

Temporal Association of *Streptococcus*, *Staphylococcus*, and Parainfluenza Pediatric Hospitalizations and Hospitalized Cases of Henoch-Schönlein Purpura

PAMELA F. WEISS, ANDREW J. KLINK, XIANQUN LUAN, and CHRIS FEUDTNER

ABSTRACT. Objective. To determine if hospitalizations for specific infectious exposures are associated with hospital admissions for Henoch-Schönlein purpura (HSP).

Methods. We conducted a retrospective cohort study using administrative data of children admitted to 40 children's hospitals between January 1, 2002, and December 31, 2008. We examined the association of standardized rates of group A β -hemolytic *Streptococcus* (GABS), *Staphylococcus aureus*, parainfluenza, influenza, adenovirus, and respiratory syncytial virus (RSV)-associated hospital admissions with standardized rates of HSP hospital admissions on a month by month basis using autoregressive moving average process models to account for temporal autocorrelation and clustering by hospital.

Results. Among the 3,132 admissions for HSP observed over the 7-year study period, hospital admissions were most frequent September through April, but with substantial variability between hospitals for each month. Accounting for these month by month differences within each hospital, the rate of HSP admissions in a given month increased significantly as the standardized rates of GABS ($p = 0.01$), *S. aureus* ($p < 0.01$), and parainfluenza ($p = 0.03$) admissions increased.

Conclusion. Our results demonstrate a local month by month temporal association between hospitalization for GABS, *S. aureus*, and parainfluenza and hospitalization for HSP. Future investigations will be required to determine causality. (First Release Sept 15 2010; J Rheumatol 2010;37:2587-94; doi:10.3899/jrheum.100364)

Key Indexing Terms:

PEDIATRIC RHEUMATOLOGY
INFECTION

EPIDEMIOLOGY

VASCULITIS

HENOCH-SCHÖNLEIN PURPURA

Henoch-Schönlein purpura (HSP) is an acute vasculitis, affecting 8 to 20 per 100,000 children each year and accounting for half of all childhood vasculitis in the United

States^{1,2}. According to the European League Against Rheumatism (EULAR), HSP is defined as occurring when there is palpable purpura plus one of the following: diffuse abdominal pain, any biopsy showing predominant IgA deposition, arthritis or arthralgias, and renal involvement (any hematuria or proteinuria)³. HSP is characterized by prominent seasonal variation, with most cases occurring in the winter or spring. While the precise etiology of HSP is unknown, IgA, genetics, and infections each appear to contribute to the pathogenesis. Decreased glycosylation of IgA1 increases its propensity to aggregate, activates the alternative complement pathway, and results in tissue deposition^{4,5}. Familial genetic aggregation studies^{6,7} and an established association with familial Mediterranean fever syndrome⁸ lend support for a genetic predisposition for HSP. Additionally, the seasonal nature suggests that antecedent infections contribute to disease pathogenesis in genetically susceptible children. HSP is preceded by an upper respiratory tract infection in 30%–50% of cases^{9,10,11}, but there is no clear and consistent evidence for an etiologic role of any single organism.

Infectious triggers reportedly associated with HSP are numerous and include Group A β -hemolytic *Streptococcus* (GABS), *Staphylococcus aureus*, *Kingella kingae*,

From the Division of Rheumatology, Division of General Pediatrics, Healthcare Analytics Unit, and Center for Pediatric Clinical Effectiveness, The Children's Hospital of Philadelphia; and Department of Pediatrics, Center for Clinical Epidemiology and Biostatistics, and Leonard Davis Institute of Health Economics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA.

Dr. Weiss was supported by the American College of Rheumatology Research and Education Foundation Clinical Investigator Fellowship Award.

P.F. Weiss, MD, MSCE, Division of Rheumatology and Center for Pediatric Clinical Effectiveness, Children's Hospital of Philadelphia, and Department of Pediatrics, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine; A.J. Klink, MPH, Division of Rheumatology, Center for Pediatric Clinical Effectiveness, Children's Hospital of Philadelphia; X. Luan, MS, Healthcare Analytics Unit and Center for Pediatric Clinical Effectiveness, Children's Hospital of Philadelphia; C. Feudtner, MD, MPH, PhD, Division of General Pediatrics and Center for Pediatric Clinical Effectiveness, Children's Hospital of Philadelphia, and Department of Pediatrics, Center for Clinical Epidemiology and Biostatistics, and Leonard Davis Institute of Health Economics, University of Pennsylvania School of Medicine.

Address correspondence to Dr. P.F. Weiss, Room 1539, North Campus, Division of Rheumatology, The Children's Hospital of Philadelphia, 3535 Market Street, Philadelphia, PA 19104. E-mail: weisspa@email.chop.edu. Accepted for publication July 27, 2010.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2010. All rights reserved.

Bartonella henselae, *Helicobacter pylori*, *Pertussis*, *Mycobacterium avium-intracellulare* complex, *Salmonella*, *Shigella*, *Campylobacter*, *Mycoplasma pneumoniae*, influenza, Epstein-Barr virus, hepatitis A, hepatitis B, human immunodeficiency virus, parvovirus B-19, adenovirus, varicella, Coxsackie virus, and herpes simplex virus. The number of purported infectious associations raises the possibility that several microbial agents trigger the necessary immunologic response, in susceptible individuals, that results in HSP.

How can the various hypotheses regarding associations between these infectious agents and the onset of HSP be tested? A direct method, involving a large cohort (or case-control study) of children screened for these agents and monitored (or selected) for onset of HSP would be ideal. An indirect method, however, would be to observe at a population level whether the timing of outbreaks of specific infectious agents is tightly correlated with outbreaks of new-onset HSP. Similar studies have been done for evaluating the association of air pollution and asthma¹². Data to perform such a study exist within the Pediatric Health Information System (PHIS) database, an administrative database that contains comprehensive inpatient data from more than 40 pediatric hospitals from all regions of the United States. Of note, the PHIS database does limit the sample to only those children who are sufficiently ill to require hospitalization, due to either a specific infectious agent or HSP, so the association would be among the most severe cases. Nonetheless, the analysis would provide evidence for an association that could then be tested by either other indirect or direct methods.

This study employs a retrospective cohort study design to preliminarily evaluate a local month by month temporal association of hospitalization due to several common upper respiratory pathogens and hospitalization for HSP. Specifically, we analyzed the PHIS database, which contains clinical data regarding all children admitted to 40 non-competing children's hospitals located throughout the US; the large sample size and diverse geographic locations of the participating hospitals enable this design to estimate the association of hospitalization due to infections and hospitalizations due to HSP across hospitals.

MATERIALS AND METHODS

Human subjects protections. This study was reviewed by The Children's Hospital of Philadelphia Committee for the Protection of Human Subjects and institutional review board and declared not human subjects research.

Study design. This retrospective cohort study utilized the PHIS administrative database to determine if specific infectious exposures are associated with hospital admission for HSP.

Data source and quality. The PHIS database is an administrative database that contains comprehensive inpatient data from pediatric hospitals from all regions of the US. Participating hospitals are affiliated with the Child Health Corporation of America (CHCA; Shawnee Mission, KS), a business alliance of children's hospitals. The database contains administrative inpatient demographic, diagnostic, and procedural data from noncompeting freestanding tertiary care pediatric hospitals in the US. Data are de-identi-

fied and subjected to rigorous reliability and validity checks prior to inclusion in the database. Data that do not meet an established error threshold are rejected and must be corrected before resubmission¹³.

Forty-one hospitals contributed to the PHIS database between January 1, 2002, and December 31, 2008. After exclusions for data quality issues, 40 hospitals and 2,377 hospital-months of data remained for the final analysis.

Eligibility. Eligible subjects were children younger than 18 years of age at admission with discharge dates from a CHCA-participating hospital between January 1, 2002, and December 31, 2008 (N = 3,275,947). Inclusion criteria were an International Classification of Diseases-9-Clinical Modification (ICD-9-CM) code indicating a discharge diagnosis of HSP, GABS, *S. aureus*, parainfluenza, influenza, adenovirus, or respiratory syncytial virus (RSV) (See Appendix for list of ICD-9-CM codes included). Subjects with a discharge diagnosis of another rheumatic condition such as Wegener's granulomatosis (WG), systemic lupus erythematosus, juvenile dermatomyositis, or polyarteritis nodosa, were excluded.

Outcomes. The primary outcome was an estimate of a temporal association between admission for HSP and GABS, *S. aureus*, parainfluenza, influenza, adenovirus, or RSV.

Independent variables. Prespecified fixed-effects covariates included standardized rates of admission for each infection, admission month, and admission year. Admitting hospital was included as a prespecified random-effects covariate. Hospital-specific admission rates were calculated based on counts of monthly admissions assigned a discharge diagnosis of HSP or any of the infections in a given 12-month period (August to July).

Statistical analysis. We used autoregressive moving average (ARMA) process modeling on the time series data to study the association between standardized rates of admission for HSP and each infection. The relation of the outcome at time y_t to previous forecasting errors is called a moving average (MA) process. The dependence of the outcome at time y_t on lagged values is called an autoregressive (AR) process. The ARMA model consists of 2 parts, an AR part for correlation of outcomes within a hospital, and an MA part for the variance caused by unobserved events. The ARMA (1,1) model fit the variance structure better than a first-order autoregressive model (AR (1)) and antedependence covariance structure (ANTE (1)). The residual plot demonstrated evenly distributed residuals around 0. The mixed-effect models were fitted using the PROC MIXED function with ARMA (1,1) covariance structure in SAS 9.2 for Windows (SAS Institute, Cary, NC, USA). Descriptive statistics were conducted using Stata 10.1 (StataCorp, College Station, TX, USA).

RESULTS

Hospital admissions. During the 7-year study period there were a total of 3,132 hospital admissions for HSP. Subject characteristics are presented in Table 1. Hospital admissions for HSP were most frequent September through April, but with substantial variability between hospitals for each month (Figure 1). This seasonal variation is consistent with observations in previous studies^{14,15,16,17}. Similar to HSP hospitalizations, there was prominent seasonal variation in hospitalizations for each infection, with wide variability in rates between hospitals for each month (Figure 2).

Association of hospitalization due to HSP with hospitalizations due to group A β -hemolytic *Streptococcus*, *S. aureus*, and parainfluenza. Accounting for the month by month differences within each hospital, HSP admissions in a given month increased significantly as admissions for GABS, *S. aureus*, and parainfluenza increased (Table 2). When *S. aureus* was subdivided into methicillin-sensitive *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) infec-

Table 1. Subjects' demographic data. Data are percentages.

	HSP (N = 3,132)	GABS (N = 19,814)	<i>S. aureus</i> (N = 53,363)	% Parainfluenza (N = 667)	Influenza (N = 14,052)	Adenovirus (N = 3,382)	RSV (N = 91,505)
Age, yrs							
< 2	4.3	28.5	41.5	58.6	55.3	53.7	89.1
2-4	27.8	20.5	14.8	21.9	19.7	24.1	8.4
5-9	46.3	26.5	14.0	10.8	12.3	13.0	1.6
10-14	15.1	16.3	16.9	4.8	8.2	6.4	0.6
15-18	6.5	8.2	12.8	3.9	4.5	2.8	0.3
Sex							
Male	58.8	54.7	54.5	54.5	56.5	59.8	56.0
Female	41.2	45.3	45.5	45.5	43.5	40.2	44.0
Race							
White	75.5	62.4	62.7	67.5	58.5	62.3	62.5
Black	7.3	24.0	24.7	18.1	26.6	24.4	21.5
Asian	4.5	2.0	1.8	3.5	2.0	2.4	1.8
Other	12.7	11.6	10.8	10.9	12.9	10.9	14.2
US census region							
Northeast	11.8	8.7	8.4	13.7	8.7	17.4	10.8
Midwest	27.8	34.1	28.4	30.6	29.8	24.0	29.3
South	35.4	37.9	43.2	25.6	40.7	34.3	38.4
West	25.0	19.3	20.0	30.1	20.8	24.3	21.5

HSP: Henoch-Schönlein purpura; GABS: group A β -hemolytic *Streptococcus*; RSV: respiratory syncytial virus.

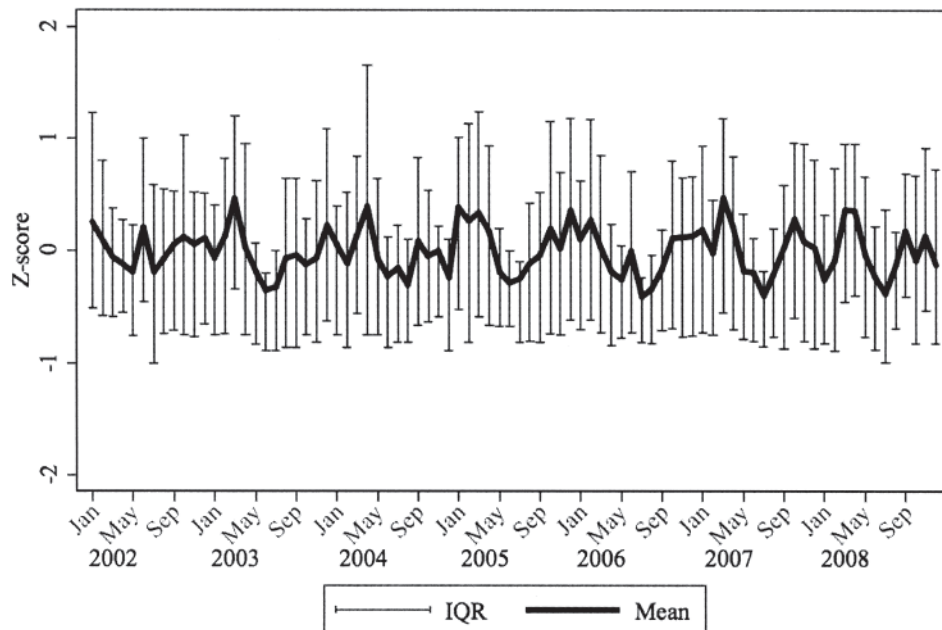


Figure 1. Hospitalizations for Henoch-Schönlein purpura (HSP). Data are Z scores and interquartile ranges (IQR) across hospitals for HSP admissions each month 2002-2008.

tions, both were significantly associated with HSP admissions. The association between HSP and GABS admissions was stronger for years 2002-03 and 2005-06 and weaker for 2006-07 (Figure 3). The association between HSP and *S. aureus* admissions was consistent across years, except for a slightly stronger association for 2004-05 (Figure 3). The

estimate of association for HSP and parainfluenza was consistent across years (Figure 3). Overall, across all study years, there was no significant association between admission for HSP and several other infections with prominent peaks in the fall and winter including influenza, adenovirus, or RSV (Figure 2).

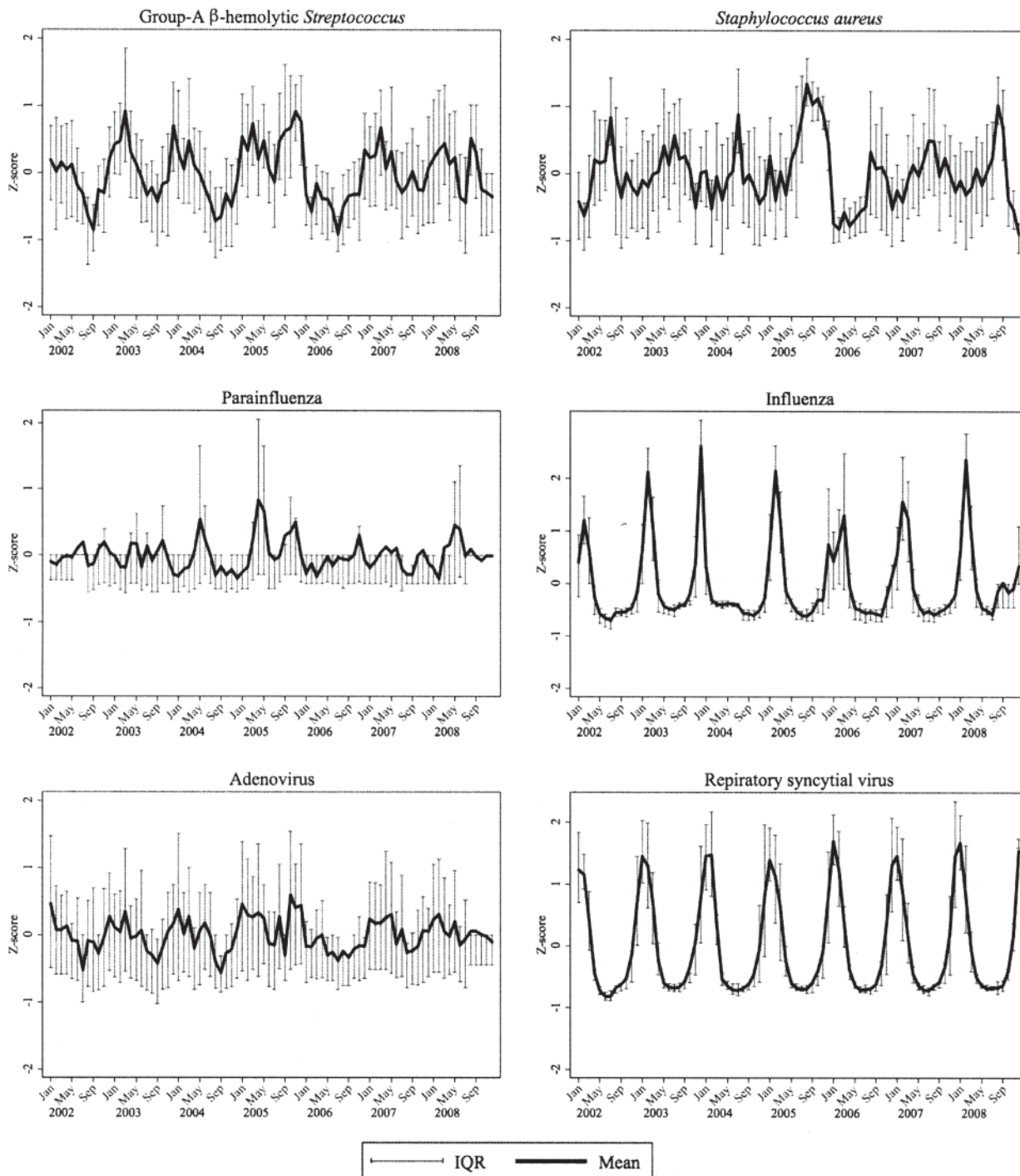


Figure 2. Hospitalizations for group A *Streptococcus* (GABS), *S. aureus*, parainfluenza, influenza, adenovirus, and respiratory syncytial virus (RSV). Data are Z scores and interquartile ranges (IQR) across hospitals for HSP admissions each month 2002-2008.

DISCUSSION

This study demonstrates a significant temporal association between admissions for HSP and admissions for GABS, *S. aureus*, and parainfluenza in US children's hospitals from 2002 to 2008. The positive association with GABS is in accord with the observations of smaller pediatric cohort studies at single institutions^{18,19,20,21}. Similarly, positive

association of HSP with *S. aureus*^{22,23,24,25,26,27} has been reported in single-center small case series or case reports. To our knowledge an association of HSP and parainfluenza has never been reported. This study surpasses existing reports by examining the relationship of multiple upper respiratory agents in a rigorous, large, multicenter approach.

The demographics of children with HSP in this study are

Table 2. Henoch-Schönlein purpura admissions associated with infection admissions. Estimates for the standardized rate of HSP admission were calculated using the autoregressive moving average (1,1) process for each infection.

Agent	Estimate (95% CI)	p
Group A β -hemolytic <i>Streptococcus</i>	0.09 (0.02, 0.15)	0.01
<i>S. aureus</i>	0.18 (0.07, 0.29)	< 0.01
MSSA	0.18 (0.09, 0.27)	< 0.01
MRSA	0.10 (0.03, 0.16)	< 0.01
Parainfluenza	0.04 (0, 0.08)	0.03
Influenza	0.03 (-0.02, 0.08)	0.19
Adenovirus	0.01 (-0.03, 0.04)	0.06
Respiratory syncytial virus	-0.01 (-0.09, 0.07)	0.75

MSSA: methicillin-sensitive *Staphylococcus aureus*, MRSA: methicillin-resistant *Staphylococcus aureus*.

similar to those reported in previous studies^{9,11,28,29}. Our results should be interpreted with the knowledge that only the most seriously ill children with HSP and the most seriously ill children with these infections were evaluated. However, these are often the children with whom physicians are most concerned. We acknowledge that management of HSP and treatment of the infections evaluated are done on an outpatient basis most of the time. Future studies should test if the correlations remain significant when the milder forms of HSP and the infections are included. Despite these considerations, our findings indicate that the association of GABS, *S. aureus*, and parainfluenza and HSP, particularly for the most severely ill patients, warrants additional study.

Time series analyses are increasingly used in epidemiology research^{12,30,31}. The PHIS database offered a unique opportunity to evaluate the association of HSP and each of the infections because each peaked at different times in different areas of the US, as demonstrated by the wide interquartile range for each condition for each month in Figure 2. In this study we analyzed data month by month at each of the 40 hospitals, and found a tight level of association down to the very local and small time scale. With this level of detail we discern that while influenza, adenovirus, and RSV wax and wane with the seasons, their outbreak epidemiology has no relation to HSP, whereas the hospital-specific monthly rates of GABS, *S. aureus*, and parainfluenza are highly associated with each hospital's rate of HSP cases.

Importantly, the association of HSP and GABS, *S. aureus*, and parainfluenza has biologic plausibility, as each is associated with other autoimmune diseases in genetically susceptible individuals. The reasons for the link between infection and autoimmunity are unclear, but may relate to continued presence of the infectious organism itself, residual antigen from the infection, or self-antigen.

GABS is capable of causing a broad spectrum of post-infectious autoimmune diseases, with rheumatic fever being the paradigmatic example. Other autoimmune conditions that GABS is associated with include movement disorders

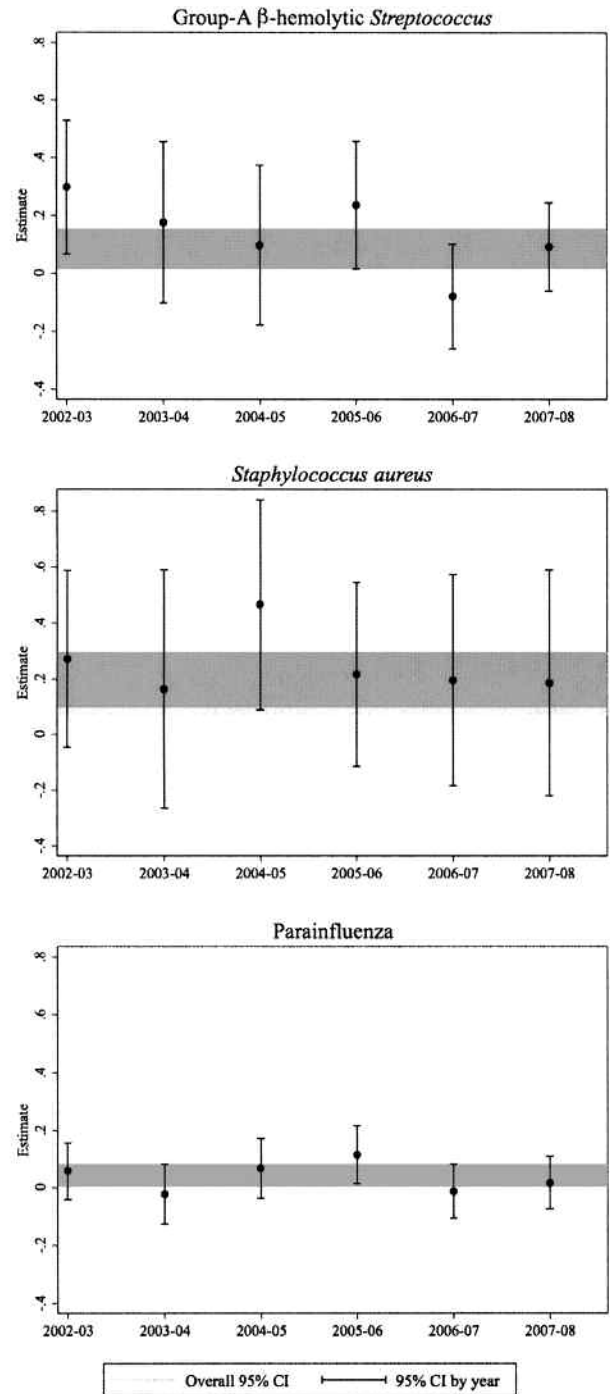


Figure 3. Association of admissions for Henoch-Schönlein purpura and for group A β -hemolytic *Streptococcus* (GABS), *S. aureus*, and parainfluenza 2002-2008. Data generated by ARMA(1,1) process; shaded area shows overall 95% CI.

(chorea, tics, Parkinsonism)³², Behçet's disease³³, and polyarteritis nodosa³⁴. The immunopathogenesis of these diseases is incompletely defined but may be due, at least for some of the cases, to molecular mimicry (whereby, in the example of rheumatic fever, host antibodies to the GABS M-protein peptides also recognize host tissue components,

namely peptides on the cardiac valves). In other conditions such as Guillain-Barré syndrome^{35,36} and antiphospholipid syndrome^{37,38} more than one organism can trigger the immune response, apparently resulting in molecular mimicry and subsequent disease. Similar mechanisms may also be at work in the pathogenesis of HSP, given the positive association of HSP with multiple infectious agents in our study and in the literature.

Similar to GABS, *S. aureus* is implicated in the pathogenesis of autoimmune diseases, including vasculitis. The pathogenesis of Kawasaki disease, a medium-size vessel vasculitis, is incompletely understood but an abnormal immune response to various microbes and superantigens derived from *S. aureus* have been suggested³⁹. Additionally, chronic nasal carriage of *S. aureus* significantly increases the risk of disease relapse in WG⁴⁰, an antineutrophil cytoplasmic antibody (ANCA)-associated small-vessel vasculitis. Theories to explain the underlying relationship between *S. aureus* and WG include superantigens^{41,42}, polyclonal activation by cell wall components⁴⁰, *S. aureus* binding of 1-antiproteinases resulting in persistent antiproteinase 3 (the antigen target of ANCA in WG)⁴³, and molecular mimicry⁴⁴.

Parainfluenza has not been as frequently reported in association with autoimmunity as GABS and *S. aureus*, but reports do exist, particularly with vasculitis. Association of

antiparainfluenza IgM antibodies and the onset of giant cell arteritis and polymyalgia rheumatica has been reported⁴⁵. Additionally, associations between parainfluenza and Kawasaki disease^{46,47} and mucocutaneous lymph-node syndrome have also been reported. In these diseases viral replication within the endothelium may cause vessel injury, which is important in the pathogenesis of vasculitis^{48,49}.

To conclude, in pediatric tertiary care hospitals across the US, there is a positive association between admissions for HSP and for GABS, *S. aureus*, and parainfluenza. Our results provide preliminary evidence of a temporal, but not necessarily causal, relationship for the most severe subset of children with HSP that should be further examined in a prospective manner to investigate causality. If causality is proven, it is plausible that the association between these infections and development of HSP may be mediated through various mechanisms including molecular mimicry, superantigen production, and endothelial injury. Additional basic and clinical studies are warranted (1) to investigate if similar associations are present in the outpatient setting; (2) to test for causality using a prospective study design; (3) to elucidate the molecular basis by which HSP is associated with these infections; and (4) to explore whether clinical outcomes vary with different infectious triggers and early treatment of these infections.

Appendix. ICD-9-CM codes used for infections of interest and Henoch-Schönlein purpura.

Infection/Disease	Code	Diagnosis Code Test
Henoch-Schönlein purpura	287.0	Allergic purpura
Group A β -hemolytic <i>Streptococcus</i>	034.0	Streptococcal sore throat
	035	Erysipelas
	038.0	Streptococcal septicemia
	041.00	<i>Streptococcus</i> infection NOS
	320.2	Streptococcal meningitis
	482.31	Pneumonia due to <i>Streptococcus</i> , Group A
	038.10	Staphylococcal septicemia, NOS
Methicillin-sensitive <i>S. aureus</i> (MSSA)	038.11	MSSA septicemia
	041.10	Staphylococcus, NOS infection in condition elsewhere classified
	041.11	MSSA infection in condition elsewhere classified
	320.3	Staphylococcal meningitis
	482.41	MSSA pneumonia
	695.81	Staphylococcal scalded skin syndrome
	038.12	MRSA septicemia
Methicillin-resistant <i>S. aureus</i> (MRSA)	041.12	MRSA infection in condition elsewhere classified
	482.42	MRSA pneumonia
	480.2	Parainfluenzal pneumonia
	487.0	Influenza with pneumonia
Parainfluenza virus	487.1	Influenza with other respiratory manifestations
	487.8	Influenza with other manifestations
	049.1	Meningitis due to adenovirus
Influenza virus	077.3	Acute adenoviral follicular conjunctivitis
	079.0	Adenovirus infection, NEC
	480.0	Pneumonia due to adenovirus
	008.62	Enteritis due to adenovirus
	079.6	RSV infection in condition elsewhere classified
Adenovirus	480.1	Pneumonia due to RSV
	466.11	Acute bronchiolitis due to RSV

REFERENCES

1. Bowyer S, Roettcher P. Pediatric rheumatology clinic populations in the United States: results of a 3 year survey. *Pediatric Rheumatology Database Research Group. J Rheumatol* 1996;23:1968-74.
2. Rostoker G. Schonlein-Henoch purpura in children and adults: diagnosis, pathophysiology and management. *BioDrugs* 2001;15:99-138.
3. Ozen S, Ruperto N, Dillon M, Bagga A, Barron K, Davin JC, et al. EULAR/PReS endorsed consensus criteria for the classification of childhood vasculitides. *Ann Rheum Dis* 2006;65:936-41.
4. Saulsbury FT. Alterations in the O-linked glycosylation of IgA1 in children with Henoch-Schonlein purpura. *J Rheumatol* 1997;24:2246-9.
5. Allen AC, Willis FR, Beattie TJ, Feehally J. Abnormal IgA glycosylation in Henoch-Schonlein purpura restricted to patients with clinical nephritis. *Nephrol Dial Transplant* 1998;13:930-4.
6. Lofters WS, Pineo GF, Luke KH, Yaworsky RG. Henoch-Schonlein purpura occurring in three members of a family. *Can Med Assoc J* 1973;109:46-8.
7. Motoyama O, Iitaka K. Familial cases of Henoch-Schonlein purpura in eight families. *Pediatr Int* 2005;47:612-5.
8. Gershoni-Baruch R, Broza Y, Brik R. Prevalence and significance of mutations in the familial Mediterranean fever gene in Henoch-Schonlein purpura. *J Pediatr* 2003;143:658-61.
9. Trapani S, Micheli A, Grisolia F, Resti M, Chiappini E, Falcini F, et al. Henoch Schonlein purpura in childhood: epidemiological and clinical analysis of 150 cases over a 5-year period and review of literature. *Semin Arthritis Rheum* 2005;35:143-53.
10. Ting TV, Hashkes PJ. Update on childhood vasculitides. *Curr Opin Rheumatol* 2004;16:560-5.
11. Calvino MC, Llorca J, Garcia-Porrua C, Fernandez-Iglesias JL, Rodriguez-Ledo P, Gonzalez-Gay MA. Henoch-Schonlein purpura in children from northwestern Spain: a 20-year epidemiologic and clinical study. *Medicine (Baltimore)* 2001;80:279-90.
12. Abe T, Tokuda Y, Ohde S, Ishimatsu S, Nakamura T, Birrer RB. The relationship of short-term air pollution and weather to ED visits for asthma in Japan. *Am J Emerg Med* 2009;27:153-9.
13. Fletcher DM. Achieving data quality. How data from a pediatric health information system earns the trust of its users. *J AHIMA* 2004;75:22-6.
14. Atkinson S, Barker DJ. Proceedings: Henoch-Schonlein purpura in Southampton. *Br J Prev Soc Med* 1974;28:66-7.
15. Atkinson SR, Barker DJ. Seasonal distribution of Henoch-Schonlein purpura. *Br J Prev Soc Med* 1976;30:22-5.
16. Saulsbury FT. Henoch-Schonlein purpura in children. Report of 100 patients and review of the literature. *Medicine (Baltimore)* 1999;78:395-409.
17. Tizard EJ, Hamilton-Ayres MJ. Henoch Schonlein purpura. *Arch Dis Child Educ Pract Ed* 2008;93:1-8.
18. Al-Sheyyab M, Batiha A, el-Shanti H, Daoud A. Henoch-Schonlein purpura and streptococcal infection: a prospective case-control study. *Ann Trop Paediatr* 1999;19:253-5.
19. Al-Sheyyab M, el-Shanti H, Ajlouni S, Batiha A, Daoud AS. Henoch-Schonlein purpura: clinical experience and contemplations on a streptococcal association. *J Trop Pediatr* 1996;42:200-3.
20. Farley TA, Gillespie S, Rasoulpour M, Tolentino N, Hadler JL, Hurwitz E. Epidemiology of a cluster of Henoch-Schonlein purpura. *Am J Dis Child* 1989;143:798-803.
21. Masuda M, Nakanishi K, Yoshizawa N, Iijima K, Yoshikawa N. Group A streptococcal antigen in the glomeruli of children with Henoch-Schonlein nephritis. *Am J Kidney Dis* 2003;41:366-70.
22. Kaneki T, Kawashima A, Hayashida M, Yamaguchi S, Ogasawara H, Tsushima K, et al. A case of Henoch-Schonlein purpura occurred after methicillin-resistant *Staphylococcus aureus* enterocolitis. *Nippon Shokakibyō Gakkai Zasshi* 2000;97:1278-82.
23. Eftychiou C, Samarkos M, Golfopoulou S, Skoutelis A, Psarra A. Henoch-Schonlein purpura associated with methicillin-resistant *Staphylococcus aureus* infection. *Am J Med* 2006;119:85-6.
24. Hirayama K, Kobayashi M, Kondoh M, Muro K, Iwabuchi S, Yoh K, et al. Henoch-Schonlein purpura nephritis associated with methicillin-resistant *Staphylococcus aureus* infection. *Nephrol Dial Transplant* 1998;13:2703-4.
25. Temkiatvises K, Nilanont Y, Pongvarin N. Stroke in Henoch-Schonlein purpura associated with methicillin-resistant *Staphylococcus aureus* septicemia: report of a case and review of the literature. *J Med Assoc Thai* 2008;91:1296-301.
26. Kitamura T, Nakase H, Iizuka H. Henoch-Schonlein purpura after postoperative *Staphylococcus aureus* infection with hepatic IgA nephropathy. *J Nephrol* 2006;19:687-90.
27. Uggeri S, Fabbian F, Catizone L. Henoch-Schonlein purpura due to methicillin-sensitive *Staphylococcus aureus* bacteremia from central venous catheterization. *Clin Exp Nephrol* 2008;12:219-23.
28. Yang YH, Hung CF, Hsu CR, Wang LC, Chuang YH, Lin YT, et al. A nationwide survey on epidemiological characteristics of childhood Henoch-Schonlein purpura in Taiwan. *Rheumatology* 2005;44:618-22.
29. Dolezalova P, Telekesova P, Nemcova D, Hoza J. Incidence of vasculitis in children in the Czech Republic: 2-year prospective epidemiology survey. *J Rheumatol* 2004;31:2295-9.
30. Ives AR, Abbott KC, Ziebarth NL. Analysis of ecological time series with ARMA(p,q) models. *Ecology* 2010;91:858-71.
31. Lin CC. Analysis of unpredictable intra-QRS potentials in signal-averaged electrocardiograms using an autoregressive moving average prediction model. *Med Eng Phys* 2010;32:136-44.
32. Dale RC. Post-streptococcal autoimmune disorders of the central nervous system. *Dev Med Child Neurol* 2005;47:785-91.
33. Kaneko F, Oyama N, Yanagihori H, Isogai E, Yokota K, Oguma K. The role of streptococcal hypersensitivity in the pathogenesis of Behcet's disease. *Eur J Dermatol* 2008;18:489-98.
34. Fink CW. The role of the streptococcus in poststreptococcal reactive arthritis and childhood polyarteritis nodosa. *J Rheumatol* 1991;18 Suppl 29:14-20.
35. Ang CW, Jacobs BC, Laman JD. The Guillain-Barre syndrome: a true case of molecular mimicry. *Trends Immunol* 2004;25:61-6.
36. Yuki N, Odaka M. Ganglioside mimicry as a cause of Guillain-Barre syndrome. *Curr Opin Neurol* 2005;18:557-61.
37. Blank M, Krause I, Fridkin M, Keller N, Kopolovic J, Goldberg I, et al. Bacterial induction of autoantibodies to beta 2-glycoprotein-I accounts for the infectious etiology of antiphospholipid syndrome. *J Clin Invest* 2002;109:797-804.
38. Gharavi AE, Pierangeli SS, Espinola RG, Liu X, Colden-Stanfield M, Harris EN. Antiphospholipid antibodies induced in mice by immunization with a cytomegalovirus-derived peptide cause thrombosis and activation of endothelial cells in vivo. *Arthritis Rheum* 2002;46:545-52.
39. Meissner HC, Leung DY. Superantigens, conventional antigens and the etiology of Kawasaki syndrome. *Pediatr Infect Dis J* 2000;19:91-4.
40. Stegeman CA, Tervaert JW, Sluiter WJ, Manson WL, de Jong PE, Kallenberg CG. Association of chronic nasal carriage of *Staphylococcus aureus* and higher relapse rates in Wegener granulomatosis. *Ann Intern Med* 1994;120:12-7.
41. Popa ER, Stegeman CA, Abdulahad WH, van der Meer B, Arends J, Manson WM, et al. *Staphylococcal* toxic-shock-syndrome-toxin-1 as a risk factor for disease relapse in Wegener's granulomatosis. *Rheumatology* 2007;46:1029-33.
42. Popa ER, Stegeman CA, Bos NA, Kallenberg CG, Tervaert JW. *Staphylococcal* superantigens and T cell expansions in Wegener's granulomatosis. *Clin Exp Immunol* 2003;132:496-504.

43. Kallenberg CG, Heeringa P, Stegeman CA. Mechanisms of disease: pathogenesis and treatment of ANCA-associated vasculitides. *Nat Clin Pract Rheumatol* 2006;2:661-70.
44. Pendergraft WF 3rd, Preston GA, Shah RR, Tropsha A, Carter CW Jr, Jennette JC, et al. Autoimmunity is triggered by cPR-3 (105-201), a protein complementary to human autoantigen proteinase-3. *Nat Med* 2004;10:72-9.
45. Duhaut P, Bosshard S, Dumontet C. Giant cell arteritis and polymyalgia rheumatica: role of viral infections. *Clin Exp Rheumatol* 2000;18 Suppl:S22-3.
46. Johnson D, Azimi P. Kawasaki disease associated with *Klebsiella pneumoniae* bacteremia and parainfluenza type 3 virus infection. *Pediatr Infect Dis* 1985;4:100.
47. Schnaar DA, Bell DM. Kawasaki syndrome in two cousins with parainfluenza virus infection. *Am J Dis Child* 1982;136:554-5.
48. Friedman HM, Macarak EJ, MacGregor RR, Wolfe J, Kefalides NA. Virus infection of endothelial cells. *J Infect Dis* 1981;143:266-73.
49. Keim DE, Keller EW, Hirsch MS. Mucocutaneous lymph-node syndrome and parainfluenza 2 virus infection. *Lancet* 1977;2:303.