

Because the physiopathology of CSS is poorly understood, a link to omalizumab is speculative. As previously reported with leukotriene receptor antagonists, 2 main hypotheses could be considered.³ First, omalizumab could play a direct causative role in the development of CSS, although there is no clear mechanistic connection yet. Second, reduction of corticosteroids, permitted by omalizumab, could reveal CSS, which, beforehand, manifests itself only by asthma (*forme fruste* of CSS).⁵ Similar cases of unmasking a CSS *forme fruste* by means of oral corticosteroid withdrawal have been previously reported with inhaled corticosteroid and leukotriene receptor antagonists.^{6,7} Consequently, asthmatic patients treated with omalizumab should be carefully monitored for the development of CSS signs and symptoms, particularly when corticotherapy doses are being tapered.

In our case omalizumab did not prevent the extensive eosinophilic infiltration. However, asthma symptoms, severe before introduction of omalizumab, did improve. If our patient's asthma is related to CSS, this suggests that omalizumab could be beneficial in CSS with persistent asthma, despite use of oral corticosteroids. Such a beneficial effect has already been reported.⁸ Further data will be necessary to confirm the role of omalizumab in CSS.

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Disclosure of potential conflict of interest: F. de Blay is on the advisory board for Novartis. The rest of the authors have declared that they have no conflict of interest.

REFERENCES

- Winchester DE, Jacob A, Murphy T. Omalizumab for asthma. *N Engl J Med* 2006; 355:1281-2.
- Strunk RC, Bloomberg GR. Omalizumab for asthma. *N Engl J Med* 2006;354: 2689-95.
- Noth I, Strek ME, Leff AR. Churg-Strauss syndrome. *Lancet* 2003;361:587-94.
- Churg A. Recent advances in the diagnosis of Churg-Strauss syndrome. *Mod Pathol* 2001;14:1284-93.
- Churg A, Brallas M, Cronin SR, Churg J. Formes frustes of Churg-Strauss syndrome. *Chest* 1995;108:320-3.
- Le Gall C, Pham S, Vignes S, Garcia C, Nunes H, Fichet D, et al. Inhaled corticosteroids and Churg-Strauss syndrome: a report of five cases. *Eur Respir J* 2000;15: 978-81.
- Wechsler ME, Finn D, Gunawardena D, Westlake R, Barker A, Haranath SP, et al. Churg-Strauss syndrome in patients receiving montelukast as treatment for asthma. *Chest* 2000;117:708-13.
- Giavina-Bianchi P, Giavina-Bianchi M, Agondi R, Kalil J. Three months' administration of anti-IgE to a patient with Churg-Strauss syndrome. *J Allergy Clin Immunol* 2007;119:1279.

doi:10.1016/j.jaci.2007.10.040

Consistency of protective antibody levels across lots of intravenous immunoglobulin preparations

To the Editor:

Although intravenous immunoglobulin (IVIG) is increasingly used to treat autoimmune conditions, it remains the primary

therapy for primary immunodeficiencies, such as X-linked agammaglobulinemia, common variable immunodeficiency, and specific antibody defects, in which endogenous antibody production is either reduced or abolished.¹ Passive immunization by IVIG has been shown to reduce infections in these patients, especially by encapsulated bacteria such as *Streptococcus pneumoniae* (pneumococcus) and *Haemophilus influenzae* type b (Hib).²

Despite the importance of IVIG in conferring protection from invasive bacteria, few studies have examined levels of antibodies to specific organisms in commercial IVIG preparations.³ Little attention has been paid to lot-to-lot variation in commercial IVIG preparations. The US Food and Drug Administration only requires that all IVIG lots have quantified levels of antibodies to measles, diphtheria, and polio.⁴ Antibodies to encapsulated pathogens such as pneumococcus and Hib are not measured. It has been recommended that once a patient has been stabilized by using 1 commercial IVIG preparation, the patient remain with this preparation over the life of the treatment.⁵ Because of this, it is important that the levels of pathogen-specific antibodies delivered to the patient do not vary significantly from lot to lot of IVIG. Our aim was to investigate specific IgG antibody levels to 14 pneumococcal serotypes, as well as to diphtheria and tetanus toxins, and to surface antigens on Hib in 44 different lots of a commercial IVIG preparation.

Forty-four separate lots of IVIG were provided by CSL Behring (Bern, Switzerland) as part of an open request for proposals initiated by the manufacturer. No financial support was provided for the study. Three separate aliquots of each lot were reconstituted to 60 mg IgG/mL, flash-frozen by the manufacturer, and shipped on dry ice to the Montreal Childrens Hospital. On receipt, the IVIG was stored at -70°C until use.

Antipneumococcal capsular antigen IgG antibody levels were determined by ELISA using a protocol based on that of Inostroza et al.⁶ This was done for 14 pneumococcal serotypes (serotypes 1, 3, 4, 6B, 7F, 9V, 11A, 12F, 14, 15B, 18C, 19F, 23F, and 33F), 7 of which are present in the currently used pneumococcal conjugate vaccine and 7 in the polysaccharide vaccine (Table I). We measured IgG antibodies to diphtheria toxin, tetanus toxin, and Hib capsular antigen by using commercial ELISA kits (diphtheria and tetanus toxin from Scimedex, Denville, NJ; Hib from The Binding Site, San Diego, Calif). Optimal dilution factors in these assays of 1:500, 1:800, 1:800, and 1:3000, respectively for diphtheria, pneumococcus, Hib, and tetanus were determined by titration experiments.

Antibodies levels to 14 different serotypes of pneumococcus in each of the 44 lots of IVIG showed considerable variation in the antibody levels to different serotypes, with antibodies to serotypes 14 and 19F the most abundant (Table I). This agrees with results of Mikolajczyk et al,⁷ although they evaluated only 5 pneumococcal serotypes. On the basis of similar calculations to Mikolajczyk et al,⁷ antipneumococcal IgG levels were high enough to confer protection against all serotypes of pneumococcus. Clinical correlation with postinfusion titers is needed to confirm this. Importantly, there was low variation in antibody levels to specific pneumococcal serotypes between individual lots of IVIG (Table I). In only 1 of the antigens was the coefficient of variation greater than 25% (Table I).

Similar results were obtained for antidiphtheria toxin IgG levels (Table II), as well as Hib anticapsular IgG antibodies (Table I). In both cases, the coefficient of variation was less than 25%. Table II also shows that there was considerable variation in

TABLE I. Antipneumococcal antigen antibodies ($\mu\text{g/mL}$)*

Serotypes in Prevnar	4	6B	9V	14	18C	19F	23F
Antibody level ($\mu\text{g/mL}$) $\pm$ SD	7.21 $\pm$ 1.35	19.59 $\pm$ 4.69	16.87 $\pm$ 2.35	40.89 $\pm$ 6.23	11.09 $\pm$ 3.04	32.86 $\pm$ 6.28	14.44 $\pm$ 3.03
Range	4.8-9.6	12.1-28.3	11.3-22.7	29.7-54.7	6.1-16.5	22.0-45.3	7.0-20.0
Coefficient of variation (%)	19.0	23.7	13.9	15.1	27.5	19.3	21.2
Serotypes not in Prevnar	1	3	7F	11A	12F	15F	33F
Antibody level ($\mu\text{g/mL}$) $\pm$ SD	10.41 $\pm$ 1.88	8.85 $\pm$ 1.20	15.02 $\pm$ 2.51	14.70 $\pm$ 1.98	6.55 $\pm$ 1.03	22.43 $\pm$ 5.38	24.98 $\pm$ 5.34
Range	6.8-13.8	6.3-12.0	9.3-20.0	9.9-17.5	4.5-8.4	11.6-30.7	14.4-36.4
Coefficient of variation (%)	17.2	13.8	16.9	13.5	15.9	24.1	21.6

*Antibody levels measured in 44 commercially available lots of intravenous immunoglobulin to 14 serotypes of pneumococcus, of which 7 are found in commercial conjugated vaccine and 7 only in unconjugated vaccines.

TABLE II. Antibody levels measured in 44 commercially available lots of intravenous immunoglobulin to commonly vaccinated antigen

Antigen	Antibody level (means $\pm$ SDs)	Range	Coefficient of variation (%)
Tetanus (IU/mL)	31.1 $\pm$ 19.9	17.4-76.5	37.6
Diphtheria (IU/mL)	3.6 $\pm$ 1.1	2.20-7.05	29.4
<i>H influenzae</i> ($\mu\text{g/mL}$)	32.43 $\pm$ 6.54	20.1-51.8	21.4

antitetanus toxin IgG levels, as shown by the high SD, and the range of antibody levels was broader than that observed in any of the other antigens.

Finally, although there were differences in antibody levels within the various lots of IVIG, there were no lots of IVIG that had antigen-specific antibody levels consistently above or below average. Antibody levels to antigens varied independently of one another.

This is the first study that examines specific antibody levels to several pathogens over a large number of different lots of IVIG from the same company. We have shown that although there is some lot-to-lot variability in antigen specific antibodies, on the whole, antibody levels were broadly consistent across 44 lots of IVIG. Antibody levels to 14 pneumococcal antigens, Hib, and diphtheria toxin all showed fairly low deviations around their respective means. Only antibodies to tetanus toxin showed a higher degree of variability, while consistently achieving high antibody levels.

The finding that levels of antipneumococcal antibodies are consistent across all lots of IVIG tested is an important one. Patients with primary antibody deficiencies have infections by encapsulated bacteria, especially pneumococcus, causing a range of diseases, from otitis and sinusitis to pneumonia and invasive bacteremia. Because IVIG is the treatment of choice in preventing these infections,¹ it is crucial that there be a consistent, high level of antipneumococcal antibodies in all lots of IVIG.

Because the manufacturing process does not vary for the lots of IVIG in this study, the specific antibody level variation between lots must be a result of differences in the plasma donor pool. Because many studies have shown that infection rates by specific antigens and vaccination compliance can vary quite significantly from region to region, it is not surprising that some differences between IVIG lots do exist. Several groups have shown that

pneumococcal serotypes vary markedly in prevalence in different geographic locations.⁸ We noted in our IVIG samples that IVIG from plasma procured in the United States had higher levels of antitetanus (45.5 ± 14.2 vs 27.7 ± 6.0 IU/mL) and antidiphtheria antibodies (4.3 ± 1.1 vs 3.0 ± 0.6 IU/mL) compared with plasma from the European Union. Presumably, infections and vaccine-related exposures in donor populations are reflected by the specific antibody levels in the IVIG derived from these populations. This may be minimized by having large donor pools (>10,000 plasma donors) as is commonly done for products available in North America. However, the consistency in antibodies against specific pathogens may or may not reflect consistency in immune modulator molecules required for autoimmune disease or inflammatory diseases.

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Disclosure of potential conflict of interest: B. Mazer is on advisory boards for Novartis and King Pharma Canada, has received grants/research support from Talecris/Bayer, and is on the speakers' bureau for Novartis and Nycomed. D. Lejtenyi has declared that he has no conflict of interest.

REFERENCES

- Orange JS, Hossny EM, Weiler CR, Ballou M, Berger M, Bonilla FA, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol* 2006;117:S525-53.
- Simon HU, Späth PJ. IVIG: mechanisms of action. *Allergy* 2003;58:543-52.
- Lamari F, Anastassiou ED, Tseganidis T, Dimitracopoulos G, Karamanos NK. An enzyme immunoassay to determine the levels of specific antibodies toward bacterial surface antigens in human immunoglobulin preparations and blood serum. *J Pharm Biomed Anal* 1999;20:913-20.
- Food and Drug Administration. 21 CFR, part 640.104: potency. Rockville (MD): Food and Drug Administration; 2004.
- Siegel J. The product: all intravenous immunoglobulins are not equivalent. *Pharmacotherapy* 2005;25:78S-84S.
- Inostroza J, Villanueva S, Mason K, Leiva LE, Sorensen RU. Effects of adsorption with pneumococcal type 22F polysaccharide on maternal, cord blood and infant immunoglobulin G antipneumococcal polysaccharide antibodies. *Clin Diagn Lab Immunol* 2005;12:722-6.
- Mikolajczyk MG, Conception NF, Wang T, Frazier D, Golding B, Frasch CE, et al. Characterization of antibodies to capsular polysaccharide antigens of *Haemophilus influenzae* type b and *Streptococcus pneumoniae* in human immune globulin intravenous preparations. *Clin Diagn Lab Immunol* 2004;11:1158-64.
- Farrell DJ, Jenkins SG, Reinert RR. Global distribution of *Streptococcus pneumoniae* serotypes isolated from paediatric patients during 1999-2000 and the *in vitro* efficacy of telithromycin and comparators. *J Med Microbiol* 2004;53:1109-17.