

More Evidence on Safety of Intramuscular Immune Serum Globulin Produced From Plasma Unscreened for Anti-Hepatitis C Virus Antibodies

The recent article by Piazza et al¹ on sexual transmission of the hepatitis C virus (HCV) and efficacy of prophylaxis with intramuscular immune serum globulins (IGs) interested us greatly. The results obtained from this controlled trial showed that HCV can be sexually transmitted by chronically infected patients and provided strong evidence of a protective role of IG produced from unscreened plasma.

More information could be obtained by investigating the presence of HCV RNA by polymerase chain reaction in the IG lots used in this trial. In a recent study,² we showed that 30 (45.5%) of 66 IG lots produced between 1990 and 1992 tested positive for HCV RNA, while 100% of the lots were strongly anti-HCV reactive by third-generation recombinant immunoblot assay. All 41 IG lots produced since 1993 from screened plasma tested negative for both HCV RNA and anti-HCV antibodies. Since IG produced from unscreened plasma was not subjected to any validated viral inactivation and/or removal step, the presence of viral RNA in such products could be a matter of concern. Nevertheless, IG has never been reported to be involved in transmission of HCV. This safety record is still unclear, and, under the present circumstances, debate is expected to continue because of the difficulty in monitoring IG recipients. One can postulate that the low dosage, the route of administration, and the occasional administration play a role in decreasing the risk of transmission of HCV by IG. Moreover, the presence of anti-HCV antibodies has been assumed to reduce the infectivity of the viral particles that may be present.³ Should any of the 4 lots used in the study by Piazza et al¹ be found positive for HCV RNA, this would be the first direct evidence that IG positive for both HCV RNA and anti-HCV antibodies is not infectious.

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In reply

We are grateful to Cristiano et al for raising the question of the presence of HCV RNA in IG prepared from unscreened plasma. Using reverse transcriptase polymerase chain reaction assays, 2 of the batches (11151 and 12069) used in our trial¹ were found to contain viral RNA, while the other 2 (11763 and 11947) did not (A. Weiner, PhD, written communication, November 12, 1997). Although the presence of HCV RNA in IG does not necessarily indicate that the IG is infectious,² our data represent the first direct evidence that IG positive for HCV RNA from unscreened donors is not infectious.

In fact, 450 partners of HCV-infected subjects received 4 mL of IG, prepared from unscreened plasma, every 2 months for a mean of 13.5 months. A total of 3260 doses of IG were administered, about 50% of which were positive for HCV RNA. Intramuscular IG did not cause infection in any of the IG recipients monitored.¹

The safety of IG can be ascribed to both the preparation method (the Cohn method) and the high concentration of neutralizing antibodies contained in unscreened IG.^{1,3} Interestingly, a recent study⁴ demonstrated a lack of infection in a chimpanzee infused with intravenous immunoglobulins containing high titers of both HCV RNA and anti-HCV that included antibodies to viral envelope proteins.

Hepatitis C viral infection is a worldwide scourge for which there is no vaccine and no efficacious preventive measures. This raises the question of exploiting the enormous quantities of HCV neutralizing antibodies contained in the blood units positive for anti-HCV that are at present discarded despite their enormous prophylactic potential.¹

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Depression, Adherence Behavior, and Coronary Disease Outcomes

The review by McDermott et al¹ of studies linking adherence behavior to coronary heart disease outcomes is interesting and provocative. The authors review findings indicating that adherence to placebo is also related to reduced morbidity and mortality and therefore suggest that adherence behavior per se is important in coronary heart disease outcomes. While we agree with the possibility suggested by the authors that "adherence is a marker of some unidentified health care behavior that is itself linked to prognosis," we would like to also propose an alternative explanation that nonadherence is a marker of psychological factors that adversely affect outcome in patients with coronary heart disease, like depression and psychological distress.^{2,3}

We recently assessed 144 patients an average of 3 days after an acute myocardial infarction (MI) to determine the presence of symptoms of depression using the Beck Depression Inventory⁴ and then again at 4 months using the Medical Outcomes Study Specific Adherence Scale⁵ to determine adherence to prescribed medical treatment regimens. Of the 130 survivors at 4 months, 31 (23.8%) were initially in the upper quartile of scores on the Beck Depression Inventory (>8), indicating elevated symptoms of depression at the time of the MI. These patients had poorer compliance (measured 4 months post-MI) with a low-fat diet, routine exercise, smoking cessation, stress reduction, and regular socializing. These data, as well as others linking depression^{6,7} and/or psychological distress⁸ to poor adherence to prescribed treatment regimens in patients with coronary heart disease, suggest that nonadherence may be a marker of depression, which has previously been identified as an independent risk factor for increased mortality following an acute MI.²

Depression may adversely affect survival, at least in part, by its association with the nonadherence with medication use. This is plausible, since nonadherence with the use of medications, which have a well-established mortality benefit in patients with coronary heart disease (eg, aspirin and β -adrenergic blocking agents), would be expected to have an adverse impact on survival. However, the review by McDermott et al¹ and the findings of previous authors⁹ that nonadherence with the use of placebo also adversely affects survival in patients with coronary heart disease indicate that the link between depression and mortality may not simply be through lower compliance with the use of beneficial medications.

In the Beta-Blocker Heart Attack Trial,¹⁰ which examined more than 2000 patients after acute MI, those who did not adhere to the use of either propranolol or pla-

cebo had an increased risk of death. In a multiple logistic regression analysis, which accounted for adherence, clinical severity, demographic features, psychosocial variables, and smoking, nonadherence with the use of placebo remained strongly associated with mortality at 1 year. Unfortunately, while depression was assessed by the Beta-Blocker Heart Attack Trial¹⁰ investigators, only measures of life stress and social isolation were included in the final analysis since they were the only psychosocial variables at the time of the analysis that had been shown to be associated with increased post-MI mortality. The prognostic importance of depression in the post-MI period has only been recognized more recently⁷ and has been subsequently linked with death due to arrhythmias.¹¹ We suggest that depression may be a missing link between poor adherence behavior and greater morbidity and mortality in patients with coronary heart disease.

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In reply

We appreciate the interest of Ziegelstein et al in our article.¹ We agree with Ziegelstein et al that psychological factors, such as depression, may be important mediators of the relationship between medication nonadherence and adverse outcomes. Defining the mechanism between medication nonadherence and adverse outcomes in coronary heart disease was not an aim of our critical review. While some results of our review suggest that adherence to medical regimens confers a protective effect on survival, further study is necessary to define the mechanism by which adherence affects outcomes and

to identify interventions that successfully increase adherence among patients at risk for coronary heart disease. Based on the data presented by Ziegelstein et al, future studies should consider depression as a potential mediator of the relationship between nonadherence and cardiovascular events.

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Intractable Hiccups Induced by the Use of Megestrol Acetate

Megestrol acetate is used for treatment of cachexia and anorexia associated with cancer and human immunodeficiency virus infection. Megestrol acetate is relatively well tolerated even when administered in high doses. Although in several double-blind prospective trials differences in the incidence of adverse reactions associated with use of megestrol acetate and placebo were often not statistically significant,¹⁻⁴ adverse effects have been documented. These include irregular vaginal bleeding, fluid retention or edema, nausea, and impotence.^{2,5} Also, although self-limited hiccups can occur without sequelae; severe or intractable hiccups may lead to difficulties with eating and sleeping resulting in malnutrition, weight loss, dehydration, fatigue, exhaustion, and depression.⁶ Reported herein are 4 cases of hiccups probably induced by megestrol acetate use occurring in persons with the acquired immunodeficiency syndrome.

Report of Cases. Patient 1 presented with a 2-week duration of worsening hiccups after receiving megestrol acetate suspension (800 mg/d) for several months. The patient discontinued use of morphine, which was started 1 month earlier for control of neuropathic pain, since he recalled an episode of hiccups 1 year earlier that he believed may have been induced by the use of a fentanyl patch. His hiccups persisted after discontinuing use of the morphine and despite therapy with chlorpromazine, 50 mg 4 times daily, and metoclopramide hydrochloride, 10 mg 4 times daily. Ultimately, use of the megestrol acetate was stopped, and the hiccups resolved. Several weeks later use of the megestrol acetate was restarted and within 1 week the hiccups recurred. Four years earlier, the patient had taken megestrol acetate tablets (320 mg/d) for appetite stimulation, but the medication use was discontinued due to stomach upset. No hiccups were noted at that time.

Patient 2 presented with 1 month of hiccups resulting in a sensation of breathlessness and interfering with his ability to eat. Therapy with megestrol acetate suspension (800 mg/d) had been started 2 months earlier for anorexia. The hiccups worsened during the next several weeks despite therapy with chlorpromazine, 50 mg 3 times daily, metoclopramide hydrochloride, 20 mg 3

times daily, and cisapride, 10 mg 3 times daily, and hiccup-associated acid reflux leading to nausea and vomiting developed. On the advice of patient 4, the use of megestrol acetate was stopped and the hiccups resolved. Since then, occasional self-limited episodes of hiccups have occurred despite continued therapy with chlorpromazine, 50 mg twice daily, and metoclopramide hydrochloride, 20 mg 3 times daily. Four months prior to using megestrol acetate, the patient had presented with hiccups that resolved with treatment for esophagitis due to *Candida*.

Patient 3 presented with hiccups that occurred while eating. Therapy with megestrol acetate tablets (40 mg twice daily) had been initiated 4 months earlier for weight loss, but 2 months later the formulation was changed to the suspension and the dosage increased (800 mg/d). The hiccups were initially controlled with chlorpromazine therapy but 2 months later intractable hiccups developed. Use of megestrol acetate was discontinued, and the hiccups resolved. Two weeks after discontinuing use of megestrol acetate, the patient presented with hyponatremia, hypotension, and hyperpigmentation, and adrenal insufficiency was diagnosed from the results of a cosyntropin stimulation test.

Patient 4 began using megestrol acetate suspension (800 mg/d) for anorexia several months prior to developing hiccups. Although he was poorly compliant with follow-up visits, the patient states that the hiccups only resolved after discontinuing use of megestrol acetate. Further documentation is not available. Clinical information on all 4 patients is presented in the **Table**. Recently, an additional patient with acquired immunodeficiency syndrome and intractable hiccups that were probably induced by use of megestrol acetate was brought to our attention.

Comment. Hiccups, which have no known physiologic function, are involuntary contractions of the inspiratory muscles followed by sudden closure of the glottis.^{6,7} Although the mechanism is not fully understood, stimulation of any part of a reflex arc appears to be sufficient to result in hiccups. The afferent portion of this arc consists of the phrenic and vagus nerve along with the sympathetic chain from T6 to T12. The efferent portion of the arc appears to consist of the phrenic nerve and the motor neurons to the anterior scalene muscles, exterior intercostal muscles, and the glottis. The 2 limbs of the hiccup reflex arc are connected in a poorly defined site between C3 and C5 and most likely also in the brainstem and midbrain.

Self-limited hiccups are often caused by gastric distension, change in environmental or gastrointestinal temperature, excitement, stress, or tobacco use.^{6,7} Persistent hiccups may indicate an underlying organic process or may have a psychogenic or idiopathic origin. Any disease that irritates part of the reflex arc can induce hiccups. Medications associated with hiccups include barbiturates, benzodiazepines, high-dose corticosteroids, and general anesthesia.⁶⁻⁹

The 4 cases of hiccups presented herein are all temporally related to use of high doses of megestrol acetate suspension. Also, discontinuing and subsequently restarting megestrol acetate use was associated with resolution and recurrence of hiccups, respectively, in pa-

Patients' Characteristics*

Patient No./ Age, y/Sex	CD4 ⁺ Cell Count, ×10 ⁹ /L (%)	Medical Conditions	Medications Used When Hiccups Developed	Therapy Given for Hiccups
1/48/M	0.003 (1)	Thrush, neuropathy, CMV retinitis, disseminated MAC, wasting	Megestrol acetate, foscarnet sodium, TMP-SMZ, fluconazole, clarithromycin, clofazimine, ethambutol hydrochloride, morphine, fluoxetine, diazepam, lorazepam, epoetin alfa	Chlorpromazine, metoclopramide hydrochloride
2/48/M	0.012 (1)	Esophagitis due to <i>Candida</i> , Kaposi sarcoma, chronic diarrhea, wasting	Megestrol acetate, zidovudine, TMP-SMZ, fluconazole	Chlorpromazine, metoclopramide, cisapride
3/49/M	0.062 (7)	Neuropathy, CMV retinitis, chronic diarrhea, wasting	Megestrol acetate, zidovudine, ganciclovir, TMP-SMZ, fluconazole, rifabutin, phenytoin, filgrastim, loperamide hydrochloride	Chlorpromazine
4/36/M	0.142 (10)	Prior endocarditis and mitral valve replacement	Megestrol acetate	None

*CMV indicates cytomegalovirus; TMP-SMZ, trimethoprim-sulfamethoxazole; and MAC, Mycobacterium avium-intracellulare complex.

tient 1. Megestrol acetate use may directly cause hiccups or could be an additive factor in individuals with a low threshold for hiccups. It is not uncommon for more than 1 etiologic agent to be present in individuals with hiccups.⁶ Prior episodes of hiccups were noted in 2 patients and 3 patients were receiving multiple medications, including diazepam and lorazepam. In addition, although no organic cause for hiccups was found in any patient, an occult pathologic process cannot be excluded.

While a mechanism for hiccups induced by use of megestrol acetate is unknown, one possibility is that megestrol acetate use induces hiccups in a manner analogous to corticosteroid use. The mechanism by which glucocorticoids use causes hiccups is not known but may involve lowering the threshold for synaptic transmission in the midbrain.⁸ The glucocorticoid effects of megestrol acetate have been documented and recently reviewed.¹⁰ Interestingly, in patient 3 adrenal insufficiency developed 2 weeks after stopping megestrol acetate therapy. Adrenal insufficiency developing after withdrawal of megestrol acetate use has been previously reported.¹⁰

A number of conditions that can occur in individuals infected with the human immunodeficiency virus are known to cause hiccups.^{6,7} Megestrol acetate use should be considered in the differential diagnosis of persistent hiccups.

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Group A Streptococcal Meningitis

Since the mid-1980s, there has been an increasing incidence of invasive infections caused by group A β -hemolytic streptococcus (GAS).¹ Invasive GAS infections are defined by the isolation of GAS from a normally sterile site in the setting of bacteremia without a focus or focal infections with or without bacteremias, including meningitis, pneumonia, peritonitis, puerperal fever, osteomyelitis, septic arthritis, necrotizing fasciitis, surgical wound infections, erysipelas, and cellulitis.² Conditions associated with increased risk of invasive GAS include human immunodeficiency virus, malignant neoplasm, heart or lung disease, diabetes mellitus, and alcoholism.¹ Meningitis caused by this organism is still very rare and accounts for less than 1% of all meningitides.³ We recently treated a middle-aged woman who developed meningitis after untreated otitis media and recovered fully.

Report of a Case. A 40-year-old woman presented to the emergency department complaining of left otalgia, headache, and fever for 3 days. She experienced photophobia and vomited twice on the day of admission. The patient is married, has 4 children, and is both a nonsmoker and nonalcoholic. No one else in the family was ill. The results of a recent test were negative for human immunodeficiency virus. On examination, her temperature was

Comorbid Conditions in 39 Patients With Group A Streptococcal Meningitis

Condition	Adults (n = 14)	Children (n = 25)
None	0	8
Pharyngitis	4	3
Otitis media	4	5
Skin inflammation	2	3
Other	1 (septic arthritis) 1 (postmyelography) 2 (head trauma)	1 (cystic gingival lesion and foot ulcer) 1 (dermal sinus of nose) 1 (fasciitis) 1 (human immunodeficiency virus) 1 (cavernous hemangioma) 1 (head trauma)

39.8°C; blood pressure, 120/70 mm Hg; pulse, 100/min; and respiratory rate, 20/min. She looked acutely ill and was obtunded. There was hyperemia of the left tympanic membrane without perforation, nuchal rigidity, and the presence of a Brudzinski sign. On admission, the white blood cell count (WBC) was $2.9 \times 10^9/L$. The results of a lumbar puncture (LP) revealed turbid cerebrospinal fluid (CSF) with a WBC of $2.6 \times 10^9/L$ (88% polymorphocytes and 12% lymphocytes). The glucose level was 1.9 mmol/L (35 mg/dL) (serum glucose, 8.0 mmol/L [145 mg/dL]), and the protein concentration was 5.1 g/L. A CSF Gram stain revealed many leukocytes and gram-positive cocci in pairs and chains. The results of latex agglutination of CSF were negative for antigens for *Streptococcus agalactiae*, *Neisseria meningitidis*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Escherichia coli*. Blood cultures grew *Streptococcus pyogenes*, although the CSF culture was negative for *S pyogenes* (antibiotics were given prior to the LP). The patient received 4 million units of intravenous penicillin G potassium every 4 hours to complete a full 2 weeks. The results of an axial computed tomographic scan of the head and paranasal sinuses were unremarkable. The results of a subsequent LP on day 4 revealed a WBC of $0.128 \times 10^9/L$ (42% polymorphocytes and 58% lymphocytes). Her mental status improved, she became afebrile after the fifth hospital day, and was discharged in good health without any neurologic residue.

Comment. Invasive GAS infections are more prevalent, but reasons for the shifts in epidemiological factors are still unclear. Some investigators¹ have proposed that the presence of virulent strains (M_1 , M_3) and factors such as streptococcal pyogenic exotoxin and protease production in association with a lack of immunity to these strains may play a role. Meningitis caused by GAS is uncommon and often associated with a focus of contiguous infection.

We reviewed an additional 38 cases of meningitis caused by *S pyogenes* that appeared in the English-language literature in the last 25 years.⁴⁻³² The majority of the cases occurred in children (64%). All adults had comorbid conditions, while only 68% had comorbid con-

ditions in the pediatric population (**Table**). Medical illnesses were similar in both children and adults; the most common illness was otitis media followed by pharyngitis and skin inflammation. The WBC counts in CSF ranged from $0 \times 10^9/L$ to $28 \times 10^9/L$, with an average of $3.38 \times 10^9/L$. Only 3 patients had extremely elevated WBC counts, reaching levels between $16 \times 10^9/L$ and $28 \times 10^9/L$. These patients developed *S pyogenes* with coexistent otitis media²⁷ and after myelography.¹⁹ One patient did not have an underlying condition.⁶

The Gram stain in the CSF revealed the organism in 17 (74%) of the 23 reported cases, and blood cultures grew GAS in 20 (51%) of 39 cases. This is close to the incidence of bacteremia with pneumococcal and meningococcal meningitis, 50% and 30%, respectively, whereas the rate of bacteremia with meningitis caused by *H influenzae* is much higher at 80%.³³ The CSF culture was sterile in our patient and one other patient²⁴ who also received antibiotics prior to the LP, although the Gram stains revealed gram-positive cocci in pairs and short chains. Cerebrospinal fluid cultures have been reportedly negative for all types of organisms in as many as 25% of patients with meningitis who received prior antimicrobial therapy.³⁴ Overall, the incidence of neurologic sequelae after GAS meningitis was 28% (11 of 39 patients). While only 2 (14%) of 14 adults experienced neurologic sequelae, which included mental retardation, seizures, and visual or hearing loss, neurologic deficits occurred in 9 (36%) of 11 children (Table). The higher rate of neurologic sequelae in GAS meningitis in children is similarly observed in children with pneumococcal meningitis (9 [31%] of 29 patients).^{35,36} The mortality rate due to GAS meningitis is 13%, which is similar to the rates due to *H influenzae* and *N meningitidis* (5% and 10%, respectively). This is contradistinctive to the rates observed with pneumococcal meningitis in which the mortality rates are approaching 25%.³⁵ Almost all patients with GAS meningitis were treated with penicillin.

In summary, GAS meningitis remains an unusual manifestation of invasive disease that usually occurs in association with some other source of infection. Children are affected more commonly and have an increased incidence of neurologic residue. Group A β -hemolytic streptococcus meningitis in adults tends to have a better outcome. Nevertheless, in the era of resurgence of invasive infections caused by *S pyogenes*, physicians should recognize that GAS meningitis is a serious yet treatable condition especially if recognized early.

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