Sudden-onset asthma exacerbations: clinical features, response to therapy, and 2-week follow-up

R.G. Barr*, P.G. Woodruff†, S. Clark*, C.A. Camargo Jr.*,# on behalf of the Multicenter Airway Research Collaboration (MARC) investigators


ABSTRACT: Sudden-onset asthma exacerbations may have different triggers and responses to treatment than slower-onset exacerbations. The authors studied this hypothesis among patients with severe asthma exacerbations.

The Multicenter Airway Research Collaboration prospectively enrolled patients presenting to 64 North American emergency departments with asthma exacerbations. Of 1,847 patients aged 18–54 yrs, 900 had severe exacerbations (peak expiratory flow rate (PEFR) <50% predicted or hospitalized without PEFR). These patients were divided into sudden-onset (≤3 h of symptoms) and slower-onset (>3 h of symptoms) groups.

Fourteen per cent (95% confidence interval, 11–16%) of patients with severe asthma exacerbations had sudden-onset exacerbations. Sudden-onset patients were similar to slower-onset patients, except triggers of their exacerbations were more often respiratory allergens, exercise or psychosocial stress and less often respiratory infections. Sudden-onset patients were more likely to have used oral β-agonists and salmeterol in the preceding 4 weeks. Although initial PEFRs and management were similar, sudden-onset patients had a greater improvement in PEFR (35 versus 28% p<0.001). Sudden-onset patients were less often discharged on systemic corticosteroids, but had similar 2-week relapse rates compared with slower-onset patients.

Among patients presenting with severe asthma exacerbations, sudden-onset exacerbations had a different pattern of triggers and greater improvement with treatment than slower-onset exacerbations.


Sudden-onset asthma exacerbations may represent a distinct clinical entity from exacerbations that present with a slower onset of symptoms [1]. Sudden-onset exacerbations have been defined previously by the development of severe airway obstruction within 1.5 h [2] or 3 h of the onset of symptoms [3–5]. A subset of patients with fatal asthma present with sudden-onset symptoms, and patients with severe sudden-onset exacerbations may share characteristics with these patients [5–9].

Prior studies have suggested that sudden-onset asthma exacerbations are less often triggered by respiratory infections and have a faster response to therapy compared with slower-onset exacerbations [3–5, 10], however those studies were retrospective and relatively small. In the present study, the authors describe the clinical features, response to therapy, and 2-week follow-up of adults with severe, sudden-onset asthma exacerbations who were prospectively enrolled and followed as part of a large, multicentre cohort.

Methods

This study combined data from four prospective cohort studies performed in October 1996 to December 1996, April 1997 to June 1997, October 1997 to December 1997, and March 1998 to April 1998 as part of the Multicenter Airway Research Collaboration (MARC) [11]. Using a standardized protocol, investigators at 64 emergency departments (ED) in the USA and Canada provided 24-h-a-day coverage for a median of 2 weeks. Inclusion criteria were physician diagnosis of asthma exacerbation, age 18–54 yrs, and the ability to give informed consent. Repeat visits by individual subjects were excluded. Patients with lost medical records (n=25) were excluded because a diagnosis of asthma could not be confirmed. All patients were managed at the discretion of the treating physician. Of 2,496 eligible patients, 1,847 (74%) patients were enrolled. The institutional review board at each of the 64 participating hospitals approved the
study, and informed consent was obtained for all participants.

For the present analysis, the cohort was restricted to patients with severe asthma exacerbations. A severe asthma exacerbation was defined according to the National Asthma Education and Prevention Program (NAEPP) criteria [12] as presentation with a peak expiratory flow rate (PEFR) <50% of predicted. In addition, patients who were hospitalized for asthma but did not have an initial PEFR measurement were considered to have had a severe exacerbation.

Sudden-onset exacerbations were defined as presentation to the ED within 3 h of the onset of symptoms; slower-onset exacerbations were defined as presentation after 3 h of asthma symptoms.

Data collection

Investigators conducted the ED interview with a standardized questionnaire to assess patients’ demographic characteristics, asthma history, and details of the current asthma exacerbation. The interview was distinct from clinical history-taking, and investigators did not participate in clinical decision-making. Data on ED management and disposition were obtained by chart review. Follow-up data were collected by telephone interview 2 weeks later. All forms were reviewed by site investigators before submission to the MARC Coordinating Centre in Boston, MA, USA, where they underwent further review by trained personnel and then double data entry.

Patients’ median household incomes were estimated as the median household income of the Zip code of residence [13]. Primary care provider status was assigned on the basis of the following question: “Do you have a primary care provider (such as a family doctor, internist, or nurse practitioner)?” Post-ED treatment failure was assigned to patients who reported “severe symptoms” during the 24 h preceding the follow-up interview (asthma symptoms “most of the time” or “severe” discomfort and distress due to their asthma) or who stated that their asthma was “about the same” or worse than at the time of their ED presentation.

PEFR was expressed as percentage of patient’s predicted value, based on race, age, sex, and height [14]. Changes in PEFR were expressed as the absolute change in percentage of predicted (e.g., an improvement from 40–70% pred would be expressed as a change of 30%).

Patients were asked to list all usual asthma triggers using a standardized list of potential triggers: respiratory infections, environmental allergens (e.g., dust, pets, pollen), tobacco smoke, other environmental factors (e.g., perfumes, paint, pollution, weather changes, cold air), exercise, ingested substances (e.g., aspirin, sulfites, food), reductive factors, psychological stress, and other factors. Patients were then asked to identify a single trigger of their current asthma exacerbation.

Statistical analysis

Analyses were performed using STATA 5.0 (StataCorp, College Station, TX, USA) and SAS 6.12 (SAS Institute, Cary, NC, USA). Data are presented as proportions (with 95% confidence intervals (CI)), means (with sd), or medians (with interquartile range (IQR)). The association between duration of symptoms (sudden onset, ≤3 h; slower onset, >3 h) and other factors was examined using Chi-squared test, Student’s t-test, and Wilcoxon rank sum test, as appropriate. Clinically relevant variables, such as age and sex, and variables associated with sudden onset at a p-value ≤0.10 were evaluated for inclusion in multivariate logistic regression models. Logistic regression was used to model the association between triggers of current exacerbation and sudden-onset exacerbations after adjustment for covariates. Logistic regression was also used to examine the relationship between sudden-onset exacerbation and hospital admissions and relapse. Linear regression was used to model the relationship between sudden-onset exacerbation and change in PEFR. All odds ratios are presented with 95% CI. All p-values are two-tailed, with p<0.05 considered statistically significant.

Results

Demographic factors

Of 1,847 patients enrolled in MARC, 900 patients had severe asthma exacerbations. Of these patients, 125 (14%, 95% CI 11–16%) had sudden-onset exacerbations. Patients with sudden-onset exacerbations were similar to patients with slower-onset exacerbations with respect to age, sex, and race/ethnicity (table 1). Measures of socioeconomic status were comparable between the two groups.

Chronic asthma severity

Table 1 also shows that indices of chronic asthma severity were alike for sudden-onset and slower-onset patients. The two groups had similar rates of childhood asthma, hayfever, current smoking and coexistent chronic obstructive pulmonary disease (COPD); they also had similar histories of systemic corticosteroid use, hospitalization and intubation. In the 12 months preceding presentation, the two groups had similar numbers of asthma-related urgent clinic visits, ED visits, and hospitalizations.

In the 4 weeks preceding presentation, proportions using inhaled β-agonists, inhaled corticosteroids and systemic corticosteroids were virtually the same, however a higher proportion of patients with sudden onset used oral β-agonists. The sudden-onset group exhibited a trend toward using more salmeterol and less anticholinergics and theophylline.

Usual triggers of exacerbations differed between the two groups. Sudden-onset patients reported that asthma exacerbations were triggered less often by upper respiratory infections and more often by exercise and psychosocial stress compared with patients with slower-onset exacerbations.

Acute triggers and presentation

Triggers of the current exacerbation also differed by duration of symptoms. The trigger of sudden-onset exacerbations was less often upper respiratory infection and more often respiratory allergens, tobacco smoke, exercise, and psychological stress (table 2). Ingested substances, menstruation, and medication noncompliance were reported infrequently and did not differ by duration of symptoms.
The presentation of sudden-onset patients was otherwise similar to that of slower-onset patients. Time of presentation, treatment prior to arrival in the ED, and triage vital signs did not differ between the two groups. Mean initial PEFR (% pred) was severely and equally reduced in both groups.

### Multivariate predictors of sudden-onset exacerbation

In the multivariate analysis, the associations of presenting triggers and sudden-onset exacerbations persisted after adjustment for age, sex, race/ethnicity, education, and insurance status (table 3). Respiratory allergens, tobacco smoke, exercise and psychological stress all were significantly more likely to trigger sudden-onset exacerbations than were respiratory infections. Odds ratios did not materially change after adjustment for markers of chronic asthma severity, except for the association of sudden-onset exacerbations with tobacco smoke, which was confounded by chronic asthma severity.

In addition, the use of oral β-agonists and salmeterol in the preceding 4 weeks were associated with sudden-onset exacerbations. The association between salmeterol with sudden-onset exacerbations was negatively confounded by socioeconomic status and demographics, the odds ratio increased from 1.6 (95% CI 0.9–2.9) to 2.0 (95% CI 1.1–3.6) with this adjustment. In contrast, anticholinergics and theophylline were not significantly associated with sudden-onset exacerbations in the multivariate model. Disease severity did not change the strength of the associations of oral β-agonists and salmeterol with sudden-onset exacerbations. Sudden-onset exacerbations were, in fact, negatively associated with a history of steroid use. Adjustment for several other measures of chronic asthma severity, including continuous oral steroid use, number of urgent clinic visits, ED visits, and admissions for asthma in the preceding year, did not change the associations appreciably (data not shown).

### Course and treatment response

Once in the ED, treatments given to patients with sudden-onset and slower-onset exacerbations were statistically similar, although the trends suggested that sudden-onset patients required less treatment than slower-onset patients (table 2).

Fewer patients with sudden-onset exacerbations required admission to the hospital (26 versus 35%; *p*<0.07), although this difference did not reach statistical significance. This difference did not change appreciably after adjustment for covariates. Among those discharged from the ED, fewer patients with sudden-onset exacerbations were prescribed systemic corticosteroids.

Despite similar treatments, patients with sudden-onset exacerbations had a higher final mean PEFR and a larger absolute change in PEFR than patients with slower-onset exacerbations (table 2). Sudden-onset exacerbations had a 7.5% greater absolute change in PEFR than slower-onset exacerbations. After adjustment for potential confounders, this difference did not materially change (table 4).
Two-week follow-up events

Two-week follow-up data were available for 626 patients (70%); patients for whom follow-up data were available had comparable mean ages, duration of symptoms and hospitalization rates to patients without follow-up data, but were more frequently female (63 versus 46%; p=0.001) and less frequently African-American (49 versus 58%; p=0.01).

Discussion

This prospective, multicentre study demonstrates that, in patients with severe asthma exacerbations, sudden-onset exacerbations are more likely to be triggered by respiratory allergens, exercise and psychological stress and less likely to be triggered by upper respiratory infections. In addition, patients with sudden-onset exacerbations demonstrate greater improvement with therapy, with no increase in subsequent risk of relapse or treatment failure.

The percentage of patients with severe asthma who presented with sudden-onset exacerbations in this study matched previously published estimates. In two smaller studies of patients with severe exacerbations who did not require intubation, the percentages with sudden onset were 13% and 17% [4, 15]. Among patients with more severe presentations, the reported per cent with sudden onset has been greater: in series of intubated patients, 7–29% had sudden onset [3, 5], and in surveys of fatal asthma, 15–58% had sudden onset [7, 16].

Woodruff et al. [4] retrospectively described sudden-onset exacerbations and found that they were less likely to be triggered by respiratory infections (17 versus 40%) and more likely to have "unknown triggers". The present study prospectively confirmed that respiratory infections were less common triggers of sudden-onset exacerbations (25 versus 40%), and identified potential unknown triggers as respiratory allergens, psychological stress and exercise. These associations were independent of each other and did not change after adjustment for disease severity. Tobacco smoke was also associated with sudden-onset exacerbations, however this finding was attributable to differences in chronic asthma severity.

The principal prior evidence for the link between respiratory allergens and sudden-onset asthma exacerbations comes from the outbreaks of soybean-associated asthma in Barcelona, Spain [17]. Triggering of sudden-onset exacerbations by soybeans is mediated by a specific immunoglobulin (Ig)E reaction to at least two allergens on the hull of the soybean [18–20]. Patients with such soy-related asthma had rapid improvement with therapy, with no increase in subsequent risk of relapse or treatment failure.

Two-week follow-up data were available for 626 patients (70%); patients for whom follow-up data were available had comparable mean ages, duration of symptoms and hospitalization rates to patients without follow-up data, but were more frequently female (63 versus 46%; p=0.001) and less frequently African-American (49 versus 58%; p=0.01).
There is less literature on the mechanisms that relate psychological stress and exercise to sudden-onset asthma. Psychological stress may cause bronchospasm via mast cell degranulation [23] and cholinergic pathways [24], both of which would be expected to result in a rapid onset of symptoms. Abrupt cessation of exercise induces a fall in forced expiratory volume in one second (FEV1) of up to 50% in certain subjects within 10–20 min of the cessation of activity [25]. This phenomenon has been clearly demonstrated experimentally, but has not, to the authors’ knowledge, previously been correlated with presentations of sudden-onset exacerbations.

Ingested substances and nonsteroidal anti-inflammatory drugs also have been described as precipitants of sudden-onset asthma in case series [26]. In the current study, reported ingested substances were too rare to evaluate with respect to sudden-onset exacerbations. This study does, however, suggest that ingested substances are an infrequent cause of severe asthma exacerbations in a relatively large sample of patients presenting with acute asthma.

Table 3. – Multivariate predictors of sudden-onset asthma exacerbation

| Parameters | Model 1 | | | Model 2 | | |
|------------|---------|----------------|-----------------|---------|----------------|
| Trigger of current exacerbation | MOR 95% CI p-value | MOR 95% CI p-value | | | |
| Upper respiratory infection | 1.0 (0.7–1.4) 0.55 | 1.0 (0.7–1.4) 0.55 | | | |
| Respiratory allergens (dust, pets, pollen, etc.) | 2.7 (1.3–5.8) 0.008 | 2.8 (1.3–6.0) 0.007 | | | |
| Tobacco smoke | 3.8 (1.1–13) 0.04 | 2.6 (0.6–11) 0.18 | | | |
| Exercise | 6.9 (2.2–22) 0.001 | 8.3 (2.5–28) <0.001 | | | |
| Psychosocial stress | 4.0 (1.7–9.4) 0.001 | 4.3 (1.8–10) <0.001 | | | |
| Other | 1.6 (0.9–2.9) 0.13 | 1.5 (0.8–2.8) 0.16 | | | |
| Salmeterol during the past 4 weeks | 1.9 (1.0–3.5) 0.05 | 1.9 (1.0–3.6) 0.06 | | | |
| Oral β-agonist during past 4 weeks | 1.8 (1.0–3.2) 0.05 | 1.9 (1.1–3.6) 0.03 | | | |
| Ever taken systemic steroid medicine for asthma | 0.6 (0.4–0.9) 0.03 | | | | |
| Admitted for asthma in past year | 1.5 (1.0–2.4) 0.08 | | | | |

MOR: multivariate odds ratio; CI: confidence interval. †: other includes ingested substances, environmental factors (cold, pollution, paint, etc.), menstruation, medication noncompliance, no identifiable or multiple triggers. Other triggers of asthma are compared to the trigger of "Upper respiratory infection", therefore upper respiratory infection is the reference value for the MOR associated with other triggers (and hence has no confidence interval). Model 1 includes variables listed as "parameters" (trigger, salmeterol and oral β-agonist), plus age, sex, race, education and insurance status. Model 2 includes variables listed as "parameters" (trigger, salmeterol, oral β-agonist, systemic steroid ever, and asthma hospital admission in last year), plus age, sex, race, education and insurance status.

Despite identical initial PEFR, patients with sudden-onset exacerbations had a 7.5% greater absolute improvement in PEFR than patients with slower-onset exacerbations. This difference is clinically significant given that patients in this study presented with a mean PEFR of 33% pred; a 7.5% absolute increase from this baseline represents a 23% relative increase in PEFR. The difference was not due to milder exacerbations or earlier presentation in a slower-onset exacerbation of equal severity, since peak flows at triage were identical in sudden-onset and slower-onset patients. Nor was the difference due to differential treatment: sudden-onset patients showed a trend toward requiring fewer β-agonists treatments and less systemic corticosteroids.

The greater improvement in PEFR carried over to a trend toward less hospitalization in patients with sudden-onset exacerbations and a shorter length of stay in those hospitalized. Furthermore, it was not associated with

Table 4. – Multivariate association of sudden-onset asthma exacerbation with absolute change in percentage of predicted peak expiratory flow rate

<table>
<thead>
<tr>
<th>Absolute change in PEFR attributable to sudden-onset %</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude</td>
<td>7.5</td>
<td>3.5–11</td>
</tr>
<tr>
<td>Adjusted for age</td>
<td>7.3</td>
<td>3.4–11</td>
</tr>
<tr>
<td>Adjusted for age, initial PEFR</td>
<td>7.1</td>
<td>3.2–11</td>
</tr>
<tr>
<td>Fully adjusted</td>
<td>5.4</td>
<td>1.0–9.7</td>
</tr>
</tbody>
</table>

PEFR: peak expiratory flow rate; CI: confidence interval. †: adjusted for age, initial PEFR, sex, race, education, neighbourhood median household income, insurance status, primary care physician, age at asthma diagnosis, coexistent chronic obstructive pulmonary disease, admission in the preceding year, number of β-agonists prior to triage, number of β-agonists given in emergency department and steroid given in emergency department.

IQR: interquartile range. †: Two week follow-up was available for 626 patients (70% of cohort); ‡: relapse event based on patient reporting a "worsening of asthma symptoms" that led to an urgent care visit; §: post-emergency department treatment failure was assigned to patients who reported "severe symptoms" during the 24 h preceding the follow-up interview (asthma symptoms "most of the time" or "severe" discomfort and distress due to their asthma) or who stated that their asthma was "about the same" or worse than at the time of their emergency department presentation.
higher rates of treatment failure or relapse over the following 2 weeks. The finding of greater reversibility of airflow obstruction is consistent with prior smaller studies [3-5, 10, 15, 27]. The combination of a distinct pattern of triggers and rapid reversibility suggests that sudden-onset asthma exacerbations may represent a distinct entity as compared to slower-onset asthma exacerbations. Various studies have suggested that sudden-onset exacerbations are immunohistologically distinct from slower-onset exacerbations. Patients who died from sudden-onset exacerbations had fewer eosinophils and more neutrophils in the airway submucosa than patients who died of slower-onset exacerbations [28, 29]. Although lymphocyte numbers, airway wall thickness, areas of smooth muscle and cartilage, and the amount of smooth muscle shortening were similar in these two groups, patients with sudden-onset asthma death had greater mucous gland area than patients with slower-onset asthma death [29]. Such an increase in gland area, with discharge of mucus into the bronchioles, could obstruct airflow if combined with moderate to severe bronchospasm. In addition, patients who died from sudden-onset exacerbations appear to have a CD8⁺ T-cells predominance and an inverted CD4:CD8 ratio, suggesting that sudden-onset exacerbations are not just an exaggeration of the immune response in chronic asthma [30]. Interestingly, this distinct inflammatory reaction occurred regardless of steroid therapy.

The findings of the independent associations of oral β-agonists and salmeterol with sudden-onset exacerbations were not specified a priori and should be interpreted with caution. They may have resulted from confounding by indication, that is, patients with more severe chronic bronchospasm might have been prescribed more intensive β-agonist regimens [31]. Salmeterol has been associated with increased ED visits, hospitalizations, and intensive care unit admissions in bivariate analyses, much or all of which has been explained by differences in chronic asthma severity [32, 33]. Similarly, the association of oral β-agonists among other medications with death and intensive care unit (ICU) admission has been largely attributed to differences in chronic asthma severity [34].

In the present analysis, patients with sudden-onset exacerbations had similar or milder chronic asthma than patients with slower-onset exacerbations. When the authors adjusted for measures of severity, the strength of the association of salmeterol and oral β-agonists with sudden-onset exacerbations did not change appreciably. In addition to steroid use and recent hospitalization, the authors attempted adjustment with all other available measures of severity and found similar results. The only large double-blinded randomized trial of salmeterol to measure mortality found a large but statistically insignificant increase in asthma mortality (RR 3.0, 95% CI 0.7-20) in the salmeterol group [35], however postmarketing surveys have not replicated this result [36]. Further examination of the safety and effectiveness of these drugs in chronic asthma will not come from further observational studies such as this one, but rather would require further clinical trials with follow-up >4 months.

This study represents the largest cohort of patients with sudden-onset asthma exacerbations of which the authors are aware, and has other strengths including the prospective collection of patients, enrollment at multiple centres, and good rates of enrollment and follow-up. However, it was not truly population-based and may therefore suffer from selection bias. Nonetheless, since most North American patients with severe asthma exacerbations present to EDs, the results should be applicable to most patients with severe asthma exacerbations. Although data were gathered prospectively, questionnaire items regarding triggers were collected during the exacerbation, and therefore may be subject to recall bias. This could affect the results if recall differed between patients with sudden and slower-onset exacerbations. Also, the best measure of chronic asthma severity, baseline chronic PEFR, was not available. However, there were multiple questionnaire items on chronic asthma severity and none differed between sudden and slower-onset patients.

The definition of a severe asthma exacerbation is somewhat arbitrary. The authors’ definition (PEFR <50 % pred) reflects the most recent NAEPP guidelines. Defining severe exacerbations according to the prior NAEPP guidelines (PEFR ≤40 % pred) produced quantitatively similar results, as did the exclusion of patients who were hospitalized without PEFR measurement. Despite these limitations, this study confirms that severe sudden-onset asthma exacerbations, if treated promptly and aggressively, have similar outcomes as slower-onset exacerbations after discharge from the emergency department. The difference in triggers suggests a difference in aetiology; further work is needed to correlate the epidemiological evidence with pathological distinctions observed thus far. Ultimately, these distinctions may allow identification of patients at risk for sudden-onset "asphyxic" asthma with the goal of prevention and early management.

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Members of the Multicenter Airways Research Collaboration. Steering Committee: J.M. Baren (Children’s Hospital of Philadelphia, Philadelphia, PA, USA), C.A. Camargo Jr. (Chairman (Massachusetts General Hospital, Boston, MA)), R.K. Cydulka (MetroHealth Medical Center, Cleveland, OH), M.A. Gibbs (Carolina Medical Center, Charlotte, NC), C.V. Pollack Jr. (Maricopa Medical Center, Phoenix, AZ), B.H. Rowe (University of Alberta Hospital, Edmonton, AB, Canada).

Operations Committee and MARC Coordinating Centre: C.A. Camargo Jr. (Chairman), S. Clark, L.T. Mayer, M.S. Radeos, C.R. Reed, A.K. Singh, R.G. Barr (all Massachusetts General Hospital, Boston, MA, USA).

Principal investigators at the 64 participating sites: F.C. Baker III (Maine Medical Center, Portland, ME, USA), S. Stahmer (Hospital of the University of Pennsylvania, Philadelphia, PA), J.M. Basior (Buffalo General Hospital, Buffalo, NY), C.A. Bethel (Mercy Hospital, Philadelphia, PA), L. Bielory (University Hospital, Newark, NJ), M.P. Blanda (Summa Health System, Akron, OH), D. Bond (Grey Nuns’ Community Hospital, Edmonton, AB, Canada), G.W. Bota (Sudbury General Hospital, Sudbury, BC, Canada), E.D. Boudreaux (Earl K. Long Memorial Hospital, Baton Rouge, LA), B.E. Brenner (The Brooklyn Hospital Center, Brooklyn, NY), J. Brown (Misericoirdia Community Hospital, Edmonton, AB, Canada), D.M. Joyce (University Hospital, SUNY HSC, Syracuse, NY), C.A. Camargo Jr. (Massachusetts General Hospital, Boston, MA), F.L. Counselman (Sentara Norfolk General Hospital, Norfolk, VA), G. Ramalanjaona (Newark Beth Israel Hospital, Newark, NJ), R.K. Cydulka (MetroHealth Medical Center, Cleveland, OH), A. Sucov (University of Rochester Hospital, Rochester, NY), D.J. Dure (University of Oklahoma Medical Center, Oklahoma City, OK), N. El Sanadi (Broward General
Hospital, Ft. Lauderdale, FL, S.D. Emond (St. Luke's/Roosevelt Hospital Center, New York, NY), T.J. Gaeta (Methodist Hospital, Brooklyn, NY and St. Barnabas Hospital, Brooklyn, NY), M.A. Gibbs (Carolinas Medical Center, Charlotte, NC), T.E. Glynn (Brooke Army Medical Center, Fort Sam Houston, TX), L.G. Graff IV (New Britain General Hospital, Philadelphia, PA), R. Harrigan (Temple University Hospital, Philadelphia, PA), S.E. Hughes (Albany Medical College, Albany, NY), A.H. Idris (University of Florida Health Center, General Hospital, Pittsburgh, PA), R. Hanrahan (Beth Israel Hospital, Boston, MA), F. Harchelroad (Allegheny General Hospital, Pittsburgh, PA), R. Harrigan (Temple University Hospital, Philadelphia, PA), J.P. Hanrahan (Beth Israel Medical Center, New York, NY), A. Guttman (Sir Mortimer B. Davis - Jewish General Hospital, Montreal, QC, Canada), S.K. Griswold (Thomas Jefferson General Hospital, New Britain, CT), R.O. Gray (Hennepin County Medical Center, Minneapolis, MN), S.K. Griswold (Thomas Jefferson Medical Center, New Hyde Park, NY), H. Smithline (Baystate Medical Center, Springfield, MA), D. Schreiber (Stanford University Medical Center, Stanford, CA), R.A. Silverman (Long Island Jewish Medical Center, New Hyde Park, NY), J. Walter (University of Pittsburgh Medical Center, Pittsburgh, PA), C.A. Terregino (Cooper Hospital/University Medical Center, Camden, NJ), J.L. Larson (University of North Carolina Hospitals, Chapel Hill, NC), A. Walker (Royal Alexandria Hospital, Edmonton, AB, Canada), J. Walter (University of Chicago Hospitals, Chicago, IL), F. W. Kreplick (Christ Hospital & Medical Center, Oak Lawn, IL), M.E. Johnson (Jackson Memorial Hospital, Miami, FL), L. White (Akron General Medical Center, Akron, OH), J.L. Zimmerman (Ben Taub General Hospital, Houston, TX).

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