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A Randomized Trial of Transfer for Primary Angioplasty Versus On-Site Thrombolysis in Patients With High-Risk Myocardial Infarction

The Air Primary Angioplasty in Myocardial Infarction Study

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OBJECTIVES The Air Primary Angioplasty in Myocardial Infarction (PAMI) study was designed to determine the best reperfusion strategy for patients with high-risk acute myocardial infarction (AMI) at hospitals without percutaneous transluminal coronary angioplasty (PTCA) capability.

BACKGROUND Previous studies have suggested that high-risk patients have better outcomes with primary PTCA than with thrombolytic therapy. It is unknown whether this advantage would be lost if the patient had to be transferred for PTCA, and reperfusion was delayed.

METHODS Patients with high-risk AMI (age >70 years, anterior MI, Killip class II/III, heart rate >100 beats/min or systolic BP <100 mm Hg) who were eligible for thrombolytic therapy were randomized to either transfer for primary PTCA or on-site thrombolysis.

RESULTS One hundred thirty-eight patients were randomized before the study ended (71 to transfer for PTCA and 67 to thrombolysis). The time from arrival to treatment was delayed in the transfer group (155 vs. 51 min, $p < 0.0001$), largely due to the initiation of transfer (43 min) and transport time (26 min). Patients randomized to transfer had a reduced hospital stay (6.1 ± 4.3 vs. 7.5 ± 4.3 days, $p = 0.015$) and less ischemia (12.7% vs. 31.8%, $p = 0.007$). At 30 days, a 38% reduction in major adverse cardiac events was observed for the transfer group; however, because of the inability to recruit the necessary sample size, this did not achieve statistical significance (8.4% vs. 13.6%, $p = 0.331$).

CONCLUSIONS Patients with high-risk AMI at hospitals without a catheterization laboratory may have an improved outcome when transferred for primary PTCA versus on-site thrombolysis; however, this will require further study. The marked delay in the transfer process suggests a role for triaging patients directly to specialized heart-attack centers. (J Am Coll Cardiol 2002;39: 1713–9) © 2002 by the American College of Cardiology Foundation

Angioplasty as the primary reperfusion strategy for acute myocardial infarction (AMI) reduces recurrent ischemia, reinfarction, stroke and death, compared with thrombolytic therapy (1–4). Despite these findings, thrombolytic therapy remains the mainstay of therapy for AMI, partly due to the fact that the majority of hospitals lack percutaneous transluminal coronary angioplasty (PTCA) capabilities.

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Although thrombolytic therapy remains an acceptable alternative for most patients, it may not be ideal for higher-risk patients. Advanced age, anterior infarction, tachycardia, hypotension and congestive heart failure are associated with early mortality rates ranging from 10% to 58% in patients treated with thrombolytic agents (5). Some trials suggested that high-risk patients have the greatest benefit from primary PTCA, when compared with thrombolysis (1,6). However, none of these earlier trials involved the transfer of patients from a primary-care hospital, a strategy that would substantially delay the time to reperfusion.

Observational studies reported few complications during transfer for primary PTCA and no correlation between transfer distance and adverse outcome (7,8). Moreover, although the efficacy of thrombolysis decreases with the

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Abbreviations and Acronyms

AMI = acute myocardial infarction
BP = blood pressure
CABG = coronary artery bypass graft surgery
CI = confidence interval
ECG = electrocardiogram
MACE = major adverse cardiac events
OR = odds ratio
PAMI = Primary Angioplasty in Myocardial Infarction study
PTCA = percutaneous transluminal coronary angioplasty

increasing age of the clot (9–11), coronary patency and clinical outcomes after primary PTCA appear to be independent of the time to treatment (12–14). Therefore, the benefits of primary PTCA may overcome the deleterious effects of the delay in reperfusion during the time required to transfer. We hypothesized that in hospitals without an interventional laboratory, patients with high-risk AMI would have improved clinical outcomes if transferred for primary PTCA, rather than being treated with conventional, on-site thrombolytic therapy.

METHODS

Patient selection. Patients were considered if they had either ST-segment elevation or presumed new left bundle branch block and the onset of AMI was <12 h. In addition, one or more of the following criteria for high risk had to be met: age >70 years, heart rate >100 beats/min, systolic blood pressure (BP) <100 mm Hg in the absence of volume depletion, Killip class II/III or an electrocardiogram (ECG) demonstrating left bundle branch block or anterior MI.

Patients were excluded from study participation if they were ineligible for thrombolytic therapy (history of stroke or transient cerebral event in the last six months, major surgery or active gastrointestinal bleeding within the previous two months, organ biopsy within two weeks, cardiopulmonary resuscitation lasting ≥10 min or resulting in rib fracture, systolic BP >200 mm Hg or diastolic BP >110 mm Hg), had cardiogenic shock (defined as systolic BP ≤80 mm Hg in the absence of bradycardia or requiring vasopressors) or had a life-expectancy of less than one year. The study was conducted according to the principles of the Declaration of Helsinki, and all patients gave written, informed consent.

Eligible high-risk patients were randomized to receive either emergent transfer for primary PTCA or on-site thrombolytic therapy. Randomization was stratified by site and accomplished by either telephone randomization from the study coordinating center (U.S. sites) or sealed envelope (non-U.S. sites). The protocol recommended low-flow nasal oxygen, nitroglycerin, oral aspirin (325 mg) and intravenous beta-blockers. Anti-arrhythmic agents and calcium blockers were not routinely administered. Heparin was given according to the treatment arm to which the patient was assigned.

Transfer for primary PTCA arm. For patients randomized to primary angioplasty, emergency transfer was arranged by the most expedient means (either air or ground transport) to the assigned interventional facility. As soon as possible after randomization, a bolus of intravenous heparin was administered, but a continuous infusion was not recommended.

Patients were taken to the cardiac catheterization laboratory immediately upon arrival. Coronary angiography and left ventriculography were performed using low-osmolar ionic contrast medium (ioxaglate, Mallinckrodt, Inc., St. Louis, Missouri). A coronary intervention was performed unless the following exclusions precluded PTCA: infarct vessel stenosis ≤70%, an infarct vessel supplying so little to the myocardium that the PTCA risk outweighed the benefit, unprotected left main stenosis >60% or disease requiring coronary artery bypass graft surgery (CABG). The goal of angioplasty was restoration of normal coronary flow with minimal residual stenosis. Stenting was encouraged for residual lesions >30% or the presence of a coronary dissection. The activated clotting time was maintained at >350 s, and administration of thrombolytic agents was discouraged.

Thrombolytic treatment arm. Patients randomized to thrombolytic therapy received the drug that was considered the standard of care for the participating hospital. If tissue plasminogen activator was administered, heparin was given as an intravenous bolus, followed by an infusion for 72 h, with the dose adjusted to raise the activated partial thromboplastin time between 60 and 80 s. If streptokinase was given, heparin was administered according to the usual practice of the patient's physician. Patients randomized to thrombolysis remained at the enrolling hospital unless it was the usual practice to transfer patients with AMI. For patients with persistent chest pain, recurrent chest pain or hemodynamic instability, it was recommended that emergency catheterization be considered.

Clinical end points. The primary end point (i.e., major adverse cardiac events [MACE]) was the combined occurrence of death, non-fatal reinfarction or disabling stroke at 30 days. It was estimated that enrollment of 430 patients was required, assuming an event rate of 25% in the thrombolytic arm and a 40% reduction in events, with a power 80%. Reinfarction was defined as recurrent ischemic symptoms in association with re-elevation of creatine kinase to three times the upper limit of normal. Disabling stroke was defined as neurologic deficits significantly affecting activities of daily life. Ischemia was defined as persistent ischemic chest pain after reperfusion therapy or recurrent symptoms with ST-segment changes, new heart failure, murmur or creatine kinase re-elevation.

Detailed case-report forms were completed by the clinical coordinators at each site. Monitoring of the case-report form and hospital records was performed by the Primary Angioplasty in Myocardial Infarction (PAMI) coordinating center. All primary end points, as well as a random sampling of 20% of patients, were reviewed by the clinical events

Table 1. Air Primary Angioplasty in Myocardial Infarction Study: Baseline Characteristics

Variable	Transfer for Primary PTCA (n = 71)	On-Site Lytic Therapy (n = 66)	p Value
Age (yrs)	62 ± 12	64 ± 12	0.59
Gender (%male)	76	65	0.16
Hypertension (%)	51	34	0.04
History of peripheral vascular disease (%)	10	5	0.32
Previous MI (%)	13	14	0.89
Previous CABG (%)	3	3	1.00
Diabetes (%)	23	20	0.68
High-risk qualifiers (%)			
Age >70 years	27	39	0.12
Heart rate >100 beats/min	37	27	0.24
SBP <100 mm Hg	38	27	0.18
Killip class I	35	23	0.20
Anterior MI	77	80	0.68
ECG with LBBB	4	2	0.62
Two or more qualifiers	63	58	0.49
Three or more qualifiers	34	27	0.41

Data are presented as the mean value ± SD or percentage of patients.
CABG = coronary artery bypass graft surgery; ECG = electrocardiogram; LBBB = left bundle branch block; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; SBP = systolic blood pressure.

committee, which was blinded to the treatment received. The case-report form was never completed for one patient randomized to on-site lytic therapy. The clinical site withdrew from the trial after randomizing one patient and declined to provide any further information.

Statistical analyses. Categorical variables, including the end points of death, reinfarction, disabling stroke and the combined primary end point of MACE, were examined using the chi-square or Fisher two-sided exact test, as appropriate. Continuous variables were examined using the Wilcoxon rank-sum test because some of the variables were not normally distributed. A step-down logistic regression analysis was completed for 30-day MACE, including independent variables with a p value <0.15. History of previous MI, diabetes, type of lytic therapy, U.S. versus non-U.S. site, and time to treatment were included regardless of the p value. All analyses were completed using SAS, version 8.0.

Table 3. Air Primary Angioplasty in Myocardial Infarction Study: Treatments Received

	Transfer for PTCA	On-Site Lytic Therapy
Intravenous lytic therapy	1 (1.4%)	66 (100%)
Catheterization	71 (100%)	36 (55%)
Revascularization	68 (96%)	34 (52%)
PTCA	62 (87%)	27 (41%)
CABG	10 (14%)	7 (11%)
Aspirin	68 (96%)	63 (95%)
ACE inhibitors	48 (68%)	43 (65%)
Beta-blockers	36 (51%)	45 (68%)
Digoxin	9 (12.7%)	6 (9.1%)

ACE = angiotensin-converting enzyme; other abbreviations as in Table 1.

RESULTS

Demographic data and high-risk characteristics. The study was terminated after 39 months, and 138 patients (32% of the anticipated sample size) were randomized. The Steering Committee decided to terminate the trial before knowledge of any of the event rates, because of poor recruitment. At that time, 71 patients had been randomized to transfer and 67 patients to on-site thrombolysis. The demographic data and high-risk enrollment criteria of the transfer and thrombolysis groups are outlined in Table 1.

Treatments and time delays. All of the 71 patients randomized to transfer were transferred (79% by ambulance and 21% by helicopter). Overall, the mean distance was 32 ± 36 miles (25th, 50th and 75th percentiles were 10, 16 and 43 miles, respectively). In general, air transfer was used for greater distances (57 ± 50 miles), compared with ground transfer (26 ± 28 miles). No patient died or required cardiopulmonary resuscitation during transfer, and minor events during transfer were observed in only three patients (2 with hypotension and 1 with confusion).

Patients transferred for PTCA had the longest time to treatment (155 vs. 51 min, p < 0.0001), due to the time involved in the transfer and starting the invasive procedure (Table 2). Among the transfer group, 100% underwent catheterization, 89% had primary PTCA, and 87% had normal flow (TIMI grade 3) established (Table 3). Eight patients randomized to transfer did not receive primary PTCA; two patients were treated medically; and six patients

Table 2. Air Primary Angioplasty in Myocardial Infarction Trial: Time to Treatment

	Transfer for PTCA		Lytic Therapy		
Intervals	Median (25th, 75th)	Mean ± SD	Median (25th, 75th)	Mean ± SD	p Value
Emergency center arrival to randomization	35 (20,53)	52 ± 57	32 (15,65)	44 ± 37	0.67
Randomization to call for transfer	6 (5,15)	15 ± 30			
Transfer call to transfer, arrives at hospital no. 1	20 (10,26)	23 ± 18			
Transfer arrives to transfer leaves hospital no. 1	12 (9,17)	14 ± 9			
Transfer time	26 (15,40)	33 ± 29			
Arrival at hospital no. 2 to catheterization laboratory	11 (5,20)	20 ± 49			
Catheterization laboratory arrival to treatment	14 (8,23)	18 ± 14			
ER to treatment	155 (118,194)	174 ± 80	51 (35,89)	63 ± 39	< 0.0001

ER = emergency room; PTCA = percutaneous transluminal coronary angioplasty.

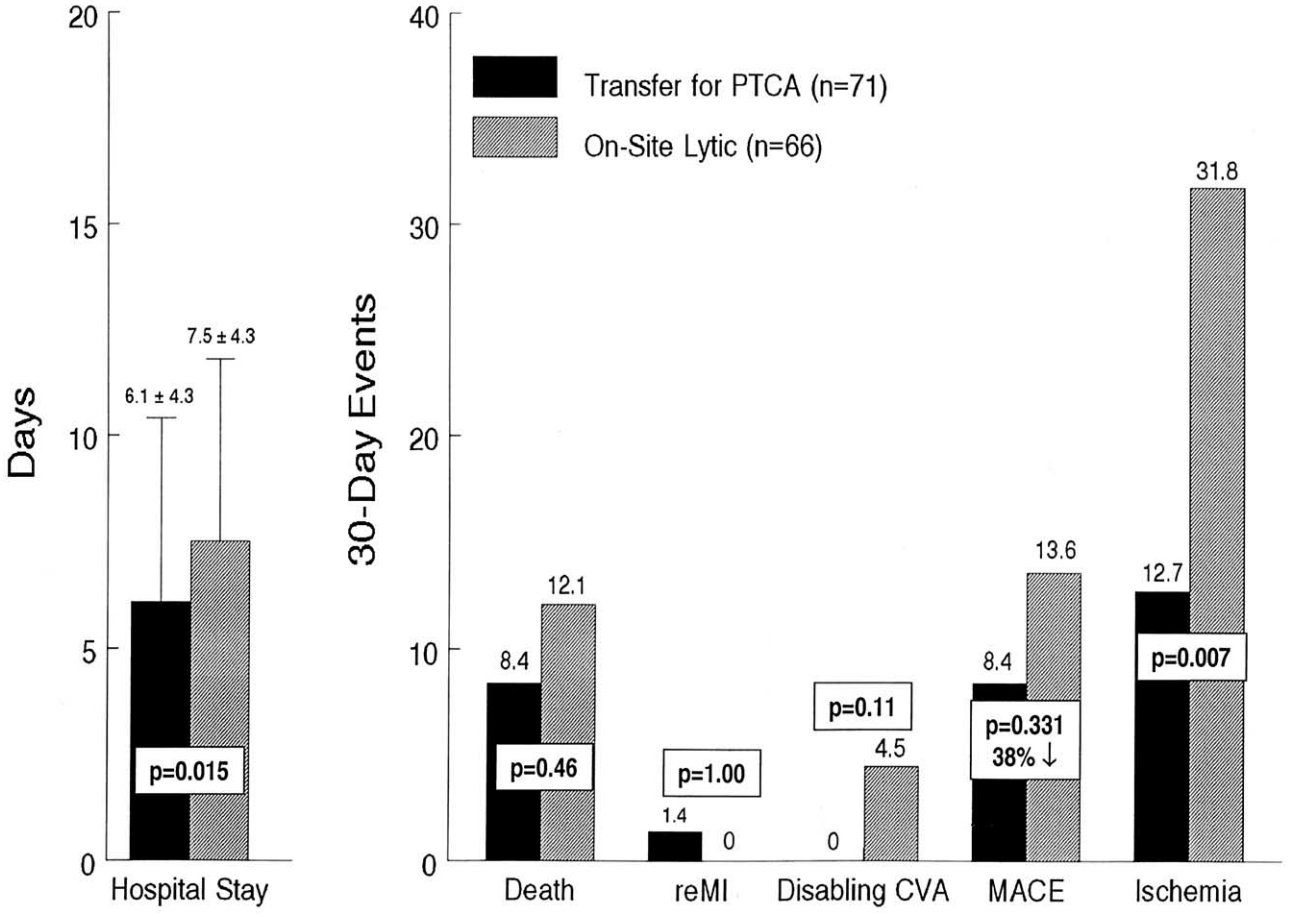

Figure 1. Thirty-day clinical events were non-significantly improved in the group transferred for primary percutaneous transluminal coronary angioplasty (PTCA). CVA = cerebrovascular accident; MACE = major adverse cardiac events (i.e., combined end point of death, repeat MI and disabling stroke); reMI = non-fatal reinfarction.

were referred for CABG. The mean ejection fraction was 47 ± 12%; 62% of patients were noted to have multivessel disease, and 34% received one or more stents.

Among patients randomized to on-site thrombolysis, 68% received a fibrin-specific agent (alteplace or reteplase) and 32% received streptokinase. Within the first 30 days, catheterization was performed in 55%, and revascularization with PTCA or CABG in 52%, of patients randomized to on-site thrombolysis.

Clinical outcomes. Patients randomized to transfer for primary PTCA had a shorter length of hospital stay (6.1 ± 4.3 vs. 7.5 ± 4.3 days, p = 0.015) and less ischemia (12.7% vs. 31.8%, p = 0.007) (Fig. 1). At 30 days, 8.4% of patients randomized to transfer reached the primary end point of death, non-fatal reinfarction or disabling stroke, compared with 13.6% of patients in the on-site thrombolysis group (odds ratio [OR] 0.571, 95% confidence interval [CI] 0.191 to 1.709, p = 0.331). In a secondary, pre-specified analysis using step-down, multivariate, logistic regression, randomization to transfer for primary PTCA was independently associated with a reduction in the primary end point (OR 0.159, 95% CI 0.031 to 0.820, p = 0.028) (Table 4).

DISCUSSION

This trial demonstrated that patients with high-risk AMI at hospitals without PTCA capabilities might have an improved outcome if transferred for emergency PTCA rather than being treated with thrombolytic therapy. Although our study was too small to achieve statistical significance, a 38% reduction in MACE was observed. Our findings are consistent with those in other recently reported randomized

Table 4. Air Primary Angioplasty in Myocardial Infarction Study: Multivariate Predictors of Major Adverse Cardiac Events at 30 Days

Variable	Odds Ratio	95% Confidence Interval	p Value
SBP <100 mm Hg	19.00	3.20–113	0.0012
Heart rate >100 beats/min	10.23	2.23–46.9	0.0028
Age >70 years	7.18	1.60–32.2	0.0100
Randomization to thrombolytic therapy	6.29	1.22–32.3	0.0278
History of hypertension	5.10	0.969–26.9	0.0545

SBP = systolic blood pressure.
Major adverse cardiac events = combined end point of death, repeat myocardial infarction or disabling stroke.

trials demonstrating improved outcomes with transfer for primary PTCA (15,16).

Transfer of patients with AMI. Despite enrollment of only high-risk patients, transfer in the early hours of AMI was found to be safe. However, the time delay in initiating the transfer (mean 52 min, median 38 min) was much longer than expected, and it added significantly to the delay in establishing reperfusion. As shown in Table 2, the delay in starting the transfer was multifactorial, but the greatest component was the wait for the ambulance or helicopter to arrive. The policy of some emergency medical systems is to assign a low priority to a patient who is already at a medical facility. Although there is some rationale for this policy, an exception should be made for patients with AMI requiring mechanical reperfusion. Moreover, the transferring and receiving institutions should work out the transfer logistics in advance to improve their response time.

Mechanism of benefit of primary PTCA. Transfer to a hospital where the patient will be managed by a cardiologist may result in greater utilization of proven medical therapies (17). We did not find this, but participating centers may not be representative of a non-study situation. Paradoxically, we found greater utilization of beta-blockers in the thrombolytic group, possibly due to treatment of recurrent angina, which occurred more frequently after thrombolytic therapy. Avoiding the use of thrombolytic agents clearly reduces the risk of intracranial bleeding (4), and previous randomized trials have shown reduced rates of reinfarction with PTCA (1–4). Primary angioplasty reduces the coronary stenosis that may predispose the vessel to reocclusion (18–20), and it avoids the platelet-aggregating effects of thrombolytic agents (21,22). Trials with angiographic follow-up suggest that patients treated with primary PTCA (2,23,24) have substantially lower rates of reocclusion, compared with those treated by thrombolytic therapy (18,19,25,26), and reocclusion may be further reduced by stent placement (27). The greatest benefit of primary PTCA may be its ability to achieve >90% rates of normal coronary flow (28) even when the patient is treated in the late stages of infarction (13,14). By contrast, thrombolytic therapy has a marked decrease in thrombolytic efficacy in patients treated more than a few hours after symptom onset (9,10).

Should thrombolytic agents be given before transfer? We have shown that the presence of spontaneous reperfusion before primary PTCA was an independent predictor of survival (29). Accordingly, there has been great interest in the concept of "facilitated" PTCA, whereby the patient is given a reduced dose of a thrombolytic agent, with an adjunctive glycoprotein IIb/IIIa or thrombin inhibitor. Theoretically, these combinations are attractive; however, two large randomized trials found no reduction in the primary end point of mortality, and there was a suggestion of a slight increase in intracranial bleeding (30,31). Although combination therapies were associated with less reinfarction in these trials, this was considered a soft end point because this strategy was not adjudicated by an independent events committee or because the study was not blinded, or both. Moreover, these trials did not incorporate a primary or facilitated angioplasty arm. The only randomized trial of facilitated percutaneous coronary intervention found that pre-treatment with tissue plasminogen activator improved the pre-procedural coronary patency but had no influence on the post-PTCA flow, ejection fraction or clinical outcome (32). More pertinent to this question are the PRAGUE and LIMI trials, both of which randomized patients with AMI at small community hospitals to transfer for primary PTCA, on-site lytic therapy, or a third arm of lytic administration before transfer (15,16). Both trials reported higher rates of bleeding in patients given lytic agents before transfer and worse clinical outcome compared with primary PTCA alone. Therefore, the available data suggest no benefit (32) or potential harm (15,16,23,30–35) by pre-treatment with thrombolytic agents before PTCA.

Primary angioplasty in hospitals without on-site surgical support. An emerging practice in some hospitals that have diagnostic catheterization laboratories is to perform on-site primary PTCA without surgical backup. A large, single-center experience (36), a retrospective review of a multicenter AMI registry (37) and a 500-patient, prospective, multicenter registry (38,39) suggest excellent clinical and angiographic outcomes if PTCA is performed by an experienced operator. The Cardiovascular Patient Outcomes Research Team (C-PORT) multicenter study randomized 451 patients with AMI at hospitals without surgical backup to receive on-site PTCA or thrombolytic therapy (40). They reported a 38% reduction in the primary end point of death, reinfarction or stroke at six months (12.4% vs. 19.9%, $p = 0.03$). Based on these reports, the American College of Cardiology/American Heart Association's guidelines for PTCA have been modified to consider primary PTCA as a class II indication at centers without on-site surgical capability (41).

Clinical implications. Given the small sample size of this trial, one must use caution when interpreting the results. Our study suggests that when a patient presents to a hospital that cannot perform primary PTCA, transfer for PTCA may be superior to on-site lytic therapy. Our results are corroborated by two other trials, but the number of patients enrolled in all three trials is low. Although these findings are provocative, they need to be confirmed in a large trial before any general recommendations can be made. On the other hand, we found that even in this study situation, the transfer process is slow, with long delays at each component. This suggests that there may be a role for obtaining ECGs in the field, transferring the patient directly from the home to a "heart-attack center" or even providing primary PTCA in smaller hospitals without on-site surgical capability.

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APPENDIX

Clinical Sites (Number of Patients Enrolled)

Instituto Modelo de Cardiologia, Cordoba, Argentina (n = 39); St. Joseph Medical Center, South Bend, Indiana (n = 29); St. Charles Medical Center, Bend, Oregon (n = 23); Wausau Hospital, Wausau, Wisconsin (n = 14); Oulu University Hospital, Oulu, Finland (n = 13); New York University Medical Center/Brooklyn Hospital, New York, New York (n = 7); William Beaumont Hospital, Royal Oak, Michigan (n = 4); Sanatorio Los Arroyos, Rosario, Argentina (n = 3); Allegheny General Hospital, Pittsburgh, Pennsylvania (n = 2); Riverside Methodist Hospital, Columbus, Ohio (n = 1); Oakwood Hospital, Dearborn, Michigan (n = 1); and Jewish Hospital, Louisville, Kentucky (n = 1).