Trends In Kawasaki Disease Hospitalizations: New York State 1990-2009

R Lin, L Krata

Citation

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Abstract

Objective: To ascertain whether Kawasaki disease (KD) hospitalization patterns have shifted in New York State. Given the known prevalence changes in other disorders which involve hypersensitivity, KD trends are of interest.Design and setting: Analysis of an administrative hospitalization database between 1990-2009 in New York was performed to determine changes in Kawasaki disease hospitalization rates and assess therapeutic interventions and clinical manifestations. For trend comparisons, hospitalization rates were also examined in 2 other disorders with hypersensitivity components: asthma and anaphylaxis.Patients: De-identified inpatient recordsMain outcome measures: Hospitalization rate changes and associated clinical features over timeResults: There was a significant increase in KD hospitalizations over the study period (negative binomial regression, $p<0.0001$). In patients under the age of 5 (78% of all patients), the hospitalization rate was 14.6 per 100,000 in 1990. By 2002, the hospitalization rate reached an apex of 22.5 per 100,000. This trend differed from asthma and anaphylaxis hospitalizations, which showed an overall decline, and an overall continued increase, respectively. In patients who were Asian, Pacific-Islanders, Native Hawaiian or Native Americans, there was a greater increase in KD hospitalization rates than in other patients (negative binomial regression, $p=0.003$). Cardiac abnormalities were coded in 6.1% of hospitalizations. Four deaths were reported, only one of which was a likely cardiac death.Conclusion: In New York State, there have been unique dynamic changes in KD hospitalization rates, which are more accentuated in the Asian population. KD continues to be an uncommon but significant disorder which results in hospitalization for young children.

BACKGROUND & INTRODUCTION

Kawasaki disease (KD) is a self-limited vasculitis and the leading cause of acquired heart disease in the United States among children less than 5 years of age (1). It has a particular predilection for Asian populations, which is evidenced by higher hospitalization rates for this disorder in Japan, Taiwan and Hawaii (2-4). Although the etiology of the disorder is unknown, it is felt to be most likely secondary to infection and/or an altered immunologic response. The former is suggested by the fact that KD occurs in epidemics, is self-limited, and has a seasonal presentation. The later is evidenced by the response to immunomodulatory treatment with intravenous immunoglobulin (5).

As there have been dynamic changes in the incidence other diseases that relate to hypersensitivity, such as asthma and anaphylaxis (6-7), it is of interest to examine whether the KD incidence has also changed. Moreover, in this study we examined a period of time and geographic area where there have been shifts in the racial proportions in a populous American state. These racial proportions have the potential for influencing the disease incidence.

METHODS

De-identified in-patient data was obtained from the New York State Department of Health Statewide Planning and Research Cooperative System (SPARCS) database (8) for 1990 through 2009. The database has been previously described and utilized in studies examining disease states and hospital practice trends (9-10). Each SPARCS patient record contains data fields that include principal and non-principal diagnostic fields, accommodation and ancillary charges, procedure codes, race, age, gender, and ethnicity information, hospital characteristics, expected reimbursement, total charges, length of stay, admission and disposition status. This study was approved by the institutional research board of New York Downtown Hospital.

Kawasaki disease was identified using the ICD-9 code

446.1. Hospitalizations with this code as the principal diagnosis were considered KD hospitalizations. To determine hospitalization rates, the number of hospitalizations for New York residents was divided by the estimated population. Estimated populations were obtained from the US census (11-12). Given known physical anthropological relationships (13), racial groupings were made based on a combination of Asian/Pacific Islander and American Indian, Eskimo, and Aleut for the decade 1990-1999, and for the years of 2000-2009 a combination of the following populations alone or in combination: Asian, American Indian, Alaska Native; Native Hawaiian and other Pacific Islander. Hospitalization ethnicity codes that were not Asian, Native Hawaiian or Pacific Islander were grouped as non-Asian. For trend comparisons, the hospitalization rates for asthma and anaphylaxis were calculated in children less than 5. Asthma hospitalizations were those which coded 493.* in the principal diagnosis, while anaphylaxis hospitalizations utilized the codes 995.0, 995.6*, and 999.4.

Hospitalizations which matched on the basis of birth year and month, gender, race, and residential zip code were identified. Gammaglobulin administration was identified through both procedural coding (injection or infusion of gamma globulin – ICD9 code 99.14) and through ancillary charge codes (other blood components) (14). Corticosteroid and antibiotic administrations were identified through procedural coding only (ICD9 codes 99.23 and 99.21 respectively). Echocardiograms and ultrasonography were identified by both procedural codes (ICD code 88.72) and ancillary charge codes (14). Kawasaki disease major criteria coding was queried in diagnostic fields using the ICD9 codes 780.6 - fever, 782.1 - dermatitis unspecified, 289.3 – adenitis unspecified, 683.* - acute adenitis, 528.0 – stomatitis and mucositis, 372.0 – acute conjunctivitis, and 77.99 – viral conjunctivitis NOS. Coronary aneurysm, pericardial fluid, heart failure, mitral valve disorder, myocarditis, cardiomyopathy and cardiac arrhythmia coding were also queried using the ICD9 codes 414.11, 432.9, 428.*, 424.0, 422.*, 425.* and 427.* respectively. Charges are reported in 2009 dollars using the consumer price index to inflation adjust yearly amounts prior to 2009.

Data analysis was performed using SPSS for Windows (Version 13, SPSS Inc, Chicago, IL, USA) for all analyses except for negative binomial regression and ANCOVA, which were performed using SAS for Windows (Version 9, SAS Institute, Cary, North Carolina, USA). Estimates and modeling of hospitalization rates were generated using the GENMOD procedure (15) in SAS with the negative binomial distribution option. Identification of potential repeat admissions was performed using the duplicate identification function in SPSS. Covariate effects were analyzed by ANCOVA using the General Linear Model in SPSS. Differences in proportion were analyzed by contingency tables in the crosstabs analysis portion in SAS.

RESULTS

GENERAL COHORT CHARACTERISTICS

Of 6030 hospitalizations identified, 5885 were for New York State residents. In 5112 hospitalizations (86.9%) there were no matching cases based on year/month of birth, gender, race and zip code. In the remaining cases, there were 370 earlier index cases which had subsequent matching admissions. 324 of these index cases had matching admissions less than 3 months after the index admission, 13 had matching admissions between 3-6 months later, and 15 had matching admissions more than 7-12 months later than the index. Twenty-seven had matching admission more than 12 months after the index. Of 337 transfer admissions, 43 (12.8%) had earlier matching index hospitalizations. 1197 hospitalizations were at institutions that were or had separate children's hospitals (20.3%). 78%, 96.9% and 99.7% of admissions were in persons less than 5, 10, and 20 years of age respectively. For the under-5 hospitalizations, there were particularly few admissions with matching earlier index cases (6.6%). The percentage of all admissions that were males was 60.7%. Asian group (previously defined) constituted 8.9% of KD hospitalizations and ranged from 4.4% in 1992 to 16.5% in 2007. Four patients expired during hospitalization, of which one was an adult. One of the 3 children who died had coronary disease as described (coronary aneurysm). The other 2 had respiratory failure and sepsis coding.

TRENDS WITH TIME

KD hospitalization rates for persons under 5, under 10 and under 20 all showed significant year effects (negative binomial regression $p<0.0001$ for year effect). This effect was not abrogated if cases which matched earlier index cases were excluded. The highest hospitalization rates were for the youngest groupings, and there appeared to be a plateau in rates starting in 2003 (Figure 1). Asthma admissions in the under 5 population showed an overall decline (Figure 1) (negative binomial regression $p<0.0001$ for year effect), which was less marked but still significant if admissions with matching earlier index cases (45.9%) were excluded (negative binomial regression $p<0.0001$ for year effect). In

contrast, anaphylaxis admissions in this age group showed significant increases (Figure 1) (negative binomial regression p<0.0001 for year effect) even if only the years (>1993) since the introduction of food anaphylaxis codes were used (negative binomial regression p<0.0001 for year effect). When the hospitalization trends in less than 5-year-olds were compared between anaphylaxis and Kawasaki disease using a full factorial model, a significant interaction effect between year and group was observed (negative binomial regression p<0.0001). The highest proportions of hospitalizations occurred between December and March. Males consistently had higher hospitalization rates, and the gender effect was highly significant, even after adjusting for year effect (negative binomial regression p<0.0001). When the Asian grouping effect was examined in patients less than 5, significant separate effects for the ethnic categorization and year were observed (negative binomial regression p<0.0001). Including an interaction effect of year by Asian grouping showed significant year, ethnicity and year by ethnicity effects (negative binomial regression, p<0.0001, p=0.0036, and p=0.0034 respectively). Graphic depiction showed annual hospitalization rates for the Asian grouping greater than 25 per 100,000 in several years since 2000 (figure 2).

HOSPITALIZATION FEATURES

The median length of stay for all years was 3 days for all years except 1990 and 1991 when it was 5 and 4 days respectively. The mean cost per admission decreased from $18,532 in 1990 to $14,916 in 2009. Conjunctivitis, unspecified rash, fever, adenitis, coronary aneurysm, and stomatitis were coded in 771 (13.1%), 199 (3.4%), 169 (2.9%), 110 (1.9%), 101 (1.7%) and 18 (.3%) hospitalizations. Any of these features were coded in 1131 (19.2%) hospitalizations and ranged from 12.4% (1993) to 31.1% (2008). Pericardial fluid, heart failure, mitral valve disorder, myocarditis, cardiomyopathy and cardiac arrhythmia were coded in 100 (1.7%), 33 (.6%), 80 (1.4), 25 (.4%), 11 (.2%) and 78 (1.3%). Coronary aneurysm, pericardial fluid, heart failure, mitral valve disorder, myocarditis, cardiomyopathy or cardiac arrhythmia was coded in 360(6.1%) hospitalizations. Other common diagnoses coded included otitis 4.7%, asthma 3.1%, streptococcal pharyngitis/scarlet fever 2.8%, urinary tract infection 1.8%, anemia unspecified 4.7%, dehydration 9.9%, hyponatremia 2%, and pneumonia 1.7%.

Thirty-six percent of hospitalizations did not have procedural coding. Of hospitalizations that did have coding for procedures or ancillary charges, 40% had coding consistent with gammaglobulin administration. These hospitalizations had a mean hospitalization cost of $16971 (SD $20366), compared to non-gammaglobulin hospitalizations, which had a mean cost of $14889 (SD $19242). The median length of stay for both of these two groupings was 3 days. With more recent years, there was an overall increase in hospitalizations which coded gammaglobulin administration (figure 3) ranging from 28.1% (1995) to 58.1% (2007). To examine whether gammaglobulin administration coding was associated with an increased hospital charges, the covariate effect of this coding was examined after adjusting for year of discharge and length of stay in hospitalizations which had procedural and ancillary charge coding. In main effects modeling, gammaglobulin administration had a significant effect on hospital charge (ANCOVA, p=0.001) but with a negative regression coefficient, unlike the effects of length of stay and year of discharge, which had highly significant positive coefficients (data not shown). If the model included 2 additional significant covariates (Asian grouping and primary expected insurance being self-pay or Medicaid), similar effects of gammaglobulin administration were observed (ANCOVA, p=0.002). In hospitalizations with any procedural coding, corticosteroid administration, antibiotic administration, thoracic computerized tomography, echocardiography and abdominal ultrasound were noted in 31 (.8%), 616 (16.4%), 19 (.4%), 1496 (39.8%) and 217(5.8%) respectively. In 1922 hospitalizations without any procedural coding, but with separate ancillary charge codes, 197 (10.2%) hospitalizations had ancillary charge coding for ultrasound. Lumbar puncture and cardiac angiography procedures were coded in 343 (9.1%) and 10 (.3%) hospitalizations respectively. Only 1 admission each had coding for infusion with immunosuppressant monoclonal antibody and thrombolytic agent infusion.

Figure 1

Figure 1. Hospitalization rates for various age groupings, some also stratified by gender. LT 5 = less than 5 years of age. LT 10 = less than 10 years of age. LT 20 = less than 20 years of age. KD = Kawasaki Disease. Asthma = hospitalizations per 1,000 in children less than 5. Anaphylaxis = hospitalizations per 100,000 in children less than 5.

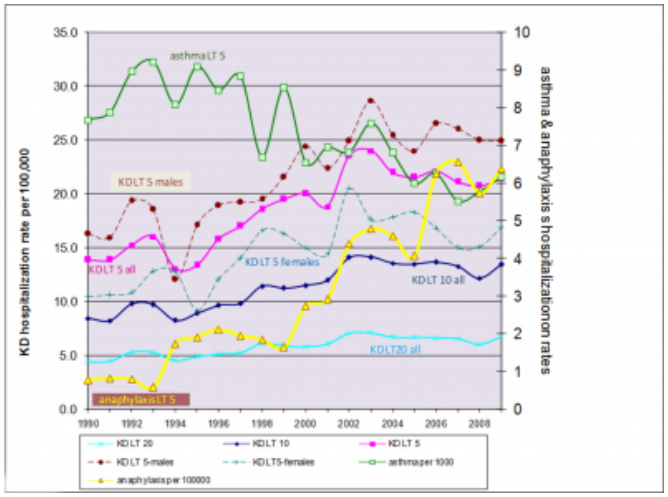


Figure 2

Figure 2. Kawasaki disease hospitalizations per 100,000 in persons under 5 years of age, stratified by Asian grouping (as defined in the text). Also show in percentages is the yearly percentage of hospitalizations that were in the Asian grouping. Inset boxes on the outer y-axes show total number of admissions in 1990 and 2009 respectively.

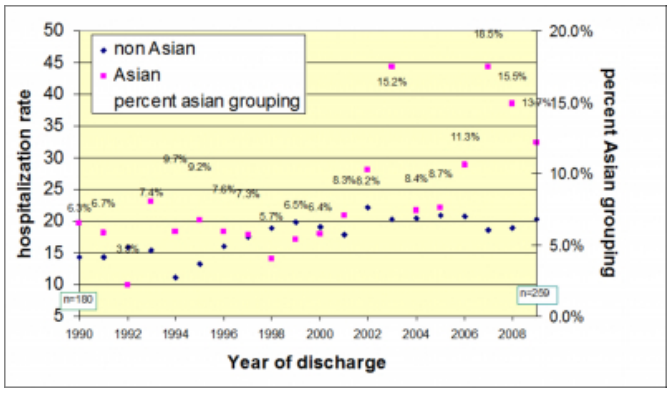
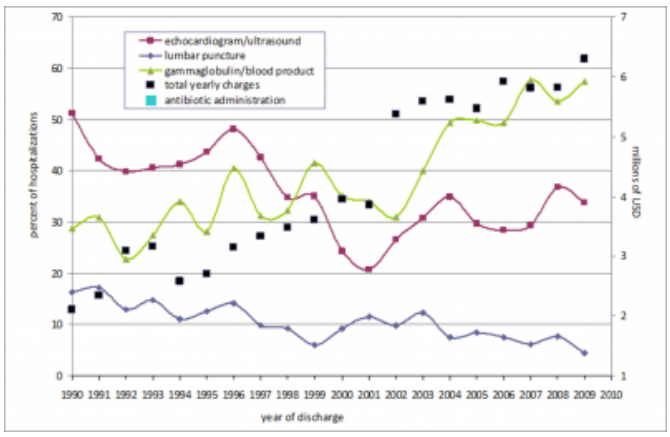


Figure 3

Figure 3. Utilization characteristics in hospitalizations of children less than 5 years of age. USD = United States dollars. Total yearly charges is the sum of all hospitalization charges for a given year. Percent of hospitalizations is the percent of evaluable hospitalizations with a given procedure or ancillary charge code



DISCUSSION

Based on sampled acute care hospitalization data in the United States 1997-2007, a recent publication suggests that United States KD hospitalizations have been static (16). Our data based on more complete data over a longer time period showed a more dynamic pattern in New York State. This appears to corroborate the findings (16) of a higher hospitalization rates in the Northeastern United States especially in recent years. Unlike the reported overall hospitalization rate in the United States (16), the incidence of KD hospitalizations has been reported to be increasing in Asian countries, including Japan (2), China (17), and Korea (18). Our study demonstrated that the increase in hospitalization rates was greater in the Asian grouping. While in some diseases Asian ethnic predilections appear to change when persons from the group immigrate (19,20), the pattern of increased and increasing Asian hospitalizations observed in our study suggests that the genetic factors in this disease process (21) are not being dampened by the local environmental factors. With the continuing increase in the Asian population in many states in the United States, it is quite conceivable that there may be further ethnic dynamic trend differences observed in the future.

KD hospitalizations showed a relatively brief length of stay, which was stable for most of the time period. Gammaglobulin administration was coded in the majority of hospitalizations by the last year of the study. As gammaglobulin is an expensive highly purified blood product, we expected that hospitalization cost would

increase if gammaglobulin was given. Our findings confirmed this hypothesis, with a mean hospital cost $2000 or 14%. For 1-year-olds weighing between 10 and 14 kilograms given 20-28 grams of IVIg at $75 average wholesale price/gram, this is within the range of expected cost. It was also interesting that the proportion of echocardiography coding hospitalizations decreased with time, which could be explained by a diminished diagnostic coding or greater outpatient testing over time. Indeed, other procedural codings such as that for lumbar puncture and antibiotic administration were all also less frequent during the latter years of the study, which could also related to clinically more focused hospitalizations. More focused hospitalizations could also explain why the mean cost per hospitalization decreased over time despite a growing proportion of hospitalizations where gammaglobulin was administered.

Although it might be expected that the vast majority of patients hospitalized KD would receive gammaglobulin (22), our study showed that no year had more than 60% of hospitalizations coding this treatment. Although coding deficiencies/priorities would most likely explain this, it is also conceivable that definitive treatment was given at another institution or in a non-institutional setting. It is also interesting that the years with the highest administration of gammaglobulin were 2004 onward (figure 3). In 2004, guidelines were developed for the treatment of patients who fulfill the diagnostic criteria for complete and incomplete KD (23). Corticosteroid treatment was predominantly associated with concomitant gammaglobulin treatment, suggesting that these very few hospitalizations represented refractory or high risk KD cases. The increasing use of inflixamab has been reported in a study of pediatric hospital admissions for KD (24). Our study, which included 20.3% pediatric hospital admissions, did not show significant coding for “infusion/injection of immunosuppressant monoclonal antibody” which would have been expected had this agent been given. Any of the 7 cardiac diagnostic codes was noted in 6.1% of hospitalizations, many of which had no echocardiogram/ultrasound coding again suggesting that diagnostic coding was more comprehensive than procedural coding. Administrative databases have been used to quantify certain quality measures in children (25). However, more complex quality constructs involving both diagnostic and treatment components have not been validated with this type of data source.

The limitations in this study relate to coding practices in a database formed primarily for reimbursement purposes and the retrospective nature of the investigation. Incomplete coding was probably most evident in procedural coding. Furthermore because of the de-identification process, repeat hospitalizations for the same patient could not be determined with certainty, thus we attempted to use matching demographic variables to identify these patients. Our finding that less than 10% of admissions had matching earlier hospitalizations contrasts with the higher re-hospitalization rate observed in pediatric hospital data (24), which probably relates to selection bias for tertiary hospitals.

The overall hospitalization rate noted in New York State for children less than 5 showed a highly significant overall increase over the past 2 decades, but appeared to plateau starting in 2002. Total yearly charges for KD hospitalizations had a very similar pattern. By 2009 the hospitalization rate was 21.2 per 100,000. That rate is quite comparable to the 2006 national rate of 20.8 per 100,000 noted by Holman et al (16).

A predominant TH_2 response and the hygiene hypothesis have been postulated as an explanation for recent increases in atopic diseases (26). Indeed, hospitalizations for disorders involving hypersensitivity have shown increases but in different patterns during the past 3 decades. Asthma hospitalizations in American children increased between 1980 the 1990s but peaked in 1997 (27), while anaphylaxis hospitalizations have been reported increases between the 1990s and the 2000s in studies of adults and children from the United Kingdom, Australia and New York state (28-30). The trends for asthma and anaphylaxis in less than 5 year olds were profiled in the present investigation and contrasted with KD hospitalizations. These differing patterns likely relate to the heterogeneity of influences on the clinical expression of different hypersensitivity disorders.

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There are no conflicts of interests for the authors regarding this manuscript

What is already known on this topic:

What this study adds:

References

1. Burns JC, Glodé MP. Kawasaki syndrome. Lancet. 2004;364(9433):533-44.
2. Nakamura Y, Yashiro M, Uehara R et al. Epidemiologic features of Kawasaki disease in Japan: results of the 2007-2008 nationwide survey. J Epidemiol. 2010;20:302-7.
3. Huang WC, Huang LM, Chang IS, et al. Pediatrics.

2009;123:e401-5.
4. Holman RC, Curns AT, Belay ED, et al. Kawasaki syndrome in Hawaii. Pediatr Infect Dis J. 2005;24:429-33.
5. Terai M, Shulman ST. Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose. J Pediatr. 1997;131:888-93.
6. Masoli M, Fabian D, Holt S, Beasley R; Global Initiative for Asthma (GINA). The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy. 2004;59:469-78.
7. Warner JO. Anaphylaxis; the latest allergy epidemic. Pediatr Allergy Immunol. 2007;18:1-2.
8. Quan JM. SPARCS: the New York State health care data system. J Clin Comput 1980;8:255-63.
9. Lin RY, Pitt TJ, Lou WY, Yi Q. Asthma hospitalization patterns in young children relating to admission age, infection presence, sex, and race. Ann Allergy Asthma Immunol 2007;98:139-45.
10. Lin RY, Cannon AG, Teitel AD. Pattern of hospitalizations for angioedema in New York between 1990 and 2003. Ann Allergy Asthma Immunol 2005;95:159-66.
11. http://www.census.gov/popest/archives/1990s/st_detail.html
12. http://www.census.gov/popest/states/asrh/tables/SC-EST2009-03-36.xls
13. . O'Rourke DH, Raff JA. The human genetic history of the Americas: the final frontier. Curr Biol. 2010;20:R202-7.
14. http://www.health.state.ny.us/statistics/sparcs/sysdoc/appi.htm
15. Gardner W, Mulvey EP, Shaw EC. Regression analyses of counts and rates: Poisson, overdispersed Poisson, and negative binomial models. Psychol Bull 1995;118:392-404
16. Holman RC, Belay ED, Christensen KY, et al. Hospitalizations for Kawasaki syndrome among children in the United States, 1997-2007. Pediatr Infect Dis J. 2010;29:483-8.
17. Ma XJ, Yu CY, Huang M, et al. Epidemiologic features of Kawasaki disease in Shanghai from 2003 through 2007.Chin Med J (Engl). 2010;123:2629-34.
18. Park YW, Han JW, Hong YM, et al. Epidemiological features of Kawasaki disease in Korea, 2006-2008. Pediatr Int. 2011;53:36-9.
19. Shek LP, Cabrera-Morales EA, Soh SE, et al. A population-based questionnaire survey on the prevalence of peanut, tree nut, and shellfish allergy in 2 Asian populations. J Allergy Clin Immunol. 2010;126:324-31, 331.e1-7.
20. Korde LA, Wu AH, Fears T, Nomura et al.Childhood soy intake and breast cancer risk in Asian American women. Cancer Epidemiol Biomarkers Prev. 2009;18:1050-9.
21. Takahashi K, Oharaseki T, Yokouchi Y. Pathogenesis of Kawasaki disease. Clin Exp Immunol. 2011;164 Suppl 1:20-2. doi: 10.1111/j.1365-2249.2011.04361.x.
22. Yellen ES, Gauvreau K, Takahashi M, et al. Performance of 2004 American Heart Association recommendations for treatment of Kawasaki disease. Pediatrics. 2010 ;125:e234-41.
23. Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation. 2004;110:27-47.
24. Son MB, Gauvreau K, Ma L, et al. Treatment of Kawasaki disease: analysis of 27 US pediatric hospitals from 2001 to 2006. Pediatrics. 2009;124:1-8.
25. McDonald KM, Davies SM, Haberland CA, et al. Preliminary assessment of pediatric health care quality and patient safety in the United States using readily available administrative data. Pediatrics. 2008;122:e416-25.
26. Okada H, Kuhn C, Feillet H, Bach JF. The 'hygiene hypothesis' for autoimmune and allergic diseases: an update. Clin Exp Immunol. 2010;160:1-9.
27. Mannino DM, Homa DM, Akinbami LJ, et al. Surveillance for asthma--United States, 1980-1999. MMWR Surveill Summ. 2002;51:1-13.
28. Poulos LM, Waters A-M, Correl PK, et al.: Trends in hospitalizations for anaphylaxis, angiooedema, and urticaria in Australia, 1993–1994 to 2004–2005. J Allergy Clin Immunol 2007, 120:878–884.
29. Gupta R, Sheikh A, Strachan DP, Anderson HR: Time trends in allergic disorders in the UK. Thorax 2007, 62:91–96.
30. Lin RY, Anderson AS, Shah SN, Nurruzzaman F: Increasing anaphylaxis hospitalizations in the first 2 decades of life: New York State, 1990–2006.Ann AllergyAsthma Immunol 2008, 101:387–393.

Author Information

Robert Y. Lin, MD
Departments of Medicine and Pediatrics, New York Downtown Hospital

Lewis M. Krata, MD
Department of Pediatrics, Brooklyn Hospital