

# Identifying undiagnosed primary immunodeficiency diseases in minority subjects by using computer sorting of diagnosis codes

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**Background:** Primary immunodeficiency diseases occur in all populations, but these diagnoses are rarely made in minority subjects in the United States.

**Objective:** We sought to develop and validate a method to identify patients without diagnoses but with immunodeficiency in an urban hospital with a substantial minority patient population.

**Methods:** We developed a scoring algorithm on the basis of International Classification of Disease, Ninth Revision (ICD-9) codes to identify all hospitalized patients age 60 years or less who had been given a diagnosis of 2 or more of 174 ICD-9-coded complications associated with immunodeficiency. Codes were weighted for severity and expressed as a sum for all admissions between October 1, 1995, and December 31, 2002. Patients with, for example, cancer or HIV or those after transplantation or major surgery were excluded. Demographic features of subjects with aggregated ICD-9 codes suggestive of immunodeficiency were compared with those of other inpatients; 59 computer-selected subjects were then tested for immune defects.

**Results:** The computer-identified group contained 533 patients (0.4% of all inpatients), who had been hospitalized 2683 times. The median age was 6.6 years. Sixty-five percent were African American or Hispanic, and 61% were insured by Medicaid, which is significantly more than other inpatients younger than 60 years of age (median age, 32.6 years; 37% minority, 27% insured by Medicaid;  $P < .0001$ ). Primary immunodeficiency was found in 17 (29%) of the 59 subjects tested. Thirteen other patients had secondary immune defects, and 86% of immunodeficient subjects were Hispanic or African American.

**Conclusions:** An ICD-9-based scoring algorithm identifies patients demographically different from other hospitalized subjects who have multiple illnesses suggestive of immunodeficiency. This group contains undiagnosed minority patients with immunodeficiency. (*J Allergy Clin Immunol* 2004;113:747-55.)

**Key words:** Primary immune deficiency, ICD-9, minority health, algorithm

## Abbreviations used

ICD-9: International Classification of Disease Ninth Revision

IDR code: Immunodeficiency disease-related code

IQR: Interquartile range

Primary immune deficiency diseases are a group of conditions that result from mutations in one or more genes that encode components of the immune system.<sup>1,2</sup> These mutations result in more than 90 known defects, with an overall incidence estimated at 1:10,000.<sup>3</sup> The cardinal manifestations of primary immune deficiency include frequent infections of the sinopulmonary and gastrointestinal tracts and systemic signs, such as fever, weight loss, and failure to thrive. Additional complications include autoimmune disease, inflammatory conditions, organ dysfunction, and cancers, especially B-cell lymphoma. The more severe forms of immune deficiencies, such as severe combined immune deficiency, can be fatal unless treated with bone marrow or stem cell transplantation. Other treatments, such as the use of intravenous immunoglobulin, have changed the overall outcome of these diseases.

Because of the specific complications and morbidity associated with immune deficiency, investigators have attempted to determine the incidence of primary immune deficiency in various populations; however, unreported or undiagnosed subjects remain uncounted.<sup>4-7</sup> Because most studies have been done with populations of a European background, there is less information about the incidence of primary immunodeficiency in different races or ethnic groups. However, the data available suggest that the diagnosis of primary immune deficiency is infrequently made in nonwhite, non-Hispanic subjects in the United States.<sup>8-10</sup> Whether the differences in frequency of diagnosis are due to genetic factors or barriers to health care delivery is unknown.

In this study an algorithm for scoring medical illnesses associated with primary immune deficiency weighted for severity was developed and applied by means of a computer program to screen and score patients admitted to a large urban hospital by using collected medical discharge diagnosis codes accumulated over time. Subjects with other medical reasons for these disease manifestations were excluded. The first goal was to

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**TABLE I.** Immune deficiency disease-related codes and weight

| ICD codes* | Description                               | Score |
|------------|-------------------------------------------|-------|
| 036        | Meningococcal meningitis                  | 3     |
| 038        | Sepsis, identified organism               | 3     |
| 047        | Viral meningitis, identified organism     | 3     |
| 136.3      | Pneumocystosis                            | 3     |
| 320        | Bacterial meningitis, identified organism | 3     |
| 480        | Viral pneumonia, identified organism      | 3     |
| 481        | Pneumococcal pneumonia                    | 3     |
| 482        | Bacterial pneumonia, identified organism  | 3     |
| 483        | Pneumonia, not specified                  | 3     |
| 484        | Pneumonia other                           | 3     |
| 485        | Bronchopneumonia                          | 3     |
| 486        | Pneumonia, not specified                  | 3     |
| 485        | Bronchopneumonia, not specified           | 3     |
| 487        | Influenza                                 | 3     |
| 494        | Bronchiectasis†                           | 3     |
| 510        | Empyema                                   | 3     |
| 513.0      | Lung abscess                              | 3     |
| 566        | Rectal abscess                            | 3     |
| 572.0      | Liver abscess                             | 3     |
| 730        | Osteomyelitis                             | 3     |
| 007.1      | Giardiasis                                | 2     |
| 283.0      | Hemolytic anemia†                         | 2     |
| 287.3      | Thrombocytopenia†                         | 2     |
| 288        | Neutropenia†                              | 2     |
| 682        | Cellulitis                                | 2     |
| 683        | Lymphadenitis                             | 2     |
| 789.2      | Splenomegaly†                             | 2     |
| 112        | Thrush-candidiasis†                       | 1     |
| 117.9      | Other mycoses†                            | 1     |
| 382        | Otitis media                              | 1     |
| 382.3      | Chronic otitis†                           | 1     |
| 383.1      | Chronic mastoiditis†                      | 1     |
| 461.0      | Acute sinusitis                           | 1     |
| 466.0      | Acute bronchitis                          | 1     |
| 473.0      | Chronic sinusitis†                        | 1     |
| 491.9      | Chronic bronchitis†                       | 1     |
| 558.9      | Noninfectious gastroenteritis             | 1     |
| 579.9      | Malabsorption†                            | 1     |
| 780.6      | Fever, unknown origin                     | 1     |
| 783.4      | Loss of weight†                           | 1     |
| 783.4      | Failure to thrive†                        | 1     |
| 785.6      | Enlarged lymph glands                     | 1     |
| 787.91     | Diarrhea                                  | 1     |

\*Only the root code is given for most; ICD codes expand to 174 separate diagnoses.

†Chronic codes, not counted twice in a 60-day period.

determine the incidence, age, ethnic-racial background, and insurance payer of subjects with recurrent illnesses suggestive of immunodeficiency and compare these with the same factors in all other inpatients. A group of patients identified by means of computer screening was then tested for immune defects to validate the algorithm.

## METHODS

### Hospital, patients, and demographics

In addition to being a tertiary referral center, Mount Sinai Medical Center serves the low-income working class communities of East,

South, and Central Harlem. Twenty-one percent of inpatients are self-identified as Hispanic, and 16% are of African American descent. The major insurance carriers for the hospital are Medicaid (21%), followed by Medicare (17%) and health maintenance organizations (18%). This study was done in HIPAA compliance after obtaining an institutional review board waiver of informed consent to review medical records. Confirmatory patient testing was done after obtaining permission from the primary doctor and informed consent from the patient or parent by using either English or Spanish institutional review board—approved consent forms.

### Disease-diagnosis codes selected

First, diagnoses suggestive of primary immunodeficiency were compiled by using standard immunologic references and translated into the corresponding International Classification of Disease, Ninth Revision (ICD-9) codes used for recording medical encounters.<sup>11</sup> The basic disease codes used (immunodeficiency disease—related [IDR] codes) are listed in Table I; expansion of these codes into all related subcodes resulted in 174 diagnoses. This list includes all illnesses or conditions resulting from congenital immunodeficiency described in reviews of primary immunodeficiency,<sup>1-3</sup> chronic granulomatous disease,<sup>9</sup> hyper-IgE syndrome,<sup>12</sup> X-linked agammaglobulinemia,<sup>13</sup> severe combined immunodeficiency,<sup>14</sup> complement deficiency,<sup>15</sup> DiGeorge syndrome,<sup>16</sup> transient hypogammaglobulinemia,<sup>17</sup> common variable immunodeficiency,<sup>10</sup> and selective IgA deficiency.<sup>18</sup> A second list of 1800 ICD-9 codes was compiled that designate a group of diseases that could lead to similar conditions, including cancers (except skin cancer); HIV; bone marrow—stem cell or organ transplantation; cardiac and other major operative procedures; quadriplegia; alcoholism; heroin, cocaine, or other drug addictions; and cystic fibrosis. Subjects with these ICD-9 codes and all subjects older than 60 years of age were excluded.

### Classifying IDR codes, assigning scores, and computer screening

Detailed demographic, diagnostic, and use data for inpatient admissions are stored in the Eagle 2000 medical record—billing system (American Healthware) and an Oracle data warehouse. Inpatient records from January 1, 1995, to October 1, 2001, were searched for admitted subjects who had been given the relevant inclusion diagnoses and to remove subjects with exclusion diagnoses. The ICD-9 codes chosen were assigned a score (1, 2, or 3) in accordance with the relative severity of the illness (Table I). Time-restricted criteria were applied to eliminate the multiple counting of readmissions for the same diagnoses for the same episode of illness, so that patients admitted with the same diagnosis codes were counted only once in a 30-day period. Because subjects might have had several hospitalizations for illnesses with a more prolonged clinical course, selected ICD-9 codes (designated here as “chronic codes,” Table I) were counted only once within a 60-day window. An IDR score for each patient was the sum of the scores acquired by each subject over the test period. A primary diagnosis and up to 7 secondary diagnoses for each admission were included. An IDR score of 6 or more was arbitrarily chosen as the threshold indicating a significant number of illnesses. Discharge diagnoses were assigned by trained chart reviewers not known to the study coordinators, who sought verifying evidence for each code, including bacteriologic or viral cultures, radiologic results, laboratory tests, review of confirmatory chart notes made by physicians, and discharge summaries.

The age, sex, race, insurance payer, and home zip code of subjects who had an IDR score of 6 or more were then compared with those of all other nonselected patients (age <60 years) hospitalized in the same time period. The SAS and Oracle programming languages were

**TABLE II.** Characteristics of inpatients: January 1995 through October 2001

|                  | Inpatients meeting screening criteria (n = 533) |      | Inpatients < 60 y, 1995-2001 (n = 135,842) |      |
|------------------|-------------------------------------------------|------|--------------------------------------------|------|
| Sex              |                                                 |      |                                            |      |
| Male             | 282                                             | 53%  | 52,550                                     | 39%  |
| Female           | 251                                             | 47%  | 83,270                                     | 61%  |
| Age*†            |                                                 |      |                                            |      |
| 0-1 y            | 43                                              | 8%   | 6792                                       | 5%   |
| 1-5 y            | 160                                             | 30%  | 24,451                                     | 18%  |
| 6-10 y           | 89                                              | 16%  | 12,226                                     | 9%   |
| 11-20 y          | 54                                              | 10%  | 7409                                       | 5%   |
| 21-30 y          | 33                                              | 6%   | 16,578                                     | 12%  |
| 31-40 y          | 40                                              | 8%   | 24,548                                     | 18%  |
| 41-50 y          | 51                                              | 10%  | 17,542                                     | 13%  |
| 51-60 y          | 63                                              | 12%  | 16,806                                     | 12%  |
| Race-ethnicity*  |                                                 |      |                                            |      |
| Hispanic         | 184                                             | 35%  | 28,496                                     | 21%  |
| White            | 89                                              | 17%  | 56,455                                     | 41%  |
| African American | 158                                             | 30%  | 21,484                                     | 16%  |
| Asian            | 4                                               | 8%   | 4357                                       | 3%   |
| Native American  | 1                                               | 0.1% | 234                                        | 0.2% |
| Other            | 49                                              | 9%   | 7984                                       | 6%   |
| Unknown          | 47                                              | 9%   | 16,289                                     | 12%  |
| Payer*           |                                                 |      |                                            |      |
| Medicaid         | 326                                             | 61%  | 37,330                                     | 27%  |
| HMO              | 90                                              | 17%  | 40,272                                     | 30%  |
| Blue Cross       | 51                                              | 10%  | 20,382                                     | 15%  |
| Commercial       | 30                                              | 6%   | 41,606                                     | 31%  |
| Medicare         | 21                                              | 4%   | 4017                                       | 3%   |
| Self-pay         | 10                                              | 2%   | 4243                                       | 3%   |
| Other            | 5                                               | 0.1% |                                            |      |

\*Significant differences between selected patients and other inpatients,  $P < .0001$ .

†Age at last admission.

used to extract the data from the repositories; Microsoft Access and Excel software packages were used to sort and manage the data.

### Testing for immune defects

A validation study was then performed to determine whether the scoring algorithm and computer program could potentially identify patients with immune defects. For this, immune functions of computer-identified hospitalized subjects admitted from January 1, 1995, to December 31, 2002 (713 patients), who had accumulated IDR scores of 6 or greater were tested by using standard blood tests to assess immune functions.<sup>1-3, 19, 20</sup> When these subjects were admitted to the hospital or appeared in a clinic, an e-mail notification was sent to the study coordinator to facilitate case finding. After this, permission from the primary doctor and patient informed consent were obtained before enrollment and blood testing. Because the most common immune defects are those of antibody production, initial tests included serum immune globulins and antibody responses to vaccine antigens. Interpretation of subnormal IgG subclasses were evaluated and verified by using antibody function tests in each case.<sup>21</sup> Lymphocyte surface markers, lymphocyte proliferation, neutrophil reduction of dihydrorhodamine, antineutrophil antibody testing, and complement testing was done by standard means.<sup>22-24</sup> Diagnoses of immune deficiency were made according to established criteria.<sup>1-3</sup>

### Statistical analysis

$\chi^2$  Tests were used for comparisons between all patient groups. For ordinal factors, a Mantel-Haenszel  $\chi^2$  test for trend was used. Median and interquartile values were determined. All tests were done with a significance level of .05.

## RESULTS

### Sorting by computer diagnoses

In the initial study a total of 321,754 inpatient visits (made by 187,093 subjects) between January 1, 1995, and October 1, 2001, were surveyed to screen for individuals with IDR score totals of 6 or more. After excluding all subjects older than 60 years of age and those with the chosen exclusion ICD-9 codes, there were 533 inpatients (0.4% of the total hospitalized group or 0.2% of the group < 60 years of age), who were hospitalized a total of 2683 times, who had an IDR score of 6 or greater and who were considered as potentially immune deficient. As a group, these individuals were hospitalized between 1 and 30 times in this period, or a mean of 5 times for each patient. Table II shows the sex, race, age, and insurance payer of the patients identified by means of computer screening.

The subjects with an IDR score of 6 or more had a median age 6.6 years (interquartile range [IQR], 2.5-23 years) and stayed in the hospital a median of 4 days per admission (IQR, 2-7 days). Other admitted patients younger than 60 years of age and not computer selected on the basis of these criteria had a median age of 32.6 years (IQR, 13-51.6 years; older,  $P < .0001$ ) and stayed in the hospital a median of 3 days (IQR, 2-6 days; shorter time,  $P < .001$ ).

**TABLE III.** Most prevalent IDR disease codes for computer-selected hospitalized subjects\*

| ICD code                     | Diagnosis                                          | No. | %†  |
|------------------------------|----------------------------------------------------|-----|-----|
| 486                          | Pneumonia, organism not specified                  | 813 | 30  |
| 038                          | Septicemia (all bacteria)                          | 136 | 5.1 |
| 783.4                        | Failure to thrive                                  | 127 | 4.7 |
| 510.9 and 510.0              | Empyema with or without fistula                    | 61  | 2.3 |
| 480 all codes;<br>484.6; 483 | Viral or fungal pneumonia;<br>mycoplasma pneumonia | 66  | 2.5 |
| 494                          | Bronchiectasis                                     | 57  | 2.1 |
| 482 all codes                | Other bacterial pneumonias                         | 56  | 2.1 |
| 730 all codes                | Osteomyelitis                                      | 24  | 1.7 |

\*Counting all discharge diagnoses, primary and up to 7 secondary ICD codes.

†On the basis of 2683 admissions for 533 computer-selected patients.

### Racial, ethnic, and insurance information for selected subjects

Significantly more members of the computer-selected group with IDR scores of 6 or more were Hispanic (35%) or African American (30%) than the other inpatients younger than 60 years of age, of whom 21% were Hispanic and 16% were African American ( $P = .0001$  for both comparators). The computer-selected patients lived in the neighborhood of Mount Sinai Medical Center (zip code 10029, East and Central Harlem) more often than other admitted subjects (24% vs 10%,  $P < .001$ ). Sixty-one percent of the selected group were insured by Medicaid, significantly more than other inpatients younger than 60 years of age, only 27% of whom had Medicaid ( $P = .0001$ ).

### Diagnoses of the computer-selected subjects

The computer-selected subjects were most often hospitalized for one of the many ICD-9 codes applied to pneumonia (Table III); 935 of the 2683 admissions involved at least one such code (35% of the total). Of these admissions, 813 (87%) hospitalizations were for pneumonia, “no organism specified” (ICD 486). For 56 other admissions, specific bacteria were given as the cause of pneumonia, and for 66 admissions, viral, fungal, or mycoplasma pneumonias were diagnosed. The majority of all admissions for pneumonia occurred in infants and children younger than 10 years. The second most common diagnosis leading to inclusion in the computer-selected group was sepsis, with 136 admissions for 113 patients. Of the patients with sepsis, 38% were younger than 10 years, and 50% were younger than 20 years. Seventy-four subjects had both sepsis and pneumonia; 54 patients who had pneumonia had empyema and were admitted to the hospital 61 times. Failure to thrive was diagnosed for 53 pediatric patients, who were admitted a total of 127 times. Osteomyelitis (24 cases), empyema (54 cases), and bronchiectasis (21 cases) were diagnosed in patients in all age groups.

**TABLE IV.** Most common ICD codes\* found for the subjects with IDR scores of more than 6

| ICD code          | Diagnosis                                       | No. | %†  |
|-------------------|-------------------------------------------------|-----|-----|
| 493.00            | Asthma without asthmaticus                      | 864 | 32  |
| 493.01            | Asthma with status asthmaticus                  | 316 | 12  |
| 282.62,<br>282.61 | Hemoglobin SS disease with or<br>without crisis | 224 | 8.3 |
| 250               | Diabetes, all codes                             | 207 | 7.7 |
| 401.9             | Hypertension                                    | 192 | 7.1 |
| 276.5             | Hypovolemia                                     | 144 | 5.4 |
| 428.0             | Congestive heart failure                        | 128 | 4.8 |
| 518.0             | Pulmonary collapse                              | 121 | 4.5 |

\*ICD codes other than those used in the calculation of the IDR scores.

†On the basis of 2683 admissions for 533 computer-selected patients.

### Other discharge diagnoses for the group

Forty-eight percent of patients with IDR scores of 6 or more had been given a diagnosis of asthma on one or more admissions (Table IV), although the concomitant diagnosis of asthma was made in only 17% of all admissions for pneumonia. Other common diagnoses included sickle cell disease, diabetes mellitus, respiratory collapse, or cardiac disease.

### Testing immune functions in computer-identified subjects

Because we had proposed that using a computer-based selection method might locate patients with immune defects, we then tested the validity and potential use of this system. For this, we approached physicians of 82 computer-identified patients who had IDR scores of 6 or more for permission to perform immune function tests at the time that these patients returned for readmission or a clinic visit. Of this group, 23 (28%) patients could not be tested because personal or parental consent could not be obtained ( $n = 13$ ), patients refused testing ( $n = 3$ ), or patients were excluded from participation because significant organ failure had developed ( $n = 4$ ) or mental status precluded obtaining informed consent ( $n = 3$ ). Fifty-nine patients were tested (36 female and 23 male patients): 28 (45%) were Hispanic; 20 (33%) were African American; 10 (16%) were white, non-Hispanic; and 1 was Asian. Of this group, 17 (27%) patients (ages, 2-60 years) were found to have a primary immune defect (Table V). An antibody deficiency was found in 9 patients, and 3 others had neutrophil defects. This group was predominantly male (65%) and mostly Hispanic or African American (94%). These 17 patients had been admitted to the hospital 48 times in the surveyed period, most commonly for pneumonia (primary code, ICD 486; 19 times) or bronchiectasis with exacerbation (ICD 494), but other infections (bacterial pneumonias and sepsis) or hematologic disorders (lymphopenia, neutropenia, immune thrombocytopenia purpura, or hemolytic anemia) were commonly found as secondary ICD codes.

Thirteen other patients of the 59 evaluated had secondary immune defects stemming from other underlying diseases: sickle cell disease ( $n = 5$ ), prior

**TABLE V.** Computer-selected patients found to have primary immune defects

| Patient no. | Age (y) | Race-ethnicity | Sex | Immune defect identified              | Other diagnoses                                             | Score | Primary ICD codes for admissions | Secondary ICD codes                                               |
|-------------|---------|----------------|-----|---------------------------------------|-------------------------------------------------------------|-------|----------------------------------|-------------------------------------------------------------------|
| 1           | 10      | B              | M   | IgG2 deficiency                       | Asthma/recurrent pneumonia/<br>gastroesophageal reflux      | 15    | 486                              | 382.9, 486                                                        |
| 2           | 49      | H              | M   | Lymphopenia, IgG1 and IgG2 deficiency | Recurrent pneumonia, asthma                                 | 14    | 486,486                          | 486, 466.0                                                        |
| 3           | 2       | H              | M   | Leukocyte adhesion deficiency 2       | Cellulitis, fever                                           | 13    | 780.6, 780.6, 486                | 486, 038.9, 787.91, 117.9, 112.0, 510.9, 682.2, 486, 487.1, 780.6 |
| 4           | 22      | H              | M   | CVID                                  | Bronchiectasis, failure to thrive                           | 13    | 494, 494, 494, 494, 494          | 038.19, 486, 038.0, 783.4, 112.0                                  |
| 5           | 48      | B              | F   | IgA deficient                         | Angioedema, sepsis endocarditis/<br>SLE                     | 12    | 486, 486, 486, 486               | 038.19, 038.11, 283.9                                             |
| 6           | 22      | H              | M   | CVID                                  | Bronchiectasis                                              | 12    | 494, 494, 494.00                 | 486, 038.8, 482.2, 487.0                                          |
| 7           | 9       | B              | M   | DiGeorge syndrome                     | Recurrent pneumonia, cardiac disease, thrush                | 12    | 486, 486, 486                    | 486, 112.0                                                        |
| 8           | 60      | W              | F   | CVID                                  | Mycoplasma pneumonia, bronchiectasis, ITP                   | 11    | 482.83, 486                      | 038.9, 494, 486, 483.0, 287.3, 112.0, 287.3                       |
| 9           | 41      | W              | F   | CVID with granuloma                   | Pneumonia, pleurisy, splenectomy, hemolytic anemia, empyema | 10    | 283.0, 572.0                     | 783.4, 461.9, 382.9, 486, 288.8, 289.59, 510.9, 283.0, 287.3      |
| 10          | 43      | H              | M   | IgG deficiency                        | Sarcoidosis, bronchiectasis, pulmonary hypertension         | 10    | 494, 482.9, 487.1                | 494                                                               |
| 11          | 7       | H              | F   | Schimke immunosseous dysplasia(?)     | ITP/sepsis/nephrotic syndrome/herpes zoster                 | 9     | 486                              | 287.3, 491.8, 283.0, 491.8, 785.6, 491.8                          |
| 12          | 6       | H              | M   | Neutropenia                           | Chronic otitis, hearing loss/seizures                       | 8     | 486, 486                         | 486, 288.0, 382.9                                                 |
| 13          | 48      | H              | F   | IgG1 deficiency                       | Asthma, recurrent pneumonia                                 | 8     | 486, 486, 486                    | 466.0, 486, 466.0, 473.9, 473.9                                   |
| 14          | 10      | B              | M   | Lymphopenia*                          | Recurrent pneumonia, failure to thrive                      | 7     | 783.4, 783.4                     | 486, 485, 513.0, 783.4, 780.6, 382.9                              |
| 15          | 9       | H              | M   | Combined T cell and B cell*           | Recurrent pneumonia                                         | 6     | 486                              | 038.40, 486, 785.6, 494.0                                         |
| 16          | 1       | B              | F   | Autoimmune neutropenia                | Pneumonia                                                   | 6     | 486, 480.10                      | 486, 288.0                                                        |
| 17          | 39      | H              | M   | IgG deficiency                        | Asthma/recurrent pneumonia                                  | 6     | 494, 494, 494.0                  | 486, 466.0                                                        |

Up to 7 secondary codes for any admission are shown. Only immune deficiency scored codes are indicated; other diagnoses given are not included here. CVID, Common variable immune deficiency; SLE, systemic lupus erythematosus; ITP, immune thrombocytopenia purpura. Race and ethnicity: W, white; B, African American; H, Hispanic, any race; A, Asian.

\*Significant lymphopenia and combined T-cell/B-cell defect: not yet clearly categorized into existing diagnostic categories.

splenectomy (n = 3), systemic autoimmune disease (n = 2), sarcoidosis on chronic steroids (n = 1), immune suppression for infantile Crohn's disease (n = 1), or bone marrow aplasia (n = 1; Table VI). The age range of these patients was wide (8-60 years), and most were female (11/12) and Hispanic or African American. Table VII shows the 29 other patients for whom no immune defect was identified; the ICD codes that brought them to attention are shown, as well as the total IDR scores acquired by each over the surveyed period. This group of subjects (age range, 1-60 years) contains patients with congenital syndromes (Riley Day, Kabuki syndrome, or osteogenesis imperfecta), other complex medical problems (Swyer

James, cardiac disease, or development delay with or without seizures), and bronchiectasis (5 patients), and there were 11 patients with poorly controlled asthma. Hispanic or African American patients were again in the majority (25/29 patients). For this group as well, pneumonia was the most common diagnosis (68 admissions). Three of these patients (nos. 11, 21, and 22) are brothers, suggesting a still undiagnosed condition.

## DISCUSSION

The Mount Sinai Medical Center serves as a referral center for patients with primary immunodeficiency

**TABLE VI.** Patients with secondary immune defects

| Patient no. | Age (y) | Race-ethnicity | Sex | Score | IDR diagnosis codes leading to inclusion*                                    | Underlying diagnoses                                                |
|-------------|---------|----------------|-----|-------|------------------------------------------------------------------------------|---------------------------------------------------------------------|
| 1           | 60      | A              | F   | 29    | Bronchiectasis, recurrent pneumonia                                          | Sarcoidosis on chronic steroids                                     |
| 2           | 11      | H              | M   | 27    | Spleen abscess, splenomegaly                                                 | Sickle cell disease                                                 |
| 3           | 3       | B              | F   | 21    | Recurrent pneumonia, liver abscess                                           | Infantile Crohn's disease on immune suppression                     |
| 4           | 8       | H              | F   | 14    | Sepsis, FUO, spleen abscess, pneumonia                                       | Sickle cell disease, splenectomy                                    |
| 5           | 8       | H              | F   | 11    | Lymphopenia, sepsis neutropenia                                              | Aplastic anemia                                                     |
| 6           | 10      | B              | F   | 11    | Recurrent pneumonia, liver abscess                                           | Sickle cell disease                                                 |
| 7           | 26      | B              | F   | 11    | Recurrent pneumonia, lymphopenia                                             | SLE and rheumatoid arthritis                                        |
| 8           | 58      | W              | F   | 10    | Lymphopenia osteomyelitis x2, ITP, neutropenia, cellulitis                   | Anemia unknown cause                                                |
| 9           | 21      | W              | F   | 9     | Recurrent pneumonia, bronchiectasis                                          | Spherocytosis, splenectomy                                          |
| 10          | 19      | H              | F   | 9     | FUO, recurrent pneumonia salmonella bacteremia                               | SLE/complement defect, neutropenia                                  |
| 11          | 27      | H              | F   | 9     | Bacterial pneumonia, autoimmune hemolytic anemia, cellulitis, bronchiectasis | Splenectomy, severe malabsorption; finally, small bowel transplant† |
| 12          | 16      | A/B            | F   | 6     | Recurrent pneumonia                                                          | Sickle cell disease                                                 |
| 13          | 14      | B              | F   | 6     | Recurrent pneumonia                                                          | Sickle cell disease                                                 |

SLE, Systemic lupus erythematosus; FUO, fever of unknown origin thrombocytopenia purpura. Race and ethnicity: W, white; B, African American; H, Hispanic, any race; A, Asian.

\*Only immune deficiency—scored codes are indicated here.

†Small bowel transplantation was done after she was identified by means of computer screening.

disease and treats a large outpatient population with these disorders. These patients have (historically) been primarily of white, non-Hispanic background (92%), in contrast to the general hospitalized patient population, which is 21% Hispanic and 16% African American.

To investigate whether patients with undiagnosed immune deficiency could be identified in our diverse inpatient hospital population, we devised a scoring algorithm and computer screening method on the basis of ICD-9 codes to survey the discharge diagnoses of all hospitalized patients over periods of time. Although clearly not perfect and requiring inclusion of all relevant codes on the basis of laboratory or radiologic confirmation,<sup>25,26</sup> ICD codes have previously been used as research tools in the computer analyses of large populations, as for example, to determine child abuse mortality,<sup>27</sup> relate HDL cholesterol to coronary heart disease,<sup>28</sup> estimate diabetes-related and infectious disease mortality,<sup>29,30</sup> and determine costs and reimbursements in sickle cell disease.<sup>31</sup>

Using the scoring system and computer program, we found that 0.4% of all inpatients (or 0.2% of admitted subjects <60 years of age) had been given a diagnosis of more than one illness often associated with immune deficiency during the surveyed period, while not being given a diagnosis of any of a large number of other conditions that might have led to these illnesses (eg, HIV or cancer). The computer-selected subjects were admitted an average of 5 times each in this period, were more often Hispanic or African American, were significantly younger, were hospitalized for longer periods, and were more likely to be insured by Medicaid than other hospitalized patients not meeting these selection criteria.

Fifty-nine computer-selected subjects were tested to investigate whether these subjects might have immune deficiency. There were 17 subjects with a form of primary immune deficiency; 13 others had conditions associated with secondary immune deficiency (eg, sickle cell disease, immune suppression, or aplastic anemia). The majority of the subjects with primary (15/17) or secondary (10/13) immune deficiency were Hispanic or African American, confirming that minority subjects with immune defects can be identified by means of this method in a diverse hospital population.

For 29 other tested subjects, no immune defect has been identified. Some of these subjects have known congenital or developmental defects or asthma or other chronic illnesses that are likely to have led to the recurrent infections experienced. The other patients in this group might have had repeated illnesses caused by unknown anatomic, nutritional, or environmental reasons; however, it is possible that some of these subjects have immune defects not tested for or immune defects that have not yet been described. For example, 3 brothers in this group who had bacterial pneumonia leading to empyema could be in this category.

How many subjects with primary immune deficiency might one expect in this inpatient group? An estimate for the prevalence of immune deficiency in the general population is 1:10,000, (excluding IgA deficiency)<sup>1-3</sup>; however, this is unlikely to be correct for hospitalized patients. Surveying populations of pediatric or adult patients with refractory sinusitis, recurrent pneumonia, or bronchiectasis, immune defects have been found in 8% to 10%.<sup>32-35</sup> For children who had recurrent pneumonia in

**TABE VII.** Patients with no identified immune defects

| Patient no. | Age (y) | Race-ethnicity | Sex | IDR score | IDR diagnosis codes leading to inclusion*                | Other diagnoses                                             |
|-------------|---------|----------------|-----|-----------|----------------------------------------------------------|-------------------------------------------------------------|
| 1           | 16      | H              | M   | 23        | Bronchiectasis                                           | Lymphoid interstitial infiltrates; Swyer-James              |
| 2           | 9       | B              | F   | 21        | Bronchiectasis, bacterial pneumonia x2                   | Asthma, developmental delay                                 |
| 3           | 10      | H              | F   | 19        | Bronchiectasis, bacterial pneumonia, chronic otitis      | Asthma                                                      |
| 4           | 9       | B              | F   | 18        | Recurrent pneumonia, failure to thrive                   | Protein calorie malnutrition                                |
| 5           | 25      | W              | F   | 18        | Bronchiectasis, recurrent pneumonia, bacterial pneumonia | Riley Day syndrome                                          |
| 6           | 51      | H              | F   | 18        | Recurrent pneumonia                                      | Cardiac arrhythmia, scheduled for valve replacement, asthma |
| 7           | 10      | H              | F   | 12        | Recurrent pneumonia, bronchiectasis                      | Asthma                                                      |
| 8           | 4       | H              | F   | 12        | Chronic sinusitis, liver abscess                         | Kabuki syndrome                                             |
| 9           | 7       | H              | F   | 10        | Recurrent pneumonia                                      | Developmental delay/seizures                                |
| 10          | 60      | H              | F   | 9         | Pneumonia, lymphopenia, sepsis                           | Cardiac disease, asthma                                     |
| 11†         | 3       | W              | M   | 9         | Recurrent pneumonia, empyema, sepsis                     | None                                                        |
| 12          | 43      | B              | M   | 9         | Recurrent pneumonia                                      | Asthma                                                      |
| 13          | 54      | H              | F   | 9         | Asthma                                                   | Asthma/COPD                                                 |
| 14          | 39      | H              | F   | 8         | Recurrent pneumonia, sepsis                              | Abdominal pain, endometriosis                               |
| 15          | 44      | W              | M   | 7         | Pneumonia, chronic sinusitis                             | Allergies                                                   |
| 16          | 8       | H              | M   | 7         | Recurrent pneumonia                                      | Asthma                                                      |
| 17          | 28      | B              | F   | 7         | Recurrent pneumonia                                      | Asthma                                                      |
| 18          | 55      | H              | F   | 6         | Recurrent pneumonia, lymphopenia, staphylococcal sepsis  | Allergies                                                   |
| 19          | 5       | U              | M   | 6         | Empyema, lung abscess                                    | Asthma                                                      |
| 20          | 31      | B              | M   | 6         | Recurrent pneumonia                                      | Asthma                                                      |
| 21†         | 10      | W              | M   | 6         | Pneumonia, empyema, ITP                                  | None                                                        |
| 22†         | 7       | W              | M   | 6         | Pneumonia, empyema                                       | None                                                        |
| 23          | 3       | H              | M   | 6         | Recurrent pneumonia                                      | Developmental delay; aspiration                             |
| 24          | 56      | B              | F   | 6         | Recurrent pneumonia                                      | Asthma                                                      |
| 25          | 13      | B              | F   | 6         | Recurrent pneumonia                                      | Osteogenesis imperfecta                                     |
| 26          | 12      | H              | M   | 6         | Recurrent pneumonia                                      | Asthma                                                      |
| 27          | 12      | B              | F   | 6         | Recurrent pneumonia                                      | Asthma                                                      |
| 28          | 1       | B              | F   | 6         | Lymphopenia, staphylococcal sepsis                       | Asthma, sleep disorder                                      |
| 29          | 39      | W              | F   | 6         | Cellulitis, osteomyelitis                                | Morbid obesity/diabetes mellitus                            |

COPD, Chronic obstructive pulmonary disease. Race and ethnicity: W, white; B, African American; H, Hispanic, any race; A, Asian.

\*Only immune deficiency—scored diagnoses are indicated here.

†These three patients are brothers with much the same history.

a previous study,<sup>33</sup> immune defects were found in 10%. Thus taking our most prevalent diagnosis in the group of 533 subjects, pneumonia (410 of these patients with 813 episodes), and assuming that 10% might be immune deficient, 41 cases of primary immune deficiency might be found in this set of patients. On the other hand, using a group of diagnoses, we found 17 (29%) patients with primary immune deficiency in a group of 59 subjects.

For inpatients with IDR scores of 6 or more, the diagnosis of asthma was common; 48% of patients had this diagnosis on at least one admission. Because regions of pulmonary asthma-associated atelectasis could be interpreted radiographically as pneumonia, a potential overlap between these 2 diagnoses was investigated; however, the 2 diagnoses were given on the same admission for only 17% of all admissions. We elected to not exclude subjects with asthma from consideration

because this diagnosis might be made in immune deficient subjects. Similarly, we did not choose to exclude subjects with sickle cell anemia or diabetes mellitus, even though these conditions can lead to frequent infections, and in our survey 8.3%, or 7.7% of hospitalizations, included these diagnosis codes. With more selective use of ICD-9 codes, a more targeted method of locating patients might be possible.

Of 1498 patients reported to the Primary Immunodeficiency Disease Registry, 6.6% are African American and 4.7% are Hispanic (NIH Primary Immunodeficiency Diseases Registry, data on file. Towson (MD): Immune Deficiency Foundation; USIDNet.org); United States census data (2000) indicate that 12.3% of the population is now African American and 12.5% is Hispanic.<sup>36</sup> These data and other published reports indicate a relative lack of minority patients given a diagnosis of primary immune deficiency<sup>8-10</sup>; this could be due to genetic differences, patient referral, scattered health care delivery, or all of these. Genetic differences in immunity are likely; selective IgA deficiency is found at a ratio of 1:400 to 1:1000 in European-related populations but occurs in only 1:14,840 Japanese blood donors.<sup>37</sup> The inheritance of the HLA-DR3, HLA-B8, and HLA-A1 haplotypes is associated with both common variable immune deficiency and IgA deficiency in European populations<sup>38</sup>; however, in African American subjects the incidence of the HLA-B8 and HLA-A1 antigens is 6% and 7% compared with 16% and 28% for persons of European descent.<sup>39</sup>

There are other reasons why some patients with underlying immune deficiency are not given diagnoses of these conditions, some of which emerged in this study; 28% of patients who had illness characteristics of immune deficiency could not be tested because informed consent could not be obtained (eg, no telephone, wrong telephone number, parent did not visit, patient or parent did not want blood drawn, no follow-up appointment kept, patient scheduled for organ transplant or valve replacement, or schizophrenic episode). In these cases these same reasons might have prevented appropriate testing and follow-up, even if immune deficiency had been previously suspected.

Disparities in health care for African American and Hispanic subjects have been noted in many other studies; barriers to health care (eg, inadequate communication and finances) are likely to be factors preventing diagnosis and treatment. For example, urban African American children with asthma receive 39% of their care in emergency departments.<sup>40</sup> Even among insured patients or those of roughly similar socioeconomic status studies have pointed to unexplained differences in diagnosis and treatment, enrollment in clinical trials, and medical outcomes.<sup>41,42</sup> Latinos, the largest minority group of children, are at particularly high risk for medical conditions and lack of health insurance.<sup>43</sup>

Delay or failure to make the diagnosis of a primary immune defect in an affected patient can result in a predictable group of medical complications. Suitable treatments are available for the majority of diseases and are cost-effective.<sup>1-3</sup> Applied to a large urban hospital

patient population, this scoring algorithm and method of computer screening identifies undiagnosed and often minority patients with immune defects. It should be kept in mind, however, that as in the application of all algorithms, this computer method will miss some patients who have immune defects and identify others who do not.

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