

# Antineutrophil cytoplasmic autoantibodies and myeloperoxidase autoantibodies in clinical expression of Churg-Strauss syndrome

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**Background:** The clinical significance of antineutrophil cytoplasmic antibodies (ANCA) in the phenotypic expression of Churg-Strauss syndrome (CSS) is uncertain.

**Objective:** We sought to investigate the relationship between ANCA status and the clinical expression of CSS in a case series derived from the US Food and Drug Administration's adverse events database.

**Methods:** All cases of CSS reported to the US Food and Drug Administration from 1997 to April 2003 were reviewed.

**Information about basic demographics, suspect medication use, clinical manifestations, histologic findings, ANCA staining patterns, and the presence of antibodies to myeloperoxidase (anti-MPO) or proteinase 3 (anti-PR3) was recorded when available.**

**Results:** There were 93 case reports of CSS with sufficient documentation, including ANCA status. There were 38 (40.9%) of 93 cases with positive ANCA results, of which 15 cases reported a positive ELISA, all of which were positive for anti-MPO. ANCA negativity was associated with an increased proportion of cardiac involvement (risk difference [RD], 38.2%; 95% CI, 25.3% to 51.0%), gastrointestinal involvement (RD, 25.5%; 95% CI, 13.9% to 37.0%), pulmonary infiltrates (odds ratio, 4.9; 95% CI, 1.5-16.2), and the outcome of a life-threatening event or death (RD, 30.9%; 95% CI, 18.7% to 43.1%) when compared with anti-MPO-positive cases. ANCA negativity was associated with a decreased proportion of peripheral neuropathy (odds ratio, 0.3; 95% CI, 0.07-0.9). **Conclusion:** These findings support the hypothesis that the presence or absence of autoantibodies influences the clinical expression and severity of CSS. (*J Allergy Clin Immunol* 2012;■■■■:■■■-■■■.)

**Key words:** Antineutrophil cytoplasmic autoantibodies, Churg-Strauss syndrome, clinical features, US Food and Drug Administration's Adverse Event Reporting System database, myeloperoxidase

## Abbreviations used

|           |                                                     |
|-----------|-----------------------------------------------------|
| AERS:     | Adverse Event Reporting System                      |
| ANCA:     | Antineutrophil cytoplasmic autoantibody             |
| Anti-MPO: | Myeloperoxidase autoantibodies                      |
| Anti-PR3: | Proteinase 3 autoantibodies                         |
| CSS:      | Churg-Strauss syndrome                              |
| FDA:      | US Food and Drug Administration                     |
| IIF:      | Indirect immunofluorescence                         |
| LTRA:     | Leukotriene receptor antagonist                     |
| MPA:      | Microscopic polyangiitis                            |
| OR:       | Odds ratio                                          |
| p-ANCA:   | Perinuclear antineutrophil cytoplasmic autoantibody |
| RD:       | Risk difference                                     |
| WG:       | Wegener granulomatosis                              |

Churg-Strauss syndrome (CSS) is a rare small-vessel vasculitis principally arising in patients with a history of asthma, atopic disease, or both.<sup>1,2</sup> The association between autoantibodies directed against neutrophil cytoplasmic antigens (antineutrophil cytoplasmic antibodies [ANCAs]) and small-vessel vasculitis was first described in patients with pauci-immune glomerulonephritis in 1982.<sup>3</sup> The precise role of ANCAs in disease pathogenesis remains unclear, although there is emerging evidence to suggest that they might directly initiate an inflammatory response in patients with small-vessel vasculitis,<sup>4-6</sup> encompassing the syndromes of Wegener granulomatosis (WG), microscopic polyangiitis (MPA), renal-limited vasculitis, and CSS.

The measurement of ANCA levels for diagnostic purposes is potentially misleading when requested as part of the assessment for autoimmune syndromes outside of small-vessel vasculitis.<sup>7</sup> Perinuclear antineutrophil cytoplasmic autoantibody (p-ANCA) and atypical ANCA staining patterns on indirect immunofluorescence (IIF) are common findings in patients with systemic lupus erythematosus, rheumatoid arthritis, and inflammatory bowel disease,<sup>8-11</sup> and the presence of antinuclear antibodies can be misclassified as a positive ANCA result.<sup>12</sup> International guidelines recommend that positive ANCA results determined by using IIF should be verified by using an ELISA because the positive predictive value for small-vessel vasculitis is substantially higher with autoantibodies to myeloperoxidase (anti-MPO) and proteinase 3 (anti-PR3) than staining patterns determined by using IIF.<sup>12-14</sup>

In patients with CSS, the presence of ANCAs is highly variable, with published case series reporting ANCA positivity in 38% to 78% of patients.<sup>15-19</sup> As a result, ANCA studies might be unreliable in patients with CSS if used for the purpose of early disease diagnosis. This is in contrast to both WG and MPA, in which ANCA levels are positive in greater than 90% of those with active disease.<sup>4</sup> In patients with ANCA-positive

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CSS, p-ANCA is the prevailing staining pattern. In those with a positive ANCA result on IIF, approximately 70% will have positive results for anti-MPO, whereas anti-PR3 is less commonly seen.<sup>15,16</sup>

Despite the variability in the presence of ANCAs in patients with CSS, measuring ANCA levels might yield some clinical value. Two previous case series have observed that the presence or absence of ANCAs appears to influence the clinical expression of CSS.<sup>16,18</sup> It has been hypothesized that specific organ involvement is related to ANCA status,<sup>18</sup> although the statistical power from these case series to detect associations between ANCA status and the clinical expression of CSS was limited by the small cohort of patients in which ELISAs were performed.

In this study we present a case series of CSS derived from the Adverse Event Reporting System (AERS) database maintained by the US Food and Drug Administration (FDA). On the basis of detailed case reports, we were able to investigate the relationship between ANCA status and the clinical and histologic expression of CSS. We were also able to compare the characteristics observed in our case series of suspected drug-induced CSS with other case series in which the development of CSS was unselected.

## METHODS

All cases in the FDA's AERS database of suspected drug-induced CSS were requested from when the condition was first coded in 1997 through April 2003. Information from the MedWatch report form was recorded in an electronic database, with methodology previously described for a related study using CSS drug surveillance data.<sup>20</sup> The FDA MedWatch report form and general instructions for its completion are presented in Fig E1 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org).

## Exclusion criteria for case reports

To select relevant cases, reports were excluded sequentially if they were not reported to the FDA by a health professional or were wrongly filed or if an alternative diagnosis was considered more likely by the reporting physician and the investigators were in agreement. Cases were also excluded if there were no details of an individual identifiable event reported, such as a report on conference proceedings.<sup>20</sup>

## Inclusion criteria for case reports

Each case report was independently reviewed by 2 investigators (B.H. and S.B.) to ensure it contained sufficient documentation to confirm both the diagnosis of CSS<sup>20</sup> and the ANCA status. Case reports had to meet 1 of the following 3 criteria, which were performed sequentially, to confirm the diagnosis of CSS:

- presence of at least four of the six 1990 American College of Rheumatology Classification criteria for CSS of asthma, chronic sinusitis, significant peripheral blood eosinophilia (>10% or 1.5 absolute eosinophil count [abs]), extravascular eosinophilia on biopsy, migratory pulmonary infiltrates, and peripheral neuropathy<sup>21</sup>;
- history of asthma and peripheral blood eosinophilia (>10% or 1.5 abs) and histology consistent with CSS; and
- postmortem findings confirming the diagnosis of CSS.

Cases were then independently reviewed to ascertain the ANCA status for inclusion in the analysis. Cases of confirmed CSS in which an ANCA result was documented were included in the case series (see below).

## Analysis of cases

Basic details of age and sex were recorded. The suspect medication was documented as stated by the reporting health professional.<sup>20</sup> Clinical

manifestations were recorded individually and then grouped collectively into specific organ involvement. When atypical disease symptoms were present, these were included if they occurred as part of the presentation of CSS and no alternative cause was apparent. Clinical outcome was coded as death, a life-threatening event, or a non-life-threatening event by 2 independent investigators (B.H. and R.S.) by using a standardized review of each case report. A life-threatening event was defined as any severe organ compromise or systemic collapse in which death would have been imminent if urgent intensive intervention had not been initiated.

Histologic characteristics from biopsies or autopsies were documented when provided. A biopsy specimen was considered positive if 1 or more of the 3 features of CSS were present, namely vasculitis, an extravascular eosinophilic infiltrate, or granuloma formation. Bone marrow, nasal, and sinus biopsies required the presence of vasculitis or granuloma formation for a positive result because bone marrow was not considered an extravascular site and because eosinophilic infiltration in the upper respiratory tract is a common finding in patients with atopic diseases.

Negative ANCA status was defined as the documented absence of ANCA by using an IIF assay, and this category included cases documenting that ANCA study results were negative without providing further specification. Positive ANCA status was defined as the documented presence of anti-MPO or anti-PR3 on ELISA, regardless of the staining pattern on IIF. A positive IIF assay result for ANCAs without confirmation of a positive anti-MPO or anti-PR3 result was considered indeterminate.

Analysis of contingency tables for the association between ANCA-negative and anti-MPO-positive cases and the proportion of cases with clinical and histologic features was done by using odds ratios (ORs) with associated 95% CIs. Where no or all patients in one group had a particular characteristic, the risk difference (RD) was calculated instead of the OR. Statistical significance was determined by using the Fisher exact test. For individual statistical tests, a *P* value of .05 was used for statistical significance. No adjustment was used for multiple statistical testing. Analyses were carried out with SAS version 9.1 software (SAS Institute, Cary, NC).

## RESULTS

There were 1274 case reports received from the FDA's AERS database.<sup>20</sup> Of these, 642 were duplicates or follow-up reports, leaving 632 individual cases. With sequential application of the exclusion criteria, 24 cases were excluded because the reporter was other than a health professional, 214 cases were excluded as a diagnosis other than CSS, and 7 were cases with no identifiable event. In 206 cases the diagnosis of CSS could not be objectively confirmed; this was due to either insufficient documentation of the clinical picture or in some cases the documented absence of typical features of CSS.

There were 181 cases that met the inclusion criteria for the diagnosis of CSS. Of these, there were 93 cases in whom ANCA status was reported and included in the case series (Table I). In 89 (96%) of 93 cases, the suspect medication included a leukotriene receptor antagonist (LTRA) either alone or in combination with a secondary suspect medication.

The most frequently observed clinical manifestations were asthma (100%), peripheral blood eosinophilia (95%), sinusitis (63%), and pulmonary infiltrates (65%). Peripheral neuropathy was common (52%), although central nervous system involvement was less frequently observed (13%). Skin involvement was present in 68% of cases, with some cases displaying more than 1 type of rash. Constitutional symptoms of fevers/night sweats and weight loss were frequently reported (45% and 30%, respectively), as were musculoskeletal symptoms of myalgia (33%) and arthralgia (36%). Cardiac involvement was present in 28% of cases, with pericardial effusion (13%), cardiomyopathy (12%), and carditis (8%) the most common cardiac manifestations.

**TABLE I.** Clinical manifestations documented in the 93 cases of CSS in which ANCA status was reported

| Clinical manifestation                            | ANCA data (%),<br>n = 93 |
|---------------------------------------------------|--------------------------|
| 1990 American College of Rheumatology criteria    |                          |
| Asthma                                            | 93 (100)                 |
| Peripheral blood eosinophilia                     | 88 (94.6)                |
| Extravascular eosinophilia                        | 53 (57.0)                |
| Chronic sinusitis                                 | 59 (63.4)                |
| Pulmonary infiltrates                             | 60 (64.5)                |
| Peripheral neuropathy                             | 48 (51.6)                |
| Pulmonary                                         |                          |
| Pulmonary nodules                                 | 5 (5.4)                  |
| Pulmonary hemorrhage                              | 4 (4.3)                  |
| Pulmonary embolism                                | 2 (2.2)                  |
| Cavities                                          | 1 (1.1)                  |
| Pleural thickening                                | 1 (1.1)                  |
| Total (including infiltrates)                     | 61 (65.6)                |
| Skin                                              |                          |
| Purpuric rash                                     | 40 (43.0)                |
| Other rash ± pruritus                             | 32 (34.4)                |
| Tongue ulceration                                 | 1 (1.1)                  |
| Skin bullae                                       | 1 (1.1)                  |
| Splinter hemorrhage                               | 1 (1.1)                  |
| Total                                             | 63 (67.7)                |
| Constitutional                                    |                          |
| Fevers/night sweats                               | 42 (45.2)                |
| Weight loss                                       | 28 (30.1)                |
| Lymphadenopathy                                   | 6 (6.5)                  |
| Total                                             | 58 (62.4)                |
| Musculoskeletal                                   |                          |
| Arthralgia                                        | 33 (35.5)                |
| Myalgia                                           | 31 (33.3)                |
| Total                                             | 49 (52.7)                |
| Cardiac                                           |                          |
| Pericardial effusion                              | 12 (12.9)                |
| Cardiomyopathy                                    | 11 (11.8)                |
| Carditis                                          | 7 (7.5)                  |
| Suspected MI/new BBB                              | 5 (5.4)                  |
| Sinus tachycardia                                 | 5 (5.4)                  |
| Arrhythmia                                        | 1 (1.1)                  |
| Coronary vasculitis                               | 1 (1.1)                  |
| Total                                             | 26 (28.0)                |
| Pleural effusion                                  | 12 (12.9)                |
| Gastrointestinal                                  |                          |
| Abdominal pain/vomiting                           | 16 (17.2)                |
| GI bleed                                          | 3 (3.2)                  |
| Mesenteric vasculitis                             | 1 (1.1)                  |
| Ascites                                           | 1 (1.1)                  |
| Ileus                                             | 1 (1.1)                  |
| Esophageal ulceration                             | 0 (0)                    |
| Total                                             | 16 (17.2)                |
| Renal                                             |                          |
| Glomerulonephritis                                | 2 (2.2)                  |
| Total                                             | 16 (17.2)                |
| Hepatic                                           |                          |
| Mild-to-moderate increase in transaminase levels* | 14 (15.1)                |

(Continued)

Pleural effusion was observed in 13% of cases; however, it was not included as a specific organ manifestation because the underlying cause (cardiac, pulmonary, or both) could not be determined in some cases. Gastrointestinal involvement was identified in 17% and renal involvement was documented in 17% of cases, of which

**TABLE I.** (Continued)

| Clinical manifestation                             | ANCA data (%),<br>n = 93 |
|----------------------------------------------------|--------------------------|
| CNS                                                |                          |
| Visual impairment†                                 | 5 (5.4)                  |
| Cerebrovascular accident/clinical stroke           | 3 (3.2)                  |
| Mental state changes, acute confusion, or delirium | 3 (3.2)                  |
| Multiple enhancement on MRI                        | 3 (3.2)                  |
| Cerebellar impairment, ataxia, or dysarthria       | 1 (1.1)                  |
| Hemorrhagic event                                  | 1 (1.1)                  |
| Ptosis                                             | 1 (1.1)                  |
| Total                                              | 12 (12.9)                |

BBB, Bundle branch block; CNS, central nervous system; GI, gastrointestinal; MI, myocardial infarction; MRI, magnetic resonance imaging.

\*In the absence of another obvious cause for increased liver transaminase levels.

†Includes retinal occlusion, diplopia, cranial nerve involvement, sudden onset blindness, and abnormal pupillary response.

2 had necrotizing glomerulonephritis. No patients underwent renal dialysis. All cases of hepatic involvement (15%) showed mild-to-moderate increases in liver transaminase levels, with no cases of fulminant hepatitis.

Among the 93 cases in which ANCA data were available, there were 55 (59%) cases with reports of a negative ANCA result and 38 (41%) that reported a positive ANCA or ELISA result. There were 28 cases with reports of a positive ANCA result on IIF. Of these, 18 (64%) were p-ANCA, 4 (14%) were cytoplasmic-ANCA, 5 (18%) had an atypical staining pattern, and 1 had an unspecified staining pattern. Confirmation of the positive ANCA result on IIF was not confirmed by using ELISA in 23 of the 28 cases, and these were considered indeterminate results. There were 15 cases with reports of a positive ELISA result, with all 15 being positive for anti-MPO. Among the anti-MPO-positive cases, the IIF staining pattern was p-ANCA positive in 5 cases, and 10 did not report an IIF pattern. There were no cases of a positive anti-PR3 result.

Comparison of organ involvement between ANCA-negative cases and anti-MPO-positive cases is shown in Table II. An RD rather than an OR is presented for eosinophilia and cardiac and gastrointestinal involvement because no cases with anti-MPO positivity demonstrated cardiac or gastrointestinal manifestations, and all anti-MPO cases displayed peripheral blood eosinophilia. The presence of asthma, sinusitis, and eosinophilia was commonly observed regardless of autoantibody status. ANCA negativity was associated with an increased proportion of cases with cardiac manifestations (RD, 38.2%; 95% CI, 25.3% to 51.0%;  $P = .003$ ), gastrointestinal manifestations (RD, 25.5%; 95% CI, 13.9% to 37.0%;  $P = .03$ ), pulmonary infiltrates (OR, 4.9; 95% CI, 1.5-16.2;  $P = .009$ ), and fevers/night sweats (OR, 3.8; 95% CI, 1.1-13.5;  $P = .042$ ). ANCA negativity was also associated with a decreased proportion of cases with peripheral neuropathy (OR, 0.3; 95% CI, 0.07-0.9;  $P = .023$ ). Although a higher percentage of renal manifestations, purpura, and musculoskeletal symptoms were noted with the presence of anti-MPO, these differences were not statistically significant.

Comparison of histologic features between ANCA-negative and anti-MPO-positive cases is shown in Table III. Vasculitis and extravascular eosinophils were common findings regardless of ANCA and anti-MPO status. Granuloma was present in approximately one third of biopsy specimens taken from ANCA-negative cases compared with none of the 11 biopsy specimens taken from the anti-MPO-positive group (RD, 32.6%; 95% CI, 19.6% to 46.2%;  $P = .051$ ).

**TABLE II.** Comparison of American College of Rheumatology criteria and specific organ involvement between ANCA-negative and anti-MPO-positive case reports

|                               | ANCA negative (%), n = 55 | Anti-MPO positive (%), n = 15 | OR or RD* (95% CI)       | P value |
|-------------------------------|---------------------------|-------------------------------|--------------------------|---------|
| Asthma                        | 55 (100)                  | 15 (100)                      |                          |         |
| Peripheral blood eosinophilia | 51 (92.7)                 | 15 (100)                      | RD: -7.3 (-14.1 to -0.4) | .37     |
| Chronic sinusitis             | 35 (63.6)                 | 9 (60.0)                      | OR: 1.2 (0.4 to 3.8)     | .22     |
| Pulmonary infiltrates         | 42 (76.4)                 | 6 (40.0)                      | OR: 4.9 (1.5 to 16.2)    | .009    |
| Peripheral neuropathy         | 23 (41.8)                 | 11 (73.3)                     | OR: 0.3 (0.07 to 0.9)    | .023    |
| Cardiac                       | 21 (38.2)                 | 0 (0.0)                       | RD: 38.2 (25.3 to 51.0)  | .003    |
| Gastrointestinal†             | 14 (25.5)                 | 0 (0.0)                       | RD: 25.5 (13.9 to 37.0)  | .03     |
| Musculoskeletal               | 26 (47.3)                 | 10 (66.7)                     | OR: 0.5 (0.1 to 1.5)     | .10     |
| Renal                         | 9 (16.4)                  | 5 (33.3)                      | OR: 0.4 (0.1 to 1.4)     | .10     |
| Hepatic                       | 10 (18.2)                 | 3 (20.0)                      | OR: 0.9 (0.2 to 3.7)     | .28     |
| Fevers/night sweats           | 32 (58.2)                 | 4 (26.7)                      | OR: 3.8 (1.1 to 13.5)    | .042    |
| Weight loss                   | 18 (32.7)                 | 5 (33.3)                      | OR: 1.0 (0.3 to 3.3)     | .24     |
| All skin manifestations       | 34 (61.8)                 | 10 (66.7)                     | OR: 0.8 (0.2 to 2.7)     | .23     |
| Purpura                       | 22 (40.0)                 | 8 (53.3)                      | OR: 0.6 (0.2 to 1.8)     | .15     |
| CNS                           | 7 (12.7)                  | 3 (20.0)                      | OR: 0.6 (0.1 to 2.6)     | .23     |

\*Where no or all cases in one group had a particular manifestation, the RD was calculated instead of the OR.

†Hepatic manifestations not included under "gastrointestinal."

**TABLE III.** Comparison of the defined histologic features of CSS between ANCA-negative and anti-MPO-positive cases

|                           | ANCA negative (%), n = 46 | Anti-MPO positive (%), n = 11 | OR or RD* (95% CI)   | P value |
|---------------------------|---------------------------|-------------------------------|----------------------|---------|
| Vasculitis                | 28 (61)                   | 9 (81)                        | OR: 0.3 (0.06-1.7)   | .11     |
| Granuloma                 | 15 (33)                   | 0 (0)                         | RD: 32.6 (19.6-46.2) | .051    |
| Extravascular eosinophils | 34 (74)                   | 8 (73)                        | OR: 1.1 (0.2-4.7)    | .29     |

\*Where no or all cases in one group had a particular histologic feature, the RD was calculated instead of the OR.

There were 16 life-threatening events and 1 death. The classification of life-threatening events and death by specific organ involvement is shown in Table IV. In ANCA-negative patients 17 (31%) experienced a life-threatening event or death compared with none in the anti-MPO group (RD, 30.9%; 95% CI, 18.7% to 43.1%;  $P = .015$ ).

## DISCUSSION

In this case series of patients with CSS, there was differential organ involvement with ANCA negativity compared with anti-MPO positivity. ANCA negativity was associated with an increased proportion of cardiac and gastrointestinal involvement, pulmonary infiltrates, and fevers/sweats when compared with anti-MPO positivity. Also, ANCA negativity was associated with a decreased proportion of peripheral neuropathy. Overall, these findings are consistent with those of Sable-Fourtassou et al<sup>18</sup> and Sinico et al,<sup>16</sup> although neither study showed an increased proportion of gastrointestinal involvement with ANCA negativity compared with ANCA positivity. These findings support the hypothesis that the presence or absence of autoantibodies influences the clinical expression of CSS.

A key strength of our study was the requirement of anti-MPO or anti-PR3 determined by using ELISA to define a positive ANCA status. Confirmation of the presence of specific antibodies to MPO and PR3 was considered important to ensure a homogenous group for comparison because the specificity of a

**TABLE IV.** Specific organ involvement in the 17 ANCA-negative cases with a life-threatening event or death

| Organ involvement          | No. (%), n = 17 |
|----------------------------|-----------------|
| Cardiac                    | 5 (29)          |
| Respiratory                | 3 (18)          |
| Central nervous system     | 2 (12)          |
| Gastrointestinal           | 2 (12)          |
| Vascular system/thrombosis | 1 (6)           |
| Addisonian crisis          | 1 (6)           |
| Multiorgan involvement*    | 3 (18)          |

\*Two or more organs contributed significantly to the adverse outcome. All cases of multiorgan involvement included cardiac involvement.

positive anti-PR3 or anti-MPO result for small-vessel vasculitis is greater than 97%.<sup>12</sup> To date, this is the only case series investigating the clinical expression of CSS in relation to ANCA status in which a positive IIF assay result required confirmation by using ELISA. This requirement might explain the lack of anti-MPO-positive cases with either cardiac or gastrointestinal involvement, a finding that was not observed in the previous 2 case series.<sup>16,18</sup>

An important clinical observation was the increased proportion of life-threatening events or deaths among ANCA-negative cases compared with the anti-MPO-positive cases. This finding has not been previously reported and implies that the absence of autoantibodies to MPO is associated with more severe organ compromise, carrying a worse prognosis. Although the pathologic processes responsible for severity of disease in patients with CSS were beyond the scope of this study, it is possible that other as yet unidentified autoantibodies might be responsible for symptom severity in patients with ANCA-negative CSS. Consideration could also be given to whether anti-MPO has a regulatory role in the immunologic response as a marker of chronic or subacute disease.

Our observation that the most common life-threatening event was due to cardiac complications is consistent with that made in 1951 by Churg and Strauss,<sup>2</sup> in which at autopsy refractory cardiac failure was noted as the immediate cause of death in more than half of their cases. Delayed detection of early cardiac

involvement has been reported to lead to complications, such as coronary artery vasculitis, myocardial infarction, sustained cardiac arrhythmia, cardiac tamponade, and intractable cardiac failure.<sup>22,23</sup> In a previous multivariate analysis of 96 patients with CSS, myocardial involvement and severe gastrointestinal involvement were the only factors significantly associated with a poor clinical outcome.<sup>15</sup>

These combined observations highlight the importance of cardiac involvement as a poor prognostic factor in patients with CSS. The findings imply that prognosis based on organ involvement is different for patients with CSS than those with WG and MPA, in whom cardiac involvement is uncommon, and the majority of life-threatening events or deaths are related to renal impairment or respiratory compromise from pulmonary hemorrhage.<sup>24,25</sup> At present, it is unclear whether the prognosis of cardiac CSS is improved with early immunosuppressive therapy,<sup>22</sup> and further research into early cardiac clinical management and outcomes is warranted.

Clinical evidence of gastrointestinal, cerebral, hepatic, and renal involvement was observed in between 13% and 17% of cases. Our observation that no patients had received dialysis at the time of reporting to the FDA is consistent with a previous case series, which reported that renal involvement in CSS rarely progresses to renal failure.<sup>15</sup> Similarly, hepatic involvement ranged from mild to moderate increases in liver transaminase levels, with no cases of fulminant hepatic failure. Although pulmonary infiltrates were present in two thirds of the cases in this series, pulmonary involvement in the absence of infiltrates occurred in less than 2%. Although pulmonary hemorrhage complicates small-vessel vasculitis in greater than 10% of patients with MPA and WG, recent case series, along with our observations, suggest it is less common in patients with CSS.<sup>15,19,26</sup>

The most common medications reported by health professionals to the FDA database were the LTRA agents, with 1 or more LTRAs listed as a suspect medication in 96% of the 93 case reports. Whether LTRA therapy, other classes of medication, or both have a directly causative role in the pathogenesis of CSS has been a topic of much debate<sup>27</sup> and is beyond the scope of this study. Here it has been observed that the range of clinical expressions of suspected drug-induced CSS is directly comparable with that reported in other published case series of unselected CSS.<sup>15-19</sup>

This case series used a large database of medication-associated reporting of CSS spanning a 7-year period.<sup>20</sup> However, there are several inherent limitations in the use of an international adverse reaction database for clinical research purposes. First, the presence of the clinical manifestations, biopsy results, and ANCA and anti-MPO results presented in this study were dependent on the quality and accuracy of the information supplied by the reporting health professional. In this regard the FDA MedWatch form is disease, drug, and device nonspecific and, as a result, does not contain queries about whether certain features of CSS were present.

Second, the study was limited by the inability to standardize the method and timing by which measurements of ANCA status were performed, and we were unable to follow cases with serial measurements. Furthermore, ANCA results were not available in approximately half of the case reports that met the inclusion criteria for CSS. In those cases excluded from this case series, it was uncertain whether ANCA levels were measured and not reported or whether measurements were not performed at all. It

is possible that some cases did not have ANCA testing preformed if the case did not meet the 1990 international clinical guidelines for ANCA testing.<sup>14</sup> Additionally, ELISA assays for anti-MPO and anti-PR3 were still relatively new in 1997, and this might explain the low numbers of confirmatory ELISA tests reported. It was not possible to determine whether ANCA measurement was performed in relation to initiation of steroid therapy, which does limit our results in that ANCA measurement by means of IIF and ELISA might disappear in some cases once active vasculitis has gone into remission.<sup>17</sup> The influence of steroid therapy on ANCA status would have reduced the ability to determine differences between the groups based on ANCA status.

Because CSS is a rare but multisystem disease, obtaining large case series is difficult. The study likely lacked statistical power to detect important associations, and some estimates of association had wide CIs. In addition, there might have been type I error rate inflation because of the multiple analyses performed.

In summary, a negative ANCA result was associated with an increased proportion of cardiac and gastrointestinal involvement, pulmonary infiltrates, and fevers/night sweats and a decreased proportion of peripheral neuropathy when compared with a positive result, as defined by the presence of anti-MPO. There was a strong association between the composite of life-threatening events and deaths and ANCA negativity, suggesting that the absence of anti-MPO might carry a worse prognosis. We conclude that the presence or absence of autoantibodies influences the clinical expression and disease severity in patients with CSS.

We thank the FDA for providing the data on suspected drug-induced CSS from the AERS database.

**Clinical implications: The presence or absence of autoantibodies influences the clinical expression and disease severity in patients with CSS.**

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U.S. Department of Health and Human Services

For VOLUNTARY reporting of adverse events, product problems and product use errors

Form Approved OMB No. 0910-0291, Expires 12/31/2011  
See OMB statement on reverse

**MEDWATCH**  
The FDA Safety Information and Adverse Event Reporting Program

Page 1 of 2

**A. PATIENT INFORMATION**

1. Patient Identifier # 2. Age at Time of Event or Date of Birth: 3. Sex: ☐ Female ☐ Male 4. Weight:  lb or  kg

**B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR**

Check all that apply:

1. ☐ Adverse Event ☐ Product Problem (e.g., defects/malfunctions)  
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event (Check all that apply):  
☐ Death (mm/dd/yyyy) ☐ Disability or Permanent Damage  
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect  
☐ Hospitalization - initial or prolonged ☐ Other Serious (important Medical Events)  
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event (mm/dd/yyyy) 4. Date of this Report (mm/dd/yyyy)

5. Describe Event, Problem or Product Use Error

6. Relevant Tests/Laboratory Data, Including Dates

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)

**C. PRODUCT AVAILABILITY**

Product Available for Evaluation? (Do not send product to FDA)  
☐ Yes ☐ No ☐ Returned to Manufacturer on: (mm/dd/yyyy)

**D. SUSPECT PRODUCT(S)**

1. Name, Strength, Manufacturer (from product label)  
#1 Name: Strength: Manufacturer:  
#2 Name: Strength: Manufacturer:

**E. SUSPECT MEDICAL DEVICE**

1. Brand Name 2. Common Device Name 3. Manufacturer Name, City and State

4. Model # Lot # 5. Operator of Device  
Catalog # Expiration Date (mm/dd/yyyy) ☐ Health Professional  
Serial # Other # ☐ Lay User/Patient ☐ Other

6. If Implanted, Give Date (mm/dd/yyyy) 7. If Expired, Give Date (mm/dd/yyyy)

8. Is this a Single-Use Device that was Reprocessed and Reused on a Patient?  
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

**F. OTHER (CONCOMITANT) MEDICAL PRODUCTS**

Product names and therapy dates (exclude treatment of event)

**G. REPORTER (See confidentiality section on back)**

1. Name and Address  
Name: Address: City: State: ZIP: Phone #: E-mail:

2. Health Professional? ☐ Yes ☐ No 3. Occupation 4. Also Reported to:  
☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FORM FDA 3500 (1/09) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

## ADVICE ABOUT VOLUNTARY REPORTING

Detailed instructions available at: <http://www.fda.gov/medwatch/report/consumer/instruct.htm>

## Report adverse events, product problems or product use errors with:

- Medications (drugs or biologics)
- Medical devices (including in-vitro diagnostics)
- Combination products (medication & medical devices)
- Human cells, tissues, and cellular and tissue-based products
- Special nutritional products (dietary supplements, medical foods, infant formulas)
- Cosmetics

## Report product problems - quality, performance or safety concerns such as:

- Suspected counterfeit product
- Suspected contamination
- Questionable stability
- Defective components
- Poor packaging or labeling
- Therapeutic failures (product didn't work)

## Report SERIOUS adverse events. An event is serious when the patient outcome is:

- Death
- Life-threatening
- Hospitalization - initial or prolonged
- Disability or permanent damage
- Congenital anomaly/birth defect
- Required intervention to prevent permanent impairment or damage (devices)
- Other serious (important medical events)

## Report even if:

- You're not certain the product caused the event
- You don't have all the details

## How to report:

- Just fill in the sections that apply to your report
- Use section D for all products except medical devices
- Attach additional pages if needed
- Use a separate form for each patient
- Report either to FDA or the manufacturer (or both)

## Other methods of reporting:

- 1-800-FDA-0178 - To FAX report
- 1-800-FDA-1088 - To report by phone
- [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm) - To report online

If your report involves a serious adverse event with a device and it occurred in a facility outside a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

If your report involves a serious adverse event with a vaccine, call 1-800-822-7967 to report.

**Confidentiality:** The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act. The reporter's identity, including the identity of a self-reporter, may be shared with the manufacturer unless requested otherwise.

The public reporting burden for this collection of information has been estimated to average 16 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
Office of Chief Information Officer  
1515 Piccard Drive, Room 408  
Rockville, MD 20850

Please DO NOT  
RETURN this form  
to this address.

OMB statement:  
"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Food and Drug Administration

FORM FDA 3500 (1/09) (Back)

Please Use Address Provided Below - Fold in Thirds, Tape and Mail

DEPARTMENT OF  
HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

Official Business  
Penalty for Private Use \$300

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FIRST CLASS MAIL PERMIT NO. 946 ROCKVILLE MD

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**MEDWATCH**  
The FDA Safety Information and Adverse Event Reporting Program  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20852-9787

NO POSTAGE  
NECESSARY  
IF MAILED  
IN THE  
UNITED STATES  
OR APO/FPO

FIG E1. The FDA safety Information and AERS MedWatch form.

U.S. Department of Health and Human Services

**MEDWATCH**The FDA Safety Information and  
Adverse Event Reporting Program

(CONTINUATION PAGE)

For VOLUNTARY reporting of  
adverse events and product problems

Page 3 of \_\_\_\_

B.5. Describe Event or Problem (continued)

B.6. Relevant Tests/Laboratory Data, Including Dates (continued)

B.7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepato/renal dysfunction, etc.) (continued)

F. Concomitant Medical Products and Therapy Dates (Exclude treatment of event) (continued)

**General Instructions for Completing the MedWatch Form FDA 3500**

For use by health professionals and consumers for VOLUNTARY reporting of adverse events, product use errors and product quality problems with:

- Drugs
- Biologics (including blood components, blood derivatives, allergenics, human cells, tissues, and cellular and tissue-based products (HCT/PS))
- Medical devices (including *in-vitro* diagnostics)
- Combination products (e.g. drug-device, biologic-device)
- Special nutritional products (dietary supplements, infant formulas, medical foods)
- Cosmetics

Adverse events involving vaccines should be reported to the Vaccine Adverse Event Reporting System (VAERS), [http://vaers.hhs.gov/pdf/vaers\\_form.pdf](http://vaers.hhs.gov/pdf/vaers_form.pdf). Adverse events involving investigational (study) drugs, such as those relating to Investigational New Drug (IND) applications, should be reported as required in the study protocol and sent to the address and contact person listed in the study protocol. They should generally not be submitted to FDA MedWatch as voluntary reports.

**Note for consumers:** If possible, please take the 3500 form to your health professional (e.g., doctor or pharmacist) so that information based on your medical record that can help in the evaluation of your report will be provided. If, for whatever reason, you do not wish to have your health professional fill out the form, you are welcome to do so yourself.

**GENERAL INSTRUCTIONS**

- Please make sure that all entries are either typed, printed in a font no smaller than 8 point, or written using black ink.
- Please complete all sections that apply to your report.
- Dates should be entered as mm/dd/yyyy (e.g., June 3, 2005 = 06/03/2005). If exact dates are unknown, please provide the best estimate (see block B3).
- For narrative entries, if the fields do not provide adequate space, attach additional pages as needed.
- If attaching additional pages, please do the following:
  - Identify all attached pages as Page \_\_\_\_ of \_\_\_\_
  - Indicate the appropriate section and block number next to the narrative continuation.
- Include the phrase continued at the end of each field that has additional information continued on to another page.
- Section D, Suspect product(s), should be used to report on special nutritional products and cosmetics as well as drugs or biologics, including human cells, tissues, and cellular and tissue-based products (HCT/PS).
- If your report involves a serious adverse event with a device and it occurred in a facility other than a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

**FIG E1. (Continued)**

## SECTION A: PATIENT INFORMATION

Complete a separate form for each patient, unless the report involves a medical device where multiple patients were adversely affected through the use of the same device. In that case, please indicate the number of patients in block B5 (Describe event or problem) and complete Section A and blocks B2, B5, B6, B7, and F for each patient. Enter the corresponding patient identifier in block A1 for each patient involved in the event.

Parent-child/fetus report(s) are those cases in which either a fetus/breast-feeding infant or the mother, or both have an adverse event that is possibly associated with a product administered to the mother during pregnancy. Several general principles are used for filing these reports:

- If there has been no event affecting the child/fetus, report only on the parent.
- For those cases describing fetal death, miscarriage or abortion, report the parent as the patient in the report.
- When only the child/fetus has an adverse reaction/event (other than fetal death, miscarriage or abortion), the information provided in Section A applies to the child/fetus. However, the information in Section D would apply to the parent who was the source of exposure to the product.
- When a newborn baby is found to have a birth defect/congenital anomaly that the initial reporter considers possibly associated with a product administered to the mother during pregnancy, the patient is the newborn baby.
- If both the parent and the child/fetus have adverse events, separate reports should be submitted for each patient.

## A1: Patient Identifier

Please provide the patient's initials or some other type of identifier that will allow you, the reporter, to readily locate

the case if you are contacted for more information. Do not use the patient's name or social security number.

The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act.

If no patient was involved (such as may be the case with a product problem), enter none.

## A2: Age at Time of Event or Date of Birth

Provide the most precise information available. Enter the patient's birth date, if known, or the patient's age at the time of event onset. For age, indicate time units used (e.g., years, months, days):

- If the patient is 3 years or older, use years (e.g., 4 years).
- If the patient is less than 3 years old, use month (e.g., 24 months).
- If the patient is less than 1 month old, use days (e.g., 5 days).
- Provide the best estimate if exact age is unknown.

## A3: Sex

Enter the patient's gender. If the adverse event is a congenital anomaly/birth defect, report the sex of the child.

## A4: Weight

Indicate whether the weight is in pounds (lb) or kilograms (kg). Make a best estimate if exact weight is unknown.

## SECTION B: ADVERSE EVENT, PRODUCT PROBLEM, PRODUCT USE ERROR

## B1: Adverse Event, Product Problem, Product Use Error, or Problem with Different Manufacturer of Same Medicine.

Choose the appropriate box(es). If a product problem may have caused or contributed to the adverse event, check both boxes.

**Adverse event:** Any incident where the use of a medication (drug or biologic, including HCT/P), at any dose, a medical device (including *in-vitro* diagnostics) or a special nutritional product (e.g., dietary supplement, infant formula or medical food) is suspected to have resulted in an adverse outcome in a patient.

To report, it is not necessary to be certain of a cause/effect relationship between the adverse event and the use of the medical product(s) in question. Suspicion of an association is sufficient reason to report. Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Please limit your submissions to those events that are serious. An event is classified as serious when the patient outcome is:

- Death
- Life-threatening
- Hospitalization (initial or prolonged)
- Disability or Permanent Damage
- Congenital Anomaly/Birth Defect
- Required Medical or Surgical Intervention to Prevent Permanent Impairment or Damage (Devices)
- Other Serious (Important Medical Events)

Please see instructions for block B2 for further information on each of these criteria.

**Product problem (e.g., defects/malfunctions):** Any report regarding the quality, performance, or safety of any medication, medical device or special nutritional product. In addition, please select this category when reporting device malfunctions that could lead to a death or serious injury if the malfunction were to recur. Product problems include, but are not limited to, such concerns as:

- Suspected counterfeit product
- Suspected contamination
- Questionable stability
- Defective components
- Therapeutic failures (product didn't work)
- Product confusion (caused by name, labeling, design or packaging)
- Suspected superpotent or subpotent medication
- Labeling problems caused by printing errors/omissions

## Product Use Error:

**Medication Use Error:** Any report of a medication error regardless of patient involvement or outcome. Also report circumstances or events that have the capacity to cause error (e.g., similar product appearance, similar packaging and labeling, sound-alike/look-alike names, etc.).

Medication errors can and do originate in all stages of the medication use system, which includes selecting and procuring drugs, prescribing, preparing and dispensing, administering and monitoring. A medication error is defined as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labeling, packaging, nomenclature, compounding, dispensing, distribution, administration, education, monitoring and use."

**Medical Device Use Error:** Health care professionals, patients, and consumers can unintentionally cause harm to patients or to themselves when using medical devices. These problems can often arise due to problems with the design of the medical device or the manner in which the device is used. Often, use errors are caught and prevented before they can do harm (close call). Report use errors regardless of patient involvement or outcome. Also report circumstances or events that could cause use errors. Medical device use errors usually occur for one or more of the following reasons:

- Users expect devices to operate differently than they do.
- Product use is inconsistent with use's expectations or intuition.
- Product use requires physical, perceptual, or cognitive abilities that exceed those of the user.
- Devices are used in ways not anticipated by the manufacturer.
- Product labeling or packaging is confusing or inadequate.
- The environment adversely affects or influences device use.

**Problem with Different Manufacturer of Same Medicine:** Any incident, to include, but not be limited to, differences in noted therapeutic response, suspected to have resulted from a switch, or change, from one manufacturer to another manufacturer of the same medicine or drug product. This could be changes from a brand name drug product to a generic manufacturer's same product, or from a generic manufacturer's product to the same

(continued on next page)

FIG E1. (Continued)

**SECTION B: ADVERSE EVENT, PRODUCT PROBLEM, PRODUCT USE ERROR** (*continued*)

product as supplied by a different generic manufacturer, or from a generic manufacturer's product to a brand name manufacturer of the same product. In order to fully evaluate the incident, please include in **Section B5**, if available, specific information relative to the switch between different manufacturers of the same medicine, to include, but not be limited to, the names of the manufacturers, length of treatment on each manufacturer's product, product strength, and any relevant clinical data.

**B2: Outcomes Attributed to Adverse Event:** Indicate all that apply to the reported event:

**Death:** Check only if you suspect that the death was an outcome of the adverse event, and include the date if known.

Do not check if:

- The patient died while using a medical product, but there was no suspected association between the death and the use of the product
- A fetus is aborted because of a congenital anomaly (birth defect), or is miscarried

**Life-threatening:** Check if suspected that:

- The patient was at substantial risk of dying at the time of the adverse event, or
- Use or continued use of the device or other medical product might have resulted in the death of the patient

**Hospitalization (initial or prolonged):** Check if admission to the hospital or prolongation of hospitalization was a result of the adverse event.

Do not check if:

- A patient in the hospital received a medical product and subsequently developed an otherwise nonserious adverse event, unless the adverse event prolonged the hospital stay

Do check if:

- A patient is admitted to the hospital for one or more days, even if released on the same day
- An emergency room visit results in admission to the hospital. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious (medically important event)

**Disability or Permanent Damage:** Check if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions. Such would be the case if the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.

**Congenital Anomaly/Birth Defect:** Check if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

**Required Intervention to Prevent Permanent Impairment or Damage (Devices):** Check if you believe that medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.

**Other Serious (Important Medical Events):** Check when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

**B3: Date of Event**

Provide the actual or best estimate of the date of first onset of the adverse event. If day is unknown, month and year are acceptable. If day and month are unknown, year is acceptable.

- When a newborn baby is found to have a congenital anomaly, the event onset date is the date of birth of the child.
- When a fetus is aborted because of a congenital anomaly, or is miscarried, the event onset date is the date pregnancy is terminated.
- If information is available as to time during pregnancy when exposure occurred, indicate that information in narrative block B5.

**B4: Date of this Report**

The date the report is filled out.

**B5: Describe Event, Problem or Product Use Error**

For an adverse event:

Describe the event in detail, including a description of what happened and a summary of all relevant clinical information (medical status prior to the event; signs and/or symptoms; differential diagnosis for the event in question; clinical course; treatment; outcome, etc.). If available and if relevant, include synopses of any office visit notes or the hospital discharge summary. To save time and space (and if permitted by your institution), please attach copies of these records with any confidential information deleted. Do not identify any patient, physician, or institution by name. The reporter's identity should be provided in full in **Section G**.

(continued on next page)

**SECTION B: ADVERSE EVENT, PRODUCT PROBLEM, PRODUCT USE ERROR** (*continued*)

Information as to any environmental conditions that may have influenced the event should be included, particularly when (but not exclusive to) reporting about a device.

- Results of relevant tests and laboratory data should be entered in block B6. (See instructions for B6.)
- Preexisting medical conditions and other relevant history belong in block B7. Be as complete as possible, including time courses for preexisting diagnoses (see instructions for B7).

If it is determined that reuse of a medical device labeled for single use may have caused or contributed to an adverse patient outcome, please report in block B5 the facts of the incident and the perceived contribution of reuse to the occurrence.

**For a product problem:** Describe the problem (quality, performance, or safety concern) in sufficient detail so that the circumstances surrounding the defect or malfunction of the medical product can be understood.

- If available, the results of any evaluation of a malfunctioning device and, if known, any relevant maintenance/service information should be included in this section.
- For a medication or special nutritional product problem, please indicate if you have retained a sample that would be available to FDA.

**For a product use error:** Describe the sequence of events leading up to the error in sufficient detail so that the circumstances surrounding the error can be understood.

- **For Medication Use Errors:** Include a description of the error, type of staff involved, work environment in which the error occurred, indicate causes or contributing factors to the error, location of the error, names of the products involved (including the trade (proprietary) and established (proper) name), manufacturer, dosage form, strength, concentration, and type and size of container.

- **For Medical Device Use Errors:** Report circumstances or events that could cause use errors. Medical device use errors usually occur for one or more of the following reasons:

- Users expect devices to operate differently than they do.
- Product use is inconsistent with user's expectations or intuition.
- Product use requires physical, perceptual, or cognitive abilities that exceed those of the user.
- Devices are used in ways not anticipated by the manufacturer.
- Product labeling or packaging is confusing or inadequate.
- The environment adversely affects or influences device use.

**For a problem with a different manufacturer of the same medicine:**

Please include specific information relative to the switch between different manufacturers of the same medicine, to include, but not be limited to, the names of the manufacturers, length of treatment on each manufacturer's product, product strength, and any relevant clinical data.

**B6: Relevant Tests/Laboratory Data, Including Dates**

Please provide all appropriate information, including relevant negative test and laboratory findings, in order to most completely convey how the medical work-up/assessment led to strong consideration of medical product-induced disease as etiology for clinical status, as other differential diagnostic considerations were being eliminated.

Please include:

- Any relevant baseline laboratory data prior to the administration or use of the medical product
- All laboratory data used in diagnosing the event
- Any available laboratory data/engineering analyses (for devices) that provide further information on the course of the event

If available, please include:

- Any pre- and post-event medication levels and dates (if applicable)
- Synopses of any relevant autopsy, pathology, engineering, or lab reports

If preferred, copies of any reports may be submitted as attachments, with all confidential information deleted. Do not identify any patient, physician or institution by name. The initial reporter's identity should be provided in full in **Section G**.

**B7: Other Relevant History, Including Preexisting Medical Conditions**

Knowledge of other risk factors can help in the evaluation of a reported adverse event. If available, provide information on:

- **Other known conditions in the patient, e.g.,**
  - Hypertension (high blood pressure)
  - Diabetes mellitus
  - Liver or kidney problems
- **Significant history**
  - Race
  - Allergies
  - Pregnancy history
  - Smoking and alcohol use, drug abuse
  - Setting

**FIG E1.** (*Continued*)

## SECTION C: PRODUCT AVAILABILITY

Product available for evaluation? (Do not send the product to FDA.)

To evaluate a reported problem with a medical product, it is often critical to be able to examine the product. Please indicate whether the product is available for evaluation. Also indicate if the product was returned to the manufacturer and, if so, the date of the return.

## SECTION D: SUSPECT PRODUCT(S)

## For adverse event reporting:

A suspect product is one that you suspect is associated with the adverse event. In **Section F** enter other concomitant medical products (drugs, biologics including human cells, tissues, and cellular and tissue-based products (HCT/Ps), medical devices, etc.) that the patient was using at the time of the event but which you do not think were involved in the event.

Up to two (2) suspect products may be reported on one form (#1=first suspect product, #2=second suspect product). Attach an additional form if there were more than two suspect products associated with the reported adverse event.

## For product quality problem reporting:

A suspect product is the product that is the subject of the report. A separate form should be submitted for each individual product problem report.

Identification of the labeler/distributor and pharmaceutical manufacturer and labeled strength of the product is important for prescription or non-prescription products.

This section may also be used to report on special nutritional products (e.g., dietary supplements, infant formula or medical foods), cosmetics, human cells, tissues, or cellular and tissue-based products (HCT/Ps) or other products regulated by FDA.

If reporting on a special nutritional or drug product quality problem, please attach labeling/packaging if available.

If reporting on a special nutritional product only, please provide directions for use as listed on the product labeling.

## D1: Name, Strength, Manufacturer

Use the trade/brand name. If the trade/brand name is not known or if there is no trade/brand name, use the generic product name and the name of the manufacturer or labeler. These names are usually found on the product packaging or labeling. Strength is the amount in each tablet or capsule, the concentration of an injectable, etc. (such as "10mg", "100 units/cc", etc.).

For human cells, tissues, and cellular and tissue-based products (HCT/Ps), please provide the common name of the HCT/P. You can also indicate if the HCT/P has a proprietary or trade name. Examples: Achilles tendon, Iliac crest bone or Islet cells.

## D2: Dose or Amount, Frequency, Route

Describe how the product was used by the patient (e.g., 500 mg QID orally or 10 mg every other day IV). For reports involving overdoses, the amount of product used in the overdose should be listed, not the prescribed amount. (See **APPENDIX** for list of **Routes of Administration** on the next page.)

## D3: Dates of Use

Provide the date administration was started (or best estimate) and the date stopped (or best estimate). If no dates are known, an estimated duration is acceptable (e.g., 2 years) or if therapy was less than one day, then duration is appropriate (e.g., 1 dose or 1 hour for an IV).

For human cells, tissues, and cellular and tissue-based products, provide the date of transplant and if applicable, the date of explantation.

## D4: Diagnosis or Reason for Use (Indication)

Provide the reason or indication for which the product was prescribed or used in this particular patient.

## D5: Event Abated After Use Stopped or Dose Reduced

If available, this information is particularly useful in the evaluation of a suspected adverse event. In addition to checking the appropriate box, please provide supporting lab tests and dates, if available, in block B6.

## D6: Lot #

If known, include the lot number(s) with all product quality problem reports, or any adverse event report with a biologic, or medication.

## D7: Expiration Date

Please include if available.

## SECTION D: SUSPECT PRODUCT(S) (continued)

## D8: Event Reappeared After Reintroduction

This information is particularly useful in the evaluation of a suspected adverse event. In addition to checking the appropriate box, please provide a description of what happened when the drug was stopped and then restarted in block B5, and any supporting lab tests and dates in block B6.

## D9: NDC # or Unique ID

The national drug code (NDC #) is requested only when reporting a drug product problem. Zeros and dashes should be included as they appear on the label. NDC # can be found on the original product label and/or packaging, but is usually not found on dispensed pharmacy prescriptions.

If the product has a unique or distinct identification code, please provide this here. This is applicable to human cells, tissues, and cellular and tissue-based products (HCT/Ps).

## Appendix - Routes of Administration

|                             |                                  |                                           |                              |
|-----------------------------|----------------------------------|-------------------------------------------|------------------------------|
| Auricular (otic) 001        | Intracerebral 018                | Intrasyovial 035                          | Perineural 052               |
| Buccal 002                  | Intracervical 019                | Intratumor 036                            | Rectal 053                   |
| Cutaneous 003               | Intracisternal 020               | Intrathecal 037                           | Respiratory (inhalation) 054 |
| Dental 004                  | Intracorneal 021                 | Intrathoracic 038                         | Retrobulbar 055              |
| Endocervical 005            | Intracoronary 022                | Intratracheal 039                         | Subconjunctival 056          |
| Endosinusial 006            | Intradermal 023                  | Intravenous bolus 040                     | Subcutaneous 057             |
| Endotracheal 007            | Intradiscal (intraspinal) 024    | Intravenous drip 041                      | Subdermal 058                |
| Epidural 008                | Intrahepatic 025                 | Intravenous (not otherwise specified) 042 | Sublingual 059               |
| Extra-amniotic 009          | Intralesional 026                | Intravesical 043                          | Topical 060                  |
| Hemodialysis 010            | Intralymphatic 027               | Iontophoresis 044                         | Transdermal 061              |
| Intra corpus cavernosum 011 | Intramedullary (bone marrow) 028 | Occlusive dressing technique 045          | Transmammary 062             |
| Intra-amniotic 012          | Intrameningeal 029               | Ophthalmic 046                            | Transplacental 063           |
| Intra-arterial 013          | Intramuscular 030                | Oral 047                                  | Unknown 064                  |
| Intra-articular 014         | Intraocular 031                  | Oropharyngeal 048                         | Urethral 065                 |
| Intra-uterine 015           | Intrapericardial 032             | Other 049                                 | Vaginal 066                  |
| Intracardiac 016            | Intrapertoneal 033               | Parenteral 050                            |                              |
| Intracavernous 017          | Intrapleural 034                 | Periarticular 051                         |                              |

(continued on next page)

FIG E1. (Continued)

**SECTION E: SUSPECT MEDICAL DEVICE**

The suspect medical device is 1) the device that may have caused or contributed to the adverse event or 2) the device that malfunctioned.

In **Section F**, report other concomitant medical products (drugs, biologics including HCT/PS, medical devices, etc.) that the patient was using at the time of the event but which you do not think were involved in the event.

If more than one suspect medical device was involved in the event, complete all of **Section E** for the first device and attach a separate completed **Section E** for each additional device.

If the suspect medical device is a single-use device that has been reprocessed, then the reprocessor is now the device manufacturer.

**E1: Brand Name**

The trade or proprietary name of the suspect medical device as used in product labeling or in the catalog (e.g., Flo-Easy Catheter, Reliable Heart Pacemaker, etc.). This information may 1) be on a label attached to a durable device, 2) be on a package of a disposable device, or 3) appear in labeling materials of an implantable device. Reprocessed single-use devices may bear the Original Equipment Manufacturer (OEM) brand name. If the suspect device is a reprocessed single-use device, enter "NA".

**E2: Common Device Name**

The generic or common name of the suspect medical device or a generally descriptive name (e.g., urological catheter, heart pacemaker, patient restraint, etc.). Please do not use broad generic terms such as "catheter," "valve," "screw", etc.

**E3: Manufacturer Name, City and State**

If available, list the full name, city and state of the manufacturer of the suspected medical device. If the answer of block **E3** is "yes", then enter the name, city and state of the reprocessor.

**E4: Model #, Catalog #, Serial #, Lot #, Expiration Date, Other #**

If available, provide any or all identification numbers associated with the suspect medical device exactly as they appear on the device or device labeling. This includes spaces, hyphens, etc.

**Model #:**

The exact model number found on the device label or accompanying packaging.

**Catalog #:**

The exact number as it appears in the manufacturer's catalog, device labeling, or accompanying packaging.

**Serial #:**

This number can be found on the device label or accompanying packaging; it is assigned by the manufacturer, and should be specific to each device.

**Lot #:**

This number can be found on the label or packaging material.

**Expiration Date (mm/dd/yyyy):**

If available, this date can often be found on the device itself or printed on the accompanying packaging.

**Other #:**

Any other applicable identification number (e.g., component number, product number, part bar-coded product ID, etc.)

**E5: Operator of Device**

Indicate the type (not the name) of person operating or using the suspect medical device on the patient at the time of the event as follows:

- Health professional = physician, nurse, respiratory therapist, etc.
- Lay user/patient = person being treated, parent/spouse/friend of the patient
- Other = nurses aide, orderly, etc.

**E6: If Implanted, Give Date (mm/dd/yyyy)**

For medical devices that are implanted in the patient, provide the implant date or your best estimate. If day is unknown, month and year are acceptable. If month and day are unknown, year is acceptable.

**E7: If Explanted, Give Date (mm/dd/yyyy)**

If an implanted device was removed from the patient, provide the explantation date or your best estimate. If day is unknown, month and year are acceptable. If month and day are unknown, year is acceptable.

**E8: Is this a Single-use Device that was returned before Reprocessed and Reused on a Patient?**

Indicate "Yes" or "No".

**E9: If Yes to Item No. 8, Enter Name and Address of Reprocessor**

Enter the name and address of the reprocessor of the single-use device. Anyone who reprocesses single-use devices for reuse in humans is the manufacturer of the reprocessed device.

**SECTION F: OTHER (CONCOMITANT) MEDICAL PRODUCTS****Product names and therapy dates (exclude treatment of event)**

Information on the use of concomitant medical products can frequently provide insight into previously unknown interactions between products, or provide an alternative explanation for the observed adverse event. Please list and provide product names and therapy dates for any other medical products (drugs, biologics including HCT/PS, medical devices, etc.) that the patient was using at the time of the event. Do not include products used to treat the event.

**SECTION G: REPORTER**

FDA recognizes that confidentiality is an important concern in the context of adverse event reporting. The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. However, to allow for timely follow-up in serious cases, the reporter's identity may be shared with the manufacturer unless specifically requested otherwise in block **G5**. FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act.

**G1: Name, Address, Phone #, E-mail**

Please provide the name, mailing address, phone number and E-mail address of the person who can be contacted to provide information on the event if follow-up is necessary. While optional, providing the fax number would be most helpful, if available. This person will also receive an acknowledgment letter from FDA on receipt of the report.

**G2: Health Professional?**

Please indicate whether you are a health professional (e.g., physician, pharmacist, nurse, etc.) or not.

**G3: Occupation:**

Please indicate your occupation (particularly type of health professional), and include specialty, if appropriate.

**G4: Also Reported to:**

Please indicate whether you have also notified or submitted a copy of this report to the manufacturer and/or distributor of the product, or, in the case of medical device reports only, to the user facility (institution) in which the event occurred. This information helps to track duplicate reports in the FDA database.

**G5: Release of reporter's identity to the manufacturer**

In the case of a serious adverse event, FDA may provide name, address and phone number of the reporter denoted in block **G1** to the manufacturer of the suspect product. If you do not want your identity released to the manufacturer, please put an X in this box.

**FIG E1. (Continued)**