Original investigation, first author Anna S Cohen, National Hospital for Neurology and Neurosurgery, London, UK

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12-4 MORE EVIDENCE ON LOW VITAMIN D LEVELS FUELS PUSH TO REVISE RECOMMENDED INTAKE

Many studies report that D deficiency and insufficiency are tied to poor health outcomes from a variety of conditions in a large proportion of the U.S, population. Conditions cited include osteoporosis and bone fracture, muscle weakness, cancer, respiratory tract illnesses, auto-immune disease, diabetes, schizophrenia, depression, lung dysfunction, kidney disease, and cardiovascular disease.

The studies are mainly retrospective. This makes it difficult for regulatory bodies or specialty societies to develop specific recommendations for raising levels for minimum D intake. And leaves some physicians reluctant to aggressively diagnose and treat patients for deficiency.

We know that D prevents rickets. We need randomized clinical trials of see if supplementation has effects on non-traditional outcomes.

The National Health and Nutrition Examination Survey (2001-2004) found that, among over 9700 children and young adults, 9% had deficiency in 25-OH-D (<15 ng/mL), and 61% had insufficiency (15-29 ng/mL). Deficiency was associated with increased parathyroid hormone levels, higher systolic BP, lower serum calcium, and lower HDL-cholesterol levels compared with D sufficiency. (*Pediatrics* 2009) Another study published in *Pediatrics* reported low D levels were strongly associated with overweight and abdominal obesity. And levels were inversely associated with systolic BP and plasma glucose levels. Another study reported D levels were lower in girls than in boys, and also lower in black and Mexican American children than in white children. (The pigmentation of blacks retards sunlight absorption.)

“Vitamin D used to be all about rickets, and whatever the level you needed to prevent rickets was the accepted level. But as other risk factors have arisen, the recommended level should also be on the rise.”

Other observers have expressed cautioned that the evidence that D is associated with various disease processes is epidemiological. This does not establish cause and effect. Randomized, controlled trials are needed.

Nevertheless, there has been some movement on minimal acceptable D intake. In 2008 the American Academy of Pediatrics recommended increasing daily intake from 200 IU to 400 IU for all infants, children, and adolescents beginning at the first days of life. The recommendation cited evidence for a potential role of D in helping to maintain innate immunity and prevention of diabetes and cancer.

The Institute of Medicine is scheduled to report regarding D intake in May 2010. It is expected that it will emphasize an increased intake of D and encourage its further use as a food additive. The IOM will look beyond bone health to consider other chronic diseases. Currently the IOM recommends that the upper intake should be limited to 1000 IU for infants up to age 1 and 2000 daily for all over age 1.

Manufacturers are reluctant to fortify foods for fear of toxicity. Others state that D is safe and the risks of reaching toxic levels are overstated. The IOM stated that it will give priority to examining whether a critical adverse effect can be selected that will allow the determination of a benchmark intake.

JAMA December 16, 2009; 302: 2527-28 "Medical News and Perspective" reported by Mike Mitka, JAMA Staff.

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A Problem Especially In Young Women With Aural Migraine Who Smoke And Use Oral Contraceptives

12-5 MIGRAINE WITH AURA AND INCREASED RISK OF ISCHEMIC STROKE

Migraine, a prevalent chronic condition, is characterized by a hyper-responsive nervous system that predisposes to recurrent episodes of autonomic disturbance.

Roughly one quarter of people with migraine experience temporary neurological symptoms (aura) before onset of the headache. Aura is distinguished from other causes of brief recurrent neurological disturbance (e, TIA) by its gradual onset and disappearance, and its shorter duration.

Visual disturbances are the most common form of aura. Sensory and motor auras also occur. To identify patients with aura, it is necessary to detect only visual aura, since 99% of people with non -visual aura also have visual aura occasionally.

The visual aura rating scale:

Duration 5 to 60 minutes	3 points
Develops gradually over 5 minutes	2

Scotomata	2
Zigzag lines	2
Unilateral visual loss	1
Total	10

Diagnosis of migraine with aura requires 5 or more points. (Sensitivity 91%; specificity 96%)

Sensitivity to light and visual blurring are common in patients with migraine, and should not be confused with aura.

A connection between migraine and vascular events such as stroke has long been suspected.

A study in this issue of BMJ[1] clearly shows that the increased risk of ischemic stroke in patients with migraine is largely confined to those with aura. The risk of TIA and angina is also related to aura. Hemorrhagic stroke is not.

Patients with aura should be followed closely and treated aggressively for modifiable cardiovascular disease risk factors. But information to patients with aura should be put in context. The absolute risk of stroke is low, so a doubling of the risk is not cause for panic. At the population level, the risk deserves attention because the prevalence of migraines is so high.

The study also found the risk of ischemic stroke in patients with migraine is magnified by the combination of smoking and contraceptive use, mostly in women under age 45. Incidence of stroke is also increased in patients with frequent migraine.

Clinicians need to identify young women with aural migraine, particularly those who seek estrogen-containing contraception. Those without aura should not be denied the benefits of hormonal contraception.

If hormonal contraception is used, it should contain the lowest tolerated dose of estrogen. It should be stopped if auras become more frequent and complex.

BMJ October 31, 2009; 339: 981-82 Editorial by Elizabeth Loder, Harvard Medical School, Boston Mass.

1 Migraine and Cardiovascular Disease: Systematic review and meta-analysis, first author Markus Schurks, Harvard Medical School, Boston Mass.

"Migraine almost doubles the risk of ischemic stroke, a finding driven by the subgroup of people who have migraine with aura, but does not alter the risk of myocardial infarction and death from cardiovascular disease." doi:10.1136/bmj.b3914

The abstract above is based on an abridged form of the longer original publication. I accessed the long pdf form through the doi to add some detail.

Pooled relative risk (**RR**) of ischemic stroke in persons with migraine with aura = 2.16 (CI = 1.53 to 3.03)

Pooled RR in persons with migraine without aura =1.23 (CI = 0.90 to 1.69) Not significant.

RR for age under 45 vs the overall group = 2.65 (CI 2.21 to 6.04)

Three studies reported RR of angina. RR= 1.29 (CI = 1.12 to 1.47)

RR for TIA was higher than for ischemic stroke. RR = 2.34 (CI 1.90 to 2.88)

Migraine is 4 times more common in women.

RR of ischemic stroke in women with migraine = 2.08 (CI 1.13 to 3.84) Not significant in men.

RR of ischemic stroke in migrainous women smokers = 9.03; in oral contraceptive users = 7.02

Only one study investigated the association between women with migraine with aura and myocardial infarction, showing a 2-fold risk of MI and cardiac death. .

Unfortunately, the study could not determine the absolute risks of stroke.

Migraine affects 10% -20% of the population, during their working lives. Up to 1/3 experience aura. Migraine with aura is common. Associated ischemic stroke on a population basis is a substantial public health problem.

The authors caution that there are many limitations to the study.

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Six of Every 100 Primary Care-Based Smokers Could Achieve Abstinence

12-6 COMPARATIVE EFFECTS OF 5 SMOKING CESSATION PHARMACOTHERAPIES IN PRIMARY CARE CLINICS

Progress has been made over the past 40 years. Prevalence of smoking in the US has declined from 42% to 20%. In part, these declines have been due to development of effective cessation treatments.

Most data on cessation comes from placebo-controlled trials conducted under ideal conditions, with motivated volunteers, inducements for participation, and extensive participant contact.

There have been few direct head-to-head comparisons of multiple pharmacotherapies in real world settings.

Primary care is the ideal environment in which to study comparative effectiveness of cessation treatments:

1) Many smokers report being receptive to advice from their primary care provider (**PCP**).

2) More than 70% of smokers visit their PCP annually.

3) Health considerations are especially salient in a clinical setting, making patient visits "teachable moments".

4) A majority of smokers express interest in cessation treatment. Many prefer more

intensive treatment.

5) Primary care based cessation treatments are cost effective.

The Public Health Service guidelines recommend brief counseling and cessation medication for smokers. This will increase likelihood of successful quitting.

This study addressed two questions:

1) When smoking cessation medication and counseling are offered at no cost in the primary care setting, what percentage of eligible smokers will make a quit attempt?

2) What are the abstinence rates of 5 different cessation pharmacotherapies in the real world of primary care?

STUDY

1. Recruited over 1300 smokers in primary care clinics. All were motivated to quit.
   Mean age = 44; age at first cigarette 14; cigarettes smoked per day 20; previous quit attempts 6
2. Randomized to 5 different pharmacotherapies (provided free of charge), in combination with telephone counseling provided through a state sponsored tobacco quit line. Participants were informed which drug(s) they were to receive.
3. The 5 pharmacotherapies (all drugs FDA approved): 1) Nicotine patch; 2) Nicotine lozenges 3) Bupropion SR; 4) Bupropion SR + nicotine lozenge; 5) Bupropion SR + nicotine patch.
4. Cessation counseling was provided by telephone, the Wisconsin Tobacco Quit Line.
5. Primary outcome = 7-day point prevalence abstinence at 1 week, 8 weeks, and 6 months after quitting. And number of days to relapse.

RESULTS

1. Among 7100 eligible smokers attending routine primary care medicine, 1300 (19%) enrolled in the study.
2. Forty % of those enrolled completed at least one counseling call.
3. Participants who used fewer than 90 minutes of counseling had an abstinence rate of 20% (almost equal to that of non-users of counseling). Those that had more than 90 minutes of counseling time had an abstinence rate of 36%.
4. Abstinence rates at 6 months: %
   1) Nicotine patch 18
   2) Nicotine lozenge 20
   3) Bupropion SR (*Zyban*; GSK) 17

4) Bupropion SR + patch. 27

5) Bupropion SR + lozenge 30

5. Of those who relapsed, the Bupropion SR + nicotine lozenge group had more days to relapse than any other group (83 days vs patch alone 59 days)

DISCUSSION

1. Combination therapies for smoking cessation were superior to the three monotherapies.
2. The bupropion + lozenge combination was especially effective relative to the monotherapies, with approximately a doubling of abstinence rates at 6 months.
3. Results were similar to another randomized, controlled efficacy study[1] that tested the same 5 treatments. The study also reported that the combined drugs were superior to monotherapies in achieving 6 month abstinence.
4. The 2008 Public Health Guidelines[2] also comment that combined therapy results in significantly higher long-term abstinence.
5. About 1 in 5 primary care smokers attending primary care are willing to undertake an unplanned quit attempt during a primary care visit that included the opportunity to receive free medication and telephone counseling.
6. There is evidence that self-reported abstinence rates are generally accurate in low-contact effectiveness studies.
7. A majority of subjects in this study did not use quit-line abstinence counseling.
8. "Assuming that 1 in 5 smokers visiting a primary care clinic for routine care will undertake an unplanned quit attempt and that up to 30 in every 100 of these smokers making a quit attempt could achieve long-term (6 month) cessation, the overall success (defined as long-term abstinence) of this intervention model corresponds to 6 of every 100 primary care-based smokers (ie, all smokers including those who are not motivated to make a quit attempt) achieving long-term abstinence."

CONCLUSION

Provision of free cessation medications plus quit line counseling arranged in the primary care setting holds promise for assisting large numbers of smokers to quit.

Archives Internal Medicine December 14/28 2009; 169: 2148-55 Original investigation, first author Stevens S Smith, University of Wisconsin School of Medicine and Public Health, Madison.

1 "A Randomized, Placebo-Controlled Clinical Trial of 5 Smoking Cessation Pharmacotherapies"

Archives General Psychiatry 2009; 66: 1253-62

All states have quit lines offering counseling free of charge Call 1-800-quitnow 1-800-784 8669
More information at www.freeclear.com

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"Suggesting A New Avenue For Therapeutic Exploration"

12-7 ANEMIA AND IRON DEFICIENCY--NEW THERAPEUTIC TARGETS IN HEART FAILURE?

Anemia in patients with heart failure (**HF**) ranges from 10% for patients with mild HF, to over 40% in patients with advanced HF. The prevalence is similar among those with systolic dysfunction as among patients with preserved systolic function.

Anemia in HF has been associated with old age, diabetes, chronic renal dysfunction, more advanced HF, lower peak exercise capacity, and worse health-related quality-of-life metrics.

Anemia is a powerful predictor of hospitalization and survival in chronic HF.

A complex interaction between impaired cardiac performance, activation of neurohumoral and inflammatory responses, drug effects, renal dysfunction, and bone marrow hypo-responsiveness appears to contribute to the anemia.

In a minority of cases, the cause may be dilutional rather than a true decrease in red-cell mass.

The erythropoietin level is typically increased in proportion to the severity of HF, but to a lesser degree than expected for the severity of the anemia. This suggests a blunted erythropoietin production.

As the hemoglobin level decreases, levels of circulating cytokines increase, leading to inhibition of renal erythropoietin and bone marrow erythroid progenitor cells. Increases in interleukin levels leads to blockage of duodenal absorption of iron, and prevents the release of iron from total body stores.

Iron deficiency may also be due to the effect of HF on absorption of dietary iron. Gastrointestinal malabsorption, long-term aspirin, and uremic gastritis may add to iron deficiency.

Chronic iron deficiency may, by itself, cause ultrastructural alterations in cardiomyocytes.

Since anemia is closely associated with poor clinical outcomes among patients with HF, it is logical to consider whether correcting anemia may improve functional capacity and survival. Thus, iron supplementation may be beneficial in patients with HF who have iron deficiency regardless of whether anemia is present.

A study in this issue of NEJM[1] reported the effect of intravenous iron given to patients with mild to moderate HF due to left ventricular systolic dysfunction, NYHA class II or III symptoms, depressed left ventricular ejection fraction, and documented iron deficiency. Overall, 84% of patients had class III

NYHA symptoms, mean left ventricular ejection fraction was 32%, serum ferritin 52 ug; 50% had anemia.

Patients were randomized to 200 mg intravenous iron (vs infused saline as control) weekly until iron stores were replete.

The IV iron rapidly increased ferritin levels to normal. And increased the hemoglobin levels in those who were anemic by 9 g per liter.

The administration of iron convincingly improved self-reported Patient Global Assessment and NYHA functional class. 50% reported they were much or moderately improved as compared with 23% in the saline group. The degree of improvement was similar in patients without anemia and those with anemia. (The reason why remains unclear.)

Patients receiving iron also improved their 6-minute walk distance by 30 m.

The study was not large enough to assess the effect of iron on patients with NYHA class II, so the effect of iron on patients with mild symptoms is not known.

This trial suggests a new avenue for therapeutic exploration.

NEJM December 17, 2010; 361:2475-76 Editorial by G William Dec, Massachusetts General Hospital, Boston.

1 "Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency " NEJM December 17, 2010; 361: 2436-48 by the Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure (FAIR-HF) Trial Investigators, first author Stefan D Anker, Charite Universitatsmidizin, Berlin Germany

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"The Potential Devastation Of Lemierre Syndrome Deserves Our Consideration."

12-8 EXPAND THE PHARYNGITIS PARADIGM FOR ADOLESCENTS AND YOUNG ADULTS

Currently, the focus on diagnosis and treatment of pharyngitis is on beta-hemolytic streptococcal infection.

Recent evidence suggests that *Fusobacterium necrobacterium* may cause as many as 10% of cases of pharyngitis in adolescents. *F necrophorum* can cause a severe complication of pharyngitis--Lemierre syndrome.

We should revise our diagnostic paradigm for pharyngitis in young adults (age 15-24) to include both group A streptococcus and *F necrobacterium*.

Lemierre described a clinical syndrome (1936) in adolescents whose illness started with tonsillitis. Although they improved initially, the adolescents developed clinical signs of bacteremia, including rigors, after about 4 days. They developed suppurative thrombophlebitis of the internal jugular vein and metastatic infections (most commonly pulmonary abscesses) due to *F necrobacterium*. The mortality rate was high.

Our current paradigm for pharyngitis started in the 1950s with the explicit goal of decreasing the incidence of acute rheumatic fever due to beta-hemolytic streptococcal infections. Now rheumatic fever is rare.

Lemierre syndrome remains life threatening. Patients may require intensive care, intubation and drainage of the abscess. Convalescence may be long.

Most patients present with pharyngitis several days before the Lemierre syndrome develops. Thus treating *F necrobacterium* with appropriate antibiotics could prevent Lemierre syndrome.

A recent PCR study of pharyngeal cultures in patients with pharyngitis yielded group A streptococci in 11% and *F necrobacterium* in 10%. In patients with pharyngitis negative for streptococci, *F necrobacterium* DNA was present in about 50% About 20% of healthy control subjects also tested positive. It is estimated that *F necrobacterium* causes about 10% of acute pharyngitis in adolescents.

Group A streptococcus and *F necrobacterium* each cause approximately 14% of acute ear, nose and throat infections requiring hospitalization.

The risk of Lemierre syndrome after *F necrobacterium* infection is likely higher than the risk of rheumatic fever after a streptococcus infection.

The diagnostic paradigm of pharyngitis in adolescents and young adults should include both group A beta-hemolytic streptococcal and *F necrobacterium* pharyngitis. (The current paradigm supports teaching students to look for streptococcus [with a rapid test] and otherwise avoid antibiotics.)

Lemierre syndrome rarely occurs in pre-adolescence. The incidence in older adults is low. “The paradigm for that group does not need to be changed.”

The author suggests that, until we have better data, we should treat adolescents and young adults who present with at least 3 of the following for *F necrobacterium*: 1) fever, 2) tonsillar exudates, 3) swollen tender anterior cervical adenopathy, or 4) lack of cough.

Macrolides (eg, erythromycin) are *not* effective against *F necrobacterium.* Penicillin-metronidazole or clindamycin should be used.

Normally, pharyngitis resolves in 3 to 5 days. When the disease does not resolve quickly, or unilateral neck swelling develops, consider an expanded differential diagnosis: peritonsillar abscess,

Lemierre syndrome, group A, C or G streptococcal pharyngitis, infectious mononucleosis, and acute HIV infection.

"The potential devastation of Lemierre syndrome deserves our consideration."

Annals Internal Medicine December 1, 2009; 151: 812015 "Perspective" by Robert M Centor, University of Alabama.

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"A Public Health Problem"

12-9 PERCEIVED INSUFFICIENT REST OR SLEEP AMONG ADULTS: United States, 2008

The importance of chronic sleep insufficiency is under-recognized as a public health problem. It is associated with numerous physical and mental health problems: injury, loss of productivity, and mortality.

About 29% of US adults report sleeping less than 7 hours per night. Millions have chronic sleep and wakefulness problems.

This report summarizes the results of a survey of 50 states and 3 territories in 2008. Among 403 981 respondents, 31% had no difficulty sleeping (reported no days of insufficient sleep or rest during the preceding 30 days), 41% reported 1 to 13 days of insufficient sleep, 17% reported 14-29 days, and 11% reported insufficient rest or sleep every day during the preceding 30 days. Females (12%) were more likely than males (10%) to report insufficient sleep. Adults under age 45 were more likely to report more days of insufficient sleep. Retired persons (44%) were more likely to report no difficulty in sleeping.

Health care providers should consider adding an assessment of chronic rest or sleep insufficiency to routine office visits so they can make needed interventions or referrals to sleep specialists.

Of interest, sleep insufficiency varied between states: 7% in North Dakota and 19% in West Virginia. The highest prevalence of sleep disturbance was in the southeastern US. The exact cause of this variation could not be determined. It may be associated with variations in occupational factors: shift work, lifestyle choices, common chronic disease such as obesity, depression, hypertension, and stroke, many of which are concentrated in the Southeast.

Racial and ethnic minorities disproportionately report sleep durations that are associated with increased mortality and might contribute to health disparities. Persons unable to work reported the greatest prevalence of rest or sleep insufficiently, which may be due to mental distress or medical problems, disabilities, or other conditions that prevent employment.

According to the National Sleep Foundation, adults need 7 to 9 hours of sleep each night. Primary care clinicians should evaluate patients who report chronic insufficient sleep and advise them of effective behavioral strategies including keeping a regular sleep schedule, and avoiding stimulating activities within 2 hours of bedtime.

"Pharmacological intervention also might be warranted."

JAMA December 16, 2009; 302: 2532-33 MMWR. 2009; 58:1175-1179 from the Center for Disease Control and Prevention Atlanta GA., based on data from the Behavioral Risk Factor Surveillance System.

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