

Recombinant Human Erythropoietin Usage in a Large Academic Medical Center

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Objective: Recombinant human erythropoietin (rhEPO) is a highly effective but expensive drug used for the treatment of certain anemias. We considered opportunities to curtail inpatient rhEPO utilization in light of therapeutic alternatives, the drug's delayed onset of action, and the available literature.

Study Design: A retrospective review of rhEPO administration in a large academic medical center between February and June 2000 was conducted by using administrative databases.

Methods: The computerized inpatient pharmacy transaction file of the Hospital of the University of Pennsylvania was queried to determine trends for rhEPO administration. We then employed CaduCIS (CareScience, Philadelphia, PA) to determine the clinical diagnoses and resources used for each inpatient receiving rhEPO.

Results: In the study period, 248 inpatients received at least 1 rhEPO dose. More than 100 different physicians, representing 20 departments and divisions, ordered approximately 17 million units of rhEPO. Hematology/Oncology accounted for 33% of all units ordered, and Surgery and General Medicine ordered 16% and 14%, respectively. The usual length of stay for patients receiving rhEPO varied considerably: 34% of patients remained in hospital for ≤ 7 days, while 31% remained ≥ 3 weeks. As many as 34% of patients began rhEPO therapy as inpatients. Of inpatients receiving rhEPO, only 49% met labeled indications for rhEPO administration.

Conclusions: At our institution, approximately one half of all inpatient rhEPO usage is for an off-label indication. Utilization patterns may suggest strategies for conserving this scarce resource.

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ment of anemia due to cancer chemotherapy,⁴⁻⁷ zidovudine-treated HIV infection,^{8,9} and elective orthopedic surgery.¹⁰⁻¹² For each of these indications (Table 1), rhEPO raises the hemoglobin concentration, reduces transfusion requirements, and in some cases improves self-reported quality of life.³⁻¹⁴ The utility of rhEPO administration also has been studied in patients with anemia due to other causes such as critical illness¹⁵⁻¹⁷ or bone marrow transplantation.¹⁸⁻²² However, current data do not support widespread use for these indications.

Today's competitive healthcare marketplace demands that expensive therapies such as rhEPO be used carefully and appropriately. Improper rhEPO administration techniques (used to reduce costs) have been linked to iatrogenic, nosocomial infections.^{23,24} Because benefits from rhEPO generally require prolonged therapy, initiation of therapy in the inpatient setting may have a limited role, especially for patients with short hospital stays. Using an administrative database, we examined inpatient use of rhEPO at our large academic medical center in the context of the available medical literature. The results suggest many opportunities for appropriately reducing inpatient rhEPO use.

METHODS

We analyzed the inpatient pharmacy transaction file of the Hospital of the University of Pennsylvania, a database generated by a computerized order entry

Erythropoietin is an endogenous glycoprotein regulating the proliferation, maturation, and differentiation of red blood cells.¹ In 1989, Amgen (Thousand Oaks, CA) began marketing recombinant human erythropoietin (rhEPO), a bio-engineered version of erythropoietin.² In the last decade, rhEPO has transformed the way physicians treat anemia, especially in patients with chronic renal failure.³ rhEPO also has received Food and Drug Administration (FDA) approval for the treat-

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system. The data reflect all rhEPO orders dispensed for patients discharged between February 1 and June 30, 2000. Fields analyzed included patient diagnosis, length of stay, department/division of the attending physician, rhEPO dose, and frequency of rhEPO administration.

We then used the CaduCIS database (CareScience, Philadelphia, PA) to determine the diagnoses and resources attributed to each individual patient who received rhEPO during the study period. CaduCIS incorporates all diagnosis codes and hospital resources from both claims data and the medical records of each unique patient. Using the CaduCIS database, we manually screened for all of the *International Classification of Diseases, 9th Revision* (ICD-9) diagnosis and procedure codes that could reflect a labeled indication, on a case-by-case basis. A patient with at least 1 of these codes was considered to have received rhEPO for a labeled indication. Patients with more than 1 labeled indication were counted only once and assigned to a single category along the following descending preference order: hemodialysis/renal failure > neoplasm, nonhematologic > HIV infection > orthopedic surgery. Patients lacking a code for a labeled indication were analyzed on a case-by-case basis in the context of all of their available administrative data. Using their clinical judgment, 2 authors (JHB, SM) assigned each patient to a single most likely indication.

RESULTS

Between February 1, 2000, and June 30, 2000, at least 1 rhEPO dose was dispensed for 248 different patients. Representing more than 20 departments and divisions, 120 physicians entered rhEPO orders for patients situated in 16 different hospital units. In total, roughly 17 million units of rhEPO were used during this period, accounting for a direct drug cost of \$172,390, or approximately \$34,000 per month.

Surgical specialists treated the most patients (21%) with rhEPO (Figure 1). Usage was spread primarily across transplant, cardiothoracic, vascular, orthopedic, and otorhinolaryngologic surgery. Medical oncologists frequently used rhEPO (17%) for patients with solid tumors receiving chemotherapy and for patients undergoing bone marrow transplantation. Use in the Obstetrics/Gynecology Department (13%) occurred both on the gynecologic oncology and neonatal floors. The Renal Division accounted for only 8% of

orders, though many patients on General Medicine or other services likely received rhEPO for a renal indication.

When data were analyzed according to the total number of units prescribed, the Hematology/Oncology Division accounted for the most rhEPO utilization (Figure 1). This ranking may be attributed to comparatively higher dosing regimens, typically 40,000 to 60,000 units per week. In contrast, neonatal rhEPO utilization was relatively insignificant when measured in prescribed units. Analysis of the route of administration revealed that 3% of orders were intramuscular, 44% were intravenous, and 53% were subcutaneous.

The distribution of the 248 patients receiving rhEPO according to length of stay is displayed in Figure 2. Forty patients (16%) were in hospital for 3 or fewer days. Seventy-seven patients (31%) were inpatients for 22 days or more. Eighty-four (34%) patients received their first rhEPO dose more than 7 days after admission, suggesting inpatient initiation of rhEPO therapy.

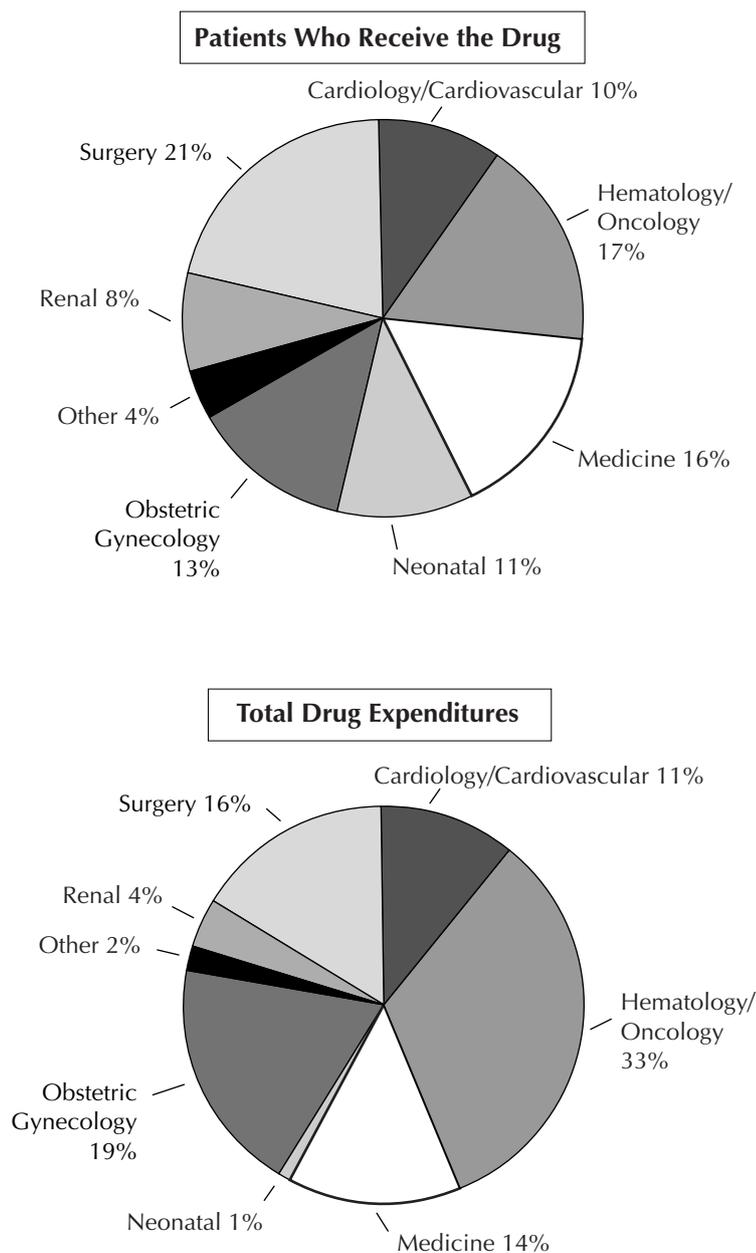
Patients receiving rhEPO had a variety of clinical diagnoses and resource utilization patterns. In total,

Table 1. Food and Drug Administration-Approved Indications for Recombinant Human Erythropoietin

Indication	Outcome
Chronic renal failure	Reduces need for red blood cell transfusion ^{1,3} and improves functional status for patients with end-stage renal disease both on dialysis ¹³ and not yet on dialysis ¹⁴
Chemotherapy-treated nonmyeloid malignancy	Reduces need for maintenance transfusion and increases hemoglobin levels for patients with nonmyeloid malignancies receiving chemotherapy ⁴⁻⁶ ; improves self-reported quality of life ⁷
Zidovudine-treated HIV infection	Raises mean hematocrit and decreases mean transfusion requirements in patients with low endogenous erythropoietin levels (≤ 500 IU/L) when dose of zidovudine is ≤ 4200 mg/week ^{8,9}
Elective orthopedic surgery	Preoperative dosing increases hemoglobin/hematocrit concentration and reduces the need for red blood cell transfusion ¹⁰⁻¹²

DRUG UTILIZATION

Figure 1. Use of Recombinant Human Erythropoietin by Department/Division According to the Percentage of Patients Receiving the Drug (top) and the Percentage of Total Drug Expenditures (bottom)



49% of patients received rhEPO for a labeled indication. Accounting for 31% of all patients receiving rhEPO, hemodialysis/renal indications were the most common in our study population. Sixteen percent of all rhEPO patients had a known history of a non-hematologic malignancy and/or were receiving

chemotherapy. A significant number of patients received rhEPO for off-label indications such as bone marrow transplantation and hematologic malignancy (13%), neo-natal care (10%), and while undergoing a neurosurgical procedure (8.2%).

DISCUSSION

Opportunities for Improvement

At our institution, rhEPO use is widespread among many hospital departments and divisions. However, oncologic indications account for more than half of all utilization, with medical oncologists prescribing 33% of all units and obstetrics/gynecology physicians accounting for 19%. Medicine, cardiology/cardiovascular, and surgery physicians also frequently prescribed rhEPO, presumably reflecting renal, transplant, and critical care indications, respectively. Given the administrative nature of our data, it is not possible to comment on whether such dosing was appropriate in a clinical context. However, our results emphasize that administrators, pharmacists, and physician leadership can target educational efforts to encourage evidence-based prescribing behavior.

Other data from this study could have an immediate impact on reducing rhEPO usage. First, 44% of patients received rhEPO intravenously. Yet the literature indicates that total weekly maintenance doses can be reduced by 23% to 52% with subcutaneous injection.²⁵⁻²⁷ Encouraging change in the preferred route of administration could result in significant cost savings. However, such a policy could be limited by doctor and patient preferences for intravenous administration, especially in the setting of hemodialysis. Second, as many as 34% of patients began rhEPO therapy as hospital inpatients. This number is remarkable, given that the onset of rhEPO action is slow

and that pretreatment iron testing, response monitoring, and dose adjustment require highly coordinated care.^{25,28} Brief delays in initiating rhEPO therapy are likely to have negligible clinical impact and could even be offset by the improved continuity of care possible in the outpatient setting.

Remembering the Literature

With the exception of elective surgery, currently approved indications for rhEPO reflect chronic, ambulatory disease states. For some patients with these conditions, anemia further impairs their functional capacity and quality of life. Once physicians have excluded other potential etiologies of chronic anemia (eg, nutritional deficiency, infection, blood loss, hemoglobinopathy, hemolysis), rhEPO may be a good therapeutic choice, because frequent red blood cell transfusions are only transiently effective and carry the risks of transfusion reaction and infection.²⁸ However, experience from patients with chronic renal failure suggests that 2-6 weeks are required for rhEPO to produce a clinically significant increase in hemoglobin concentration.^{1,3} Thus, red blood cell transfusion for symptomatic anemia remains necessary in acute settings²⁸ and, in turn, for the majority of inpatient indications.

Table 2 highlights selected off-label indications for rhEPO proposed in the literature.¹⁵⁻²² Available data are either inconclusive or insufficient to support the widespread use of rhEPO for these indications. Yet clearly, many clinicians use the drug for off-label indications (**Table 3**), drawing on a particular subset of the medical literature or perhaps reasoning that rhEPO is well tolerated, preferable to treatment alternatives, and possibly helpful. Our study is not intended to encourage or dissuade physicians from prescribing rhEPO in any given clinical situation. Rather, it is meant to serve as a common reference point for health systems seeking to promote evidence-based prescribing behaviors.

Limitations to Curtailing Inpatient rhEPO Use

At our institution, approximately one half of all inpatient rhEPO administration is clinically appropriate, based on FDA-approved indications. Certainly, patients maintained on rhEPO as outpa-

Figure 2. Usual Length of Stay for Patients Receiving Recombinant Human Erythropoietin

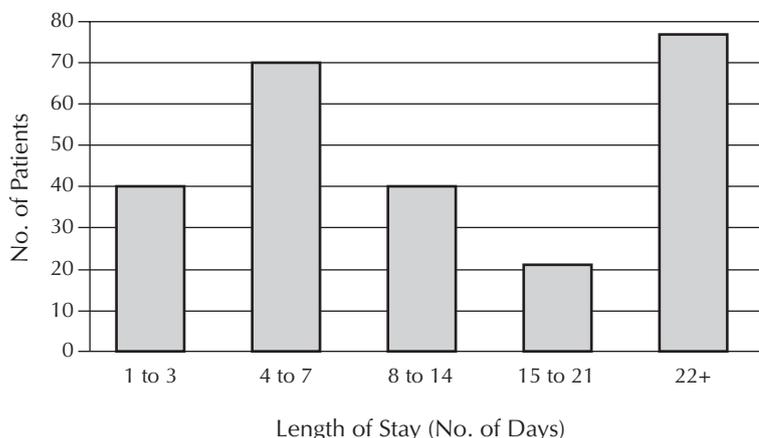


Table 2. Off-label Uses of Recombinant Human Erythropoietin: Understanding Diverse Practice Patterns for Selected Indications

Indication	Factors Favoring Use	Reasons to Pause
Anemia of critical illness	Fewer RBC units transfused in ICU patients who received rhEPO ¹⁵ ; endogenous erythropoietin levels in ICU patients appear inappropriately low ¹⁶ ; studies ongoing	Reference 15 has broad exclusion criteria and is underpowered; in the setting of liberal RBC transfusion, higher target hematocrit is not associated with mortality benefit ²⁶
BMT	For allogenic BMT, rhEPO increases hemoglobin concentration and reduces RBC transfusion requirements ¹⁷⁻²⁰	For autologous BMT, no improvements were seen ^{20,21} ; usage in allogenic BMT varies by institution
Anemia of prematurity	Treated infants had increased hemoglobin concentration and reduced RBC transfusion requirements ²⁷⁻²⁹	Risks have not been well defined; subpopulation most likely to benefit is unclear; anemia usually resolves spontaneously with time ³⁰⁻³²

BMT = bone marrow transplantation; ICU = intensive care unit; RBC = red blood cell; rhEPO = recombinant human erythropoietin.

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Table 3. Prescribing Indications, by Diagnosis and Care Setting, for All Inpatients Receiving Recombinant Human Erythropoietin

Diagnosis/Setting	Percentage of Patients
Labeled indications	
Hemodialysis/renal failure	31
Neoplasm, nonmyeloid	16
HIV infection	2
Orthopedic surgery	<1
Total	50
Selected off-label indications	
Hematologic malignancies/bone marrow transplantation	13
Neonatal	10
Neurosurgery	8
Critical illness	6
Cardiothoracic and vascular surgery	6
Other/unknown	7
Total	50

tients, regardless of the indication, should continue to receive rhEPO on hospital admission. Hospitals should respect the long-standing treatment decisions made by outpatient physicians so long as the decisions are safe and reasonable. There may even be a physiologic justification for continuing rhEPO therapy in hospital, as early data suggest that acute withdrawal of rhEPO may exacerbate anemia through a process known as neocytolysis.³³⁻³⁵

Physicians with long-standing practice habits may be reluctant to change their behavior. Many nephrologists, for example, have been using rhEPO for more than a decade and may not be interested in changing their preferred route of administration or delaying the initiation of rhEPO a few days until after hospital discharge. Alternatively, the drive to conserve scarce resources, particularly in the inpatient pharmacy setting, may bring new energy to evidence-based prescribing recommendations.

Many off-label indications highlighted in Table 2 may be clinically appropriate, given the associated potential (albeit unproven) benefits to an individual patient. For example, rhEPO therapy after bone marrow transplantation for a hematologic malignancy may represent a significant advance in the care of

these patients. The clinical literature surrounding rhEPO use for many of these indications continues to evolve. Moreover, local physician behavior may render rhEPO use for a particular off-label indication as the de facto standard of care.

Figure 2 suggests there may be an opportunity to reduce inpatient rhEPO utilization by delaying the initiation of therapy. Yet any programmatic initiative to reduce inpatient rhEPO utilization should incorporate the option to begin rhEPO therapy in newly diagnosed inpatients with chronic renal failure, chemotherapy-treated malignancy, or HIV. Delaying the initiation of rhEPO until after hospital discharge is less appealing when the inpatient stay is long and the anemia particularly symptomatic.

CONCLUSION

Our report is only a first step in ensuring efficient, appropriate rhEPO usage in the inpatient setting. It supports continuing prescriber education, linked to an order review/approval strategy with a department of pharmacy. More work is needed to explore whether patients on chronic rhEPO therapy continue to respond clinically during acute illness. Moreover, the pharmacodynamic effects of a brief delay (eg, 3 to 5 days) in therapy remain unclear. New data must be scrutinized carefully to ensure that reported outcomes are relevant to treated populations. Although rhEPO can improve quality of life and reduce transfusion requirements in certain chronically ill, outpatient populations,³⁻¹⁴ other outcomes such as mortality benefit or hospital length of stay may be more relevant in the inpatient setting. Finally, the risks, benefits, and costs of treatment alternatives such as watchful waiting, volume replacement, and red blood cell transfusion must be considered for all rhEPO candidates.²⁸

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