# Trends in Use, Cost, and Outcomes of Human Recombinant Erythropoietin, 1989-98

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*In this article the authors present descriptive data showing trends in human recombinant erythropoietin (EPO) doses, charges, and patient hematocrits from the fourth quarter of calendar year 1989 to the first quarter of 1998 for all recipients and recent data for patients treated by in-center hemodialysis. In 1997 nearly all in-center hemodialysis patients received EPO regularly at an average cost per recipient of $6,245 per year for total allowed charges of $842.2 million per year. The study shows that policy changes may have both anticipated and unanticipated effects on medical practice.*

## INTRODUCTION

EPO was the first recombinant deoxyribonucleic acid (DNA) drug to enter common medical use in the United States. In June 1989 it was approved for the treatment of the chronic anemia associated with end stage renal disease (ESRD). Nine years later, in 1997, nearly all in-center hemodialysis patients received EPO regularly at an average cost per recipient of $6,245 per year, for total allowed charges of $842.2 million per year. Allowed charges for all EPO recipients, including home-dialysis ESRD patients and a few non-ESRD patients, were $901.5 million. (Medicare pays 80 percent of the allowed charges after the annual deductible is met.) The average dose has doubled from about 2,700 units in 1990 to 5,400 units in 1997. During this time, the mean hematocrit rose from 28.3 to 32.3.

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Medicare is by far the largest payer for EPO because Medicare covers about 93 percent of dialysis patients. As a result Medicare coverage and payment regulations significantly influence the financial environment physicians and dialysis facilities face in attempting to balance the best care for patients with the fiscal reality. Furthermore, the single manufacturer for all EPO sold in the United States has a marketing arrangement with the other domestic distributor, giving it effective monopoly power over the prices dialysis facilities must pay for EPO. These unusual market characteristics give the use and outcome data an interest beyond the renal community. The fact that Medicare spends about $720 million per year on the drug (Medicaid probably contributes another $40-50 million) makes it of major interest to HCFA and to stock market investors with an interest in the biotechnology industry.

Balancing the sometimes conflicting goals of reimbursing providers and sellers of EPO fairly, while at the same time not excessively, and ensuring that patients receive quality EPO therapy has proven to be a complex task for all parties. Several government agencies examined cost and pricing data before EPO was approved. On June 22, 1989, a month after approval by the U.S. Food and Drug Administration (FDA), HCFA announced that EPO was covered effective June 1, 1989, if administered by dialysis facilities or incident to a physician's services. HCFA announced a provisionary payment policy of $40 per administration with a $30 supplement for injections of 10,000 units or more. The first

EPO bills were paid in November. Later, two Omnibus Budget Reconciliation Acts changed EPO reimbursement, first to $11 per 1,000 units, effective January 1, 1991, and then to $10 per 1,000 units, effective January 1, 1994. During much of 1990-91, intravenous iron, needed by many patients for EPO to be effective, was off the market.

A number of studies have examined the initial impact of EPO coverage on the Medicare program and on ESRD patients (Griffiths et al., 1994; Powe, Eggers, and Johnson, 1994; de Lissovoy et al., 1994; Powe et al., 1992, 1993). However, these studies were conducted in the first few years after coverage was given. In this article we examine the trends in EPO use and expenditures through 1998.

## DATA AND METHODS

In creating a bill-handling system for the new drug, HCFA recognized a need for an EPO monitoring system to provide near-real-time data on EPO use and costs. HCFA made two decisions that allow the billing data to be used for a variety of outcomes monitoring, quality improvement, and policymaking purposes. First, HCFA required providers to include the average dose administered and the patient's hematocrit. Second, HCFA initiated a monitoring system to generate reports on EPO use patterns based on all EPO bills approved by fiscal intermediaries and carriers. HCFA summarized EPO data from all bills processed during each month (changed to each quarter after April 1995) and created reports for internal use that were often available 2-6 weeks after the end of the month. Although the reports contain only a few summary statistics, they provide an internally consistent record of EPO use from the first bills received by HCFA in September 1989.

The data from the monitoring system suffer from four major limitations:

- The underlying bill-processing system has undergone substantial changes over the years (e.g., when the UB-92 replaced the earlier billing form and more recently for year 2000 compliance), so additional analyses other than those that were included in the reports may require extensive programming.
- Because the reports were issued on a real-time basis for bills recently paid, the data do not reflect use during a well-defined time period. Although most bills are submitted and processed 1-3 months after the date of service, a small number may be approved or revised several months later. As a rough guideline, 30-40 percent of bills processed in a given quarter are for use during the quarter and 50-60 percent for the previous one.
- The data from 1989 through 1995 are for all Medicare bills containing EPO data. It is not possible to disaggregate by place of service, type of dialysis, or even whether the patient was on dialysis. More recent reports include a few analyses by type and place of dialysis.
- The charges that appear on the bills, in particular from hospital-based dialysis facilities, are sometimes higher than allowed by Medicare. The charge data presented in this article are estimated from the payment policy in effect when the bills were processed, that is, at $40 times the number of administrations before 1991 and at $11 or $10 times the number of units administered thereafter.

## RESULTS

Table 1 presents data on EPO use, patient outcomes (as measured by hematocrit level), and costs as reflected in

## Table 1

## EPO Dose, Hematocrit, and Charges, by Date Bill Was Processed: 1989-98

| Year and Quarter Bill Was Processed | Mean Dose in Units | Mean Hematocrit | Percent of Patients With Hematocrit ≥31 | Number of Administrations in Thousands | Allowed Charges in Millions |
|---|---|---|---|---|---|
| **1989** | | | | | |
| Fourth Quarter | 2,700 | 27.3 | 22.1 | 435 | $17.4 |
| **1990** | | | | | |
| First Quarter | 2,673 | 27.7 | 27.2 | 1,151 | 46.1 |
| Second Quarter | 2,662 | 28.4 | 29.7 | 1,527 | 61.1 |
| Third Quarter | 2,695 | 28.6 | 31.9 | 1,711 | 68.5 |
| Fourth Quarter | 2,745 | 28.7 | 32.1 | 1,971 | 78.8 |
| **1991** | | | | | |
| First Quarter | 2,821 | 28.8 | 33.5 | 2,010 | 80.4 |
| Second Quarter | 3,054 | 29.0 | 34.5 | 3,099 | 104.1 |
| Third Quarter | 3,233 | 29.1 | 35.3 | 2,722 | 96.8 |
| Fourth Quarter | 3,392 | 29.1 | 35.3 | 3,025 | 112.9 |
| **1992** | | | | | |
| First Quarter | 3,564 | 29.0 | 35.4 | 2,651 | 103.9 |
| Second Quarter | 3,704 | 29.1 | 36.3 | 2,766 | 112.7 |
| Third Quarter | 3,915 | 29.4 | 39.3 | 2,779 | 119.7 |
| Fourth Quarter | 3,996 | 29.6 | 40.7 | 2,107 | 92.6 |
| **1993** | | | | | |
| First Quarter | 4,092 | 29.6 | 41.8 | 3,353 | 150.9 |
| Second Quarter | 4,178 | 29.7 | 42.9 | 2,965 | 136.3 |
| Third Quarter | 4,257 | 30.0 | 45.7 | 3,025 | 141.7 |
| Fourth Quarter | 4,377 | 30.1 | 46.3 | 2,664 | 128.3 |
| **1994** | | | | | |
| First Quarter | 4,406 | 30.1 | 47.3 | 3,164 | 139.4 |
| Second Quarter | 4,455 | 30.4 | 49.9 | 3,207 | 142.9 |
| Third Quarter | 4,490 | 30.6 | 51.8 | 3,440 | 154.4 |
| Fourth Quarter | 4,695 | 30.8 | 54.2 | 3,279 | 153.9 |
| **1995** | | | | | |
| First Quarter | 4,866 | 30.9 | 55.0 | 3,491 | 169.9 |
| Second Quarter | 4,902 | 31.1 | 57.7 | 3,594 | 176.2 |
| Third Quarter | 4,950 | 31.3 | 60.4 | 3,664 | 181.4 |
| Fourth Quarter | 5,041 | 31.4 | 60.6 | 3,611 | 182.1 |
| **1996** | | | | | |
| First Quarter | 5,170 | 31.5 | 61.5 | 3,952 | 204.3 |
| Second Quarter | 5,292 | 31.8 | 64.5 | 4,023 | 212.9 |
| Third Quarter | 5,347 | 31.9 | 66.1 | 4,149 | 221.9 |
| Fourth Quarter | 5,428 | 32.1 | 67.4 | 4,122 | 223.7 |
| **1997** | | | | | |
| First Quarter | 5,470 | 32.3 | 68.7 | 4,187 | 229.0 |
| Second Quarter | 5,423 | 32.5 | 70.9 | 4,259 | 230.9 |
| Third Quarter | 5,298 | 32.3 | 70.8 | 4,109 | 217.7 |
| Fourth Quarter | 5,342 | 32.2 | 69.2 | 4,190 | 223.8 |
| **1998** | | | | | |
| First Quarter | 5,472 | 32.2 | 68.9 | 4,148 | 227.0 |

NOTES: EPO is human recombinant erythropoietin. The table includes all bills that contain EPO charges paid by Medicare and includes some patients who may not have end stage renal disease. The quarter is the one in which the bill was processed by Medicare, usually 1-3 months after the date of service but occasionally much longer. Charge data appearing on the bills is sometimes higher than allowed by Medicare. The allowed charges shown are estimated from the average dose and number of administrations. During 1989-90, Medicare paid $40 per administration with a $30 supplement for doses of more than 10,000 units. Medicare allowed $11 per 1,000 units from January 1991 to December 1993 and $10 per 1,000 units beginning January 1994. Medicare pays 80 percent of the allowed charge (after the deductible has been met) and the beneficiary (or his/her secondary insurer) is responsible for the remainder.

SOURCE: Health Care Financing Administration; compilation by the authors.

Medicare billing data. Table 1 supports the following findings:

- The average dose began low and remained little changed until the first quarter of calendar year 1991. Since then it has grown rapidly, doubling from an average of 2,694 units during 1990 to 5,383 units 7 years later.
- The number of administrations has grown rapidly and continuously, reflecting the rapid adoption by patients and providers. The number of administrations shows surprisingly large quarter-to-quarter variation. This short-term variability is introduced by variations in the timing of the billing and bill-processing system, because data by date of service show much less short-term variation.
- The mean hematocrit of EPO recipients remained between 32.2 and 32.5 throughout 1997. A little more than two-thirds of the patients achieved a hematocrit of 31 or higher. During 1990 and 1991, only one-third of the patients achieved this level.
- EPO charges grew very rapidly during 1989-90 as existing patients began EPO therapy. Growth slackened during 1991-92, revived during 1993-95, and slowed again during 1996-97. Because charges are calculated from the number of administrations, there is significant quarterly variation.

Table 2 shows similar data for 1996 to early 1998 but differs in two major respects:

- The data are for patients submitting bills for in-center hemodialysis only.
- The data are aggregated by date of service as opposed to the date processed. Because the data reflect only bills processed during or before May 1998, the count of administrations and charges for the first quarter of 1998, and to a lesser extent the fourth quarter of 1997, is incomplete.

This table is included because hemodialysis patients receive the overwhelming bulk of EPO administrations and because much is known about this group. Because hemodialysis patients generally receive EPO three times per week at each dialysis session, they account for nearly all administrations. They do not account for as high a proportion of charges, in part because the mean dose for home dialysis patients is higher to compensate for their less-frequent injections.

The data in Table 2 support the following findings:

- Differences between Table 1 and Table 2 suggest that home dialysis patients have a higher mean dose per administration but fewer administrations than do in-center hemodialysis patients. This is supported by disaggregated data not shown.
- Differences between Table 1 and Table 2 suggest that the mean hematocrit for home dialysis patients is lower than for center hemodialysis patients. This is supported by disaggregated data not shown.
- Total allowed charges for hemodialysis patients during 1997 were $842.2 million. The average allowed charge per patient was $6,245 per year. This amount is much less than the average cost of EPO for a full year because not all patients were alive, treated by in-center hemodialysis, and receiving EPO for all of 1997.
- Medicare pays approximately 80 percent of allowed charges, leaving the average patient responsible for coinsurance charges of $1,249 per year (assuming the yearly deductible has been met) for EPO alone.
- A hypothetical in-center hemodialysis patient who received the mean dose per administration (5,278 units) three times per week for all of 1997 would have allowed charges of $8,233. This estimate is above what the “average” in-center hemodialysis patient would bill Medicare because even a patient who was treated by hemodialysis and receiv-

**Table 2**

**EPO Use and Cost for In-Center Hemodiaysis Patients: 1996-98**

| Year and Quarter of EPO Service | Mean Dose per Administration | Median Hematocrit | Mean Hematocrit | Number of Administrations in Thousands | Allowed Charges in Millions |
|---|---|---|---|---|---|
| **1996** | | | | | |
| First Quarter | 5,089 | 32.0 | 31.6 | 3,712 | $188.9 |
| Second Quarter | 5,212 | 32.3 | 31.9 | 3,879 | 202.2 |
| Third Quarter | 5,272 | 32.5 | 32.1 | 4,008 | 211.3 |
| Fourth Quarter | 5,359 | 32.7 | 32.3 | 4,110 | 220.2 |
| **1997** | | | | | |
| First Quarter | 5,363 | 32.9 | 32.5 | 4,001 | 214.6 |
| Second Quarter | 5,320 | 33.0 | 32.6 | 3,982 | 211.8 |
| Third Quarter | 5,197 | 33.0 | 32.5 | 3,982 | 207.0 |
| Fourth Quarter | 5,231 | 33.0 | 32.4 | 3,993 | 208.8 |
| **1998** | | | | | |
| First Quarter | 5,388 | 32.9 | 32.4 | 3,519 | 189.6 |

NOTES: EPO is human recombinant erythropoietin. Data are by date of service and include only in-center hemodialysis patients. Mean dose per administration is defined differently than Mean Dose in Table 1. Data are based on outpatient bills processed by May 1998. Data for first quarter of 1998 are preliminary. Allowed charges are calculated as $10 times mean dose per administration times number of administrations. HCFA pays the provider 80 percent of allowed charges after the deductible has been met.

SOURCE: Health Care Financing Administration; compilation by the authors.

ing EPO for a full calendar year would miss administrations as a result of hospital stays, missed dialysis sessions, dialysis twice a week, etc.

Figures 1 and 2 illustrate the trends in EPO dose and achieved mean hematocrit and in Medicare allowed charges presented in Table 1. Added to both charts are vertical lines marking major changes in Medicare EPO payment and coverage policies. It is likely that some of the trends visible in the charts are attributable to changes in provider behavior in response to the policy changes. This does not prove causality but, to the extent that patterns change after the implementation of payment changes, policy effects are likely to have had an impact.

## DISCUSSION

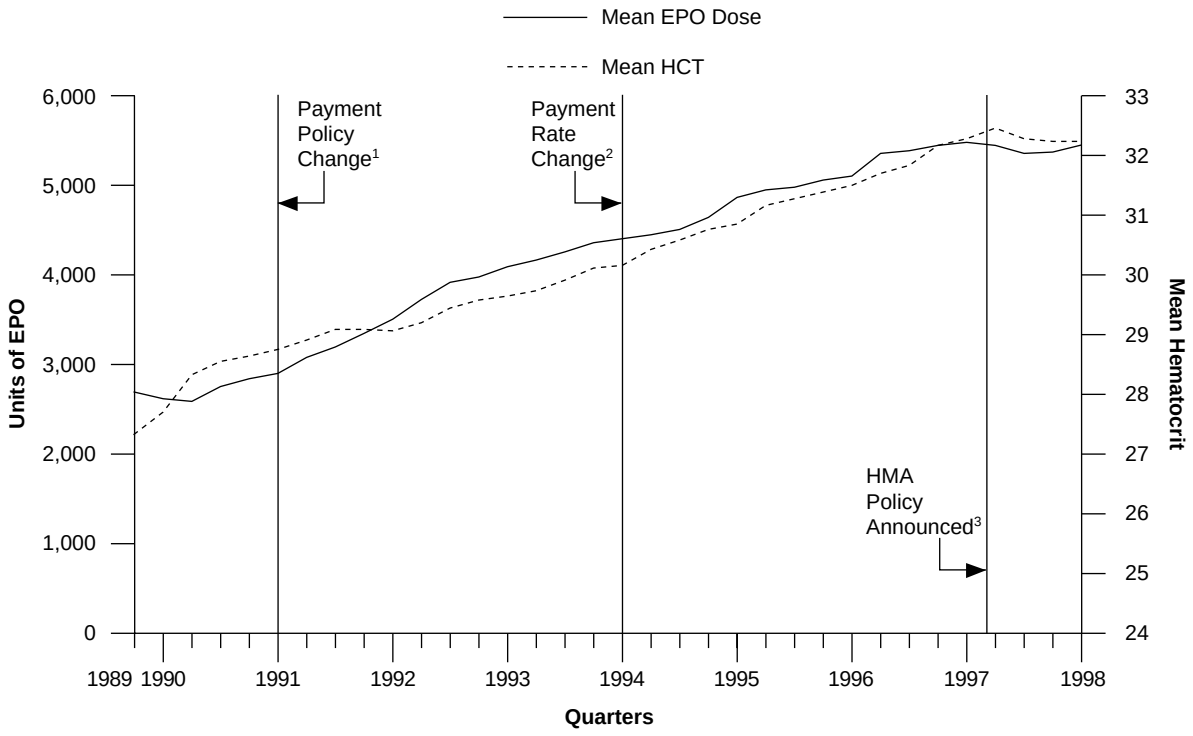
The initial Medicare reimbursement for EPO was $40 per injection with a $30 supplement for doses greater than 10,000 units. Given the high cost of the drug itself, this amount implied that facilities lost money on any patient who received more than about 3,500 units. (Very few patients received more than 10,000 units.) Although this loss could, on average, be offset by profits on patients needing less EPO, facilities could increase profits by using lower doses. Average doses were 2,600-2,700 during this period—low enough to ensure a profit. Because of the modest profit from EPO, facilities had an incentive to begin EPO therapy on many patients. Data on numbers of patients are not presented because no single, consistent data series covers the entire 9 years. However, the data do show rapid adoption of EPO technology by dialysis facilities.

As might be expected from the relatively low doses, the mean hematocrit rose slowly, except for an initial jump, as new EPO recipients reached their maintenance hematocrit level. From the second half of 1990 until the middle of 1992, there was little further rise in achieved hematocrit.

Effective January 1, 1991, providers began receiving $11 per 1,000 units. Under the new payment policy, larger doses produced higher profits, and it appears that providers responded accordingly. Patients began receiving larger doses in late 1990 and the rise continued until late 1997.

**Figure 1**

**Mean EPO Dosage and Mean Hematocrit, by Date Bill Was Processed: 1989-98**




[1] Change from $40 per administration to $11 per 1,000 units.

[2] Rate lowered to $10 per 1,000 units.

[3] The HMA policy was intended to deny payment for EPO administered to patients whose 3-month moving average hematocrit rose above 36.5.

NOTES: EPO is human recombinant erythropoietin. HMA is hematocrit management audit. HCT is hematocrit.

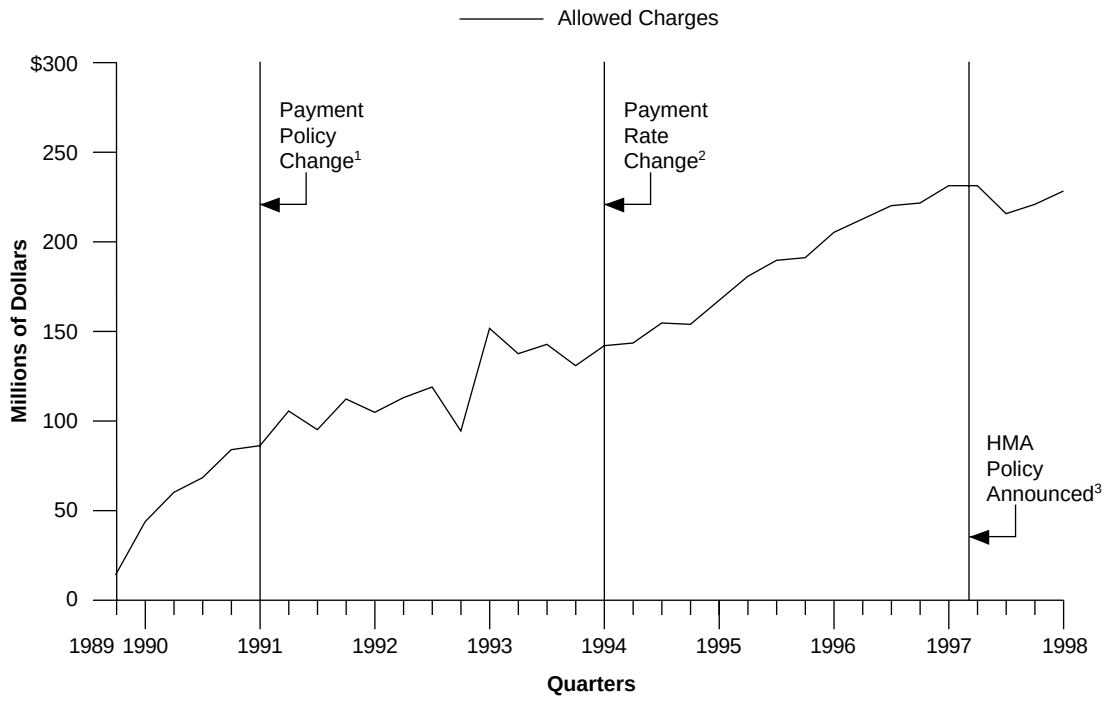
SOURCE: Health Care Financing Administration; compilation by the authors.

Had there been no increase in dosing, the policy change would have reduced Medicare payments for EPO. At the average dose of 2,700, the average allowed charge at $11 per 1,000 units would have been $29.70, much less than $40. In Figure 2 there is a temporary pause in the rise in expenditures, although it is not obvious because of the short-term variability. An examination of monthly data (not shown) indicates that providers increased the average dose so rapidly that the large drop in Medicare payments in January 1991 was gone by April. It is extremely difficult to predict how quickly or by how much consumers or businesses will respond to changes in price or payment policy. One solution is to ignore such changes, even though the direction of the change but not the magnitude is predictable. In this particular case, the synergism of good medical practice and good business practice combined in such a way that a policy that might have reduced expenditures ended up costing more.

The second payment policy change was a reduction in the allowed charge to $10 per 1,000 units effective January 1, 1994. There appears to have been little change in behavior this time; both dose and hematocrit appear to have continued to rise at about the same rate. However, the lower payment did arrest the rapid growth in expenditures to some extent. Total

**Figure 2**

**EPO Allowed Charges, by Date Bill Was Processed: 1989-98**




[1] Change from $40 per administration to $11 per 1,000 units.

[2] Rate lowered to $10 per 1,000 units.

[3] The HMA policy was intended to deny payment for EPO administered to patients whose 3-month moving average hematocrit rose above 36.5.

NOTES: EPO is human recombinant erythropoietin. HMA is hematocrit management audit. HCT is hematocrit.

SOURCE: Health Care Financing Administration; compilation by the authors.

allowed charges for 1994 ($590 million) were only 6 percent greater than in 1993 ($557 million). Without the payment reduction (and the same use patterns), total allowed charges in 1994 would have been $650 million, a 17-percent increase from 1993.

The most recent policy change marked on the graphs is the announcement in March 1997 (with implementation in October 1997) of the hematocrit management audit (HMA) policy, which would deny payment for EPO administered to patients whose 3-month moving average hematocrit rose above 36.5. It is still too soon to make reliable before-and-after comparisons. However, the preliminary data suggest that providers reacted strongly and immediately to the threat of having payments denied for a few patients but over time returned to earlier practice, perhaps because they realized that the policy mostly affected only the minority of patients who could regularly achieve hematocrits at or above 34 or 35. Early in 1998, too recently for any impact to show in the data presented, the HMA policy was suspended. The graphs suggest provider behavior changes coincident with the announcement of the HMA policy, but more recent data are needed to see what, if any, longer term impact follows. It seems clear from the charts that two of the three payment policy changes—including the one intended to have a direct

impact only on a small number of patients—were followed by changes in the way doctors prescribe and facilities administer a medical therapy.

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