Renal disease

Edited by **Dr C G Winearls** DPhil, FRCP, *Churchill Hospital, Oxford*

We acknowledge with thanks an educational grant from Janssen-Cilag Ltd.

The clinical impact of recombinant human erythropoietin

N Muirhead, MD, FRCCP, MRCP(UK), *Professor of Medicine, University of Western Ontario, London, Ontario, Canada*

In the past decade, the single most important advance in the clinical care of patients with end-stage renal disease (ESRD) has been the introduction of recombinant human erythropoietin (rHuEPO) as a treatment for renal anaemia. It is appropriate, therefore, to review the clinical impact that rHuEPO has had on the management of renal anaemia, with particular reference to the quality of the evidence for its beneficial effects, and to consider its potential impact in other conditions.

Pathogenesis of renal anaemia

Anaemia is an almost invariable consequence of chronic renal failure (CRF). In broad terms, the severity of the anaemia roughly parallels the decline in renal function. Many factors have been implicated in the pathogenesis of renal anaemia in patients with ESRD (Table 1), including iatrogenic blood loss, occult gastrointestinal bleeding, and blood loss through the extracorporeal circuit in haemodialysis patients. Rarer causes include haemolysis (eg in patients with sickle-cell disease) and the microcytic anaemia accompanying aluminium intoxication. However, the deficiency of renal EPO production is by far the most important cause.

The onset of anaemia from causes other than renal failure is usually accompanied by an increase in serum EPO levels. In CRF, serum EPO levels remain within or slightly below the normal range even with severe anaemia, reflecting a relative lack of EPO production in response to anaemia.

Clinical efficacy of recombinant human erythropoietin in renal anaemia

Experiments with sheep EPO in the 1970s confirmed that renal anaemia was likely to respond to treatment with EPO – all that was required was a reliable source of EPO. The discovery and cloning of the human EPO gene in the early 1980s paved the way for the development of a recombinant DNA-derived human EPO product, rHuEPO, which was available for large-scale clinical trials by the mid-1980s. The first preparation, epoetin alfa (Eprex) was used in most of the major trials quoted in this article; epoetin beta (Recormon) is almost identical. Some authors do not state which preparation was used, so the generic term rHuEPO is employed in this review.

The two original descriptions of the clinical use of rHuEPO in patients with ESRD appeared within a month of each other, from London/Oxford[1] in December 1985, and from Seattle[2] in January 1986. These two papers were aimed largely at providing information on dose and efficacy. Eschbach *et al*[2] were able to show a dose-response curve for rHuEPO given intravenously (IV) at doses of 10–500 units/kg three times weekly, the haemoglobin (Hb) response being limited only by the availability of iron for new red cell synthesis.

Several large prospective trials of rHuEPO therapy in haemodialysis patients followed, all of which confirmed that rHuEPO produced a predictable increase in Hb in more than 90% of patients treated, provided that adequate iron was administered[3–5]. Side effects, mainly the development or worsening of hypertension,

Table 1. Causes of anaemia in end-stage renal disease.

- Lack of erythropoietin
- Blood loss:
  - iatrogenic (ie blood sampling)
  - gastrointestinal bleeding
  - losses via the extracorporeal circuit
  - menstrual losses
- Haemolysis
- Aluminium intoxication
- Deficiency of iron/other haematinics
- Hyperparathyroidism

haemodialysis access failure and seizures were reported; some authors thought that these were important potential barriers to the generalised use of rHuEPO (Table 2). There has been only one large-scale, placebo-controlled trial of rHuEPO therapy for anaemia in haemodialysis patients[5]. This confirmed its efficacy and suggested that, while hypertension and access failure were real complications of rHuEPO therapy, there was no increased rate of seizures compared to placebo-treated patients. Data from the Canadian haemodialysis morbidity study[9], which examined the rate of access failure, hypertension, seizures, infections and other outcomes in a cohort of over 1,300 Canadian haemodialysis patients, again suggested that the annual rate of seizures was no different for rHuEPO-treated patients and untreated patients.

Longer-term studies, and also studies in other ESRD populations, have confirmed that hypertension will develop or worsen in about one-third of patients during rHuEPO therapy, but the severity can be limited by starting with a lower rHuEPO dose (50 units/kg three times weekly) and/or allowing Hb to rise relatively slowly[10]. An increased rate of haemodialysis access failure seems to be confined to patients with implanted arteriovenous grafts as opposed to native arteriovenous fistulae[10–12].

Randomised controlled trials of rHuEPO therapy in other ESRD populations, notably patients on chronic peritoneal dialysis[12] and those not yet on dialysis, confirmed the efficacy of rHuEPO in improving anaemia for all types of ESRD patients[6,8]. Dose requirements, clinical response rates and adverse event rates are similar to those for haemodialysis patients. The results are similar for the few small studies of rHuEPO in patients with anaemia related to a failing renal transplant.

Effect on renal function

Studies on patients who are not dialysis dependent have shown no change in the rate of decline of their renal function after starting rHuEPO therapy, as judged by serial reciprocal creatinine readings[7]. In the one large controlled trial of rHuEPO in which glomerular filtration rate was measured by ^{125}I-iothalamate over a year[14], renal function declined slightly (but not significantly) faster in the control group than in the treated group and the number requiring dialysis was virtually identical (Fig 1). On current evidence, rHuEPO is safe in patients with native kidney function, provided that blood pressure is carefully monitored. A study in Paris suggested that 35–42% of patients with CRF would benefit from rHuEPO therapy for an average of seven months before starting dialysis[13].

Table 2. Incidence of commonly reported side effects in clinical trials of recombinant human erythropoietin.

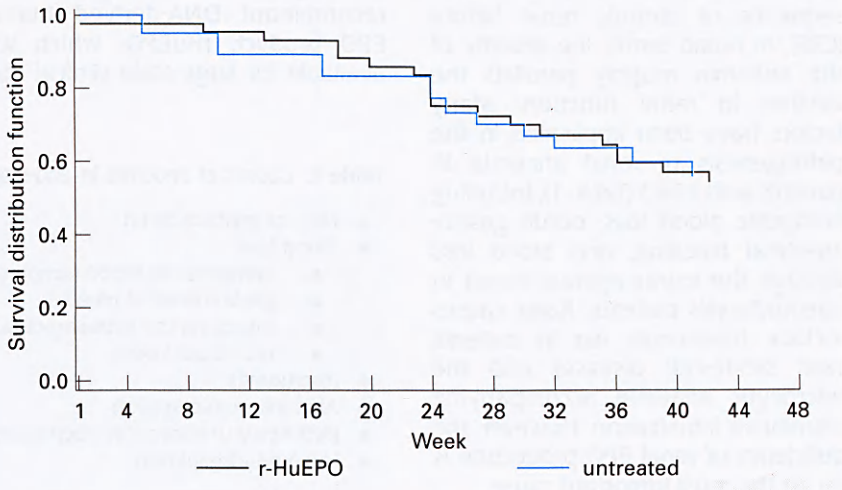
Author	Patients studied	Hypertension (%)	Access failure (%)	Seizure (%)
Sundal[3]	Haemodialysis	32	14.7	2.7
Eschbach[4]	Haemodialysis	35	11.7	5.4
CESG[5]	Haemodialysis	34	14.1	1.0
Nissenson[6]	Peritoneal dialysis	55	–	0
Nissenson[7]	Pre-dialysis	23	–	0
Austrian multicentre[8]	Pre-dialysis	0*	–	0

* Note made of a few patients who required adjustment of antihypertensives.
CESG = Canadian Erythropoietin Study Group.

Effect on quality of life and target haemoglobin level

In parallel with the improvement in anaemia seen during clinical trials of rHuEPO therapy, a number of studies have reported clinically important improvements in general and disease-specific quality of life as well as in maximal and submaximal exercise capacity[5,15–18]. These important functional correlates of anaemia

Figure 1. 'Renal survival' curves (start of dialysis indicates 'renal death') for patients receiving recombinant human erythropoietin (rHuEPO) vs controls, showing no significant difference. *Reproduced from Ref 14, with permission of the publisher WB Saunders Company.*



correction in rHuEPO-treated ESRD patients have led to general acceptance of rHuEPO as the preferable approach to anaemia management for most patients with ESRD. The UK guidelines on the treatment of adult patients with renal failure[19] state:

> The anaemia of CRF should be corrected by the administration of erythropoietin. The haemoglobin concentration has a major effect on the quality of life, exercise capacity and sexual function.

The guidelines set a minimum standard of an Hb concentration of 10–12 g/dl in at least 80% of the dialysis population. However, the ideal Hb or haematocrit (Hct) level has not been firmly established. The benefits in terms of quality of life (Figs 2a and b) and exercise capacity increase up to a Hct of over 35%, but the mean level achieved in renal units is well below that[18]. This is largely due to cost: even in the US, where the costs of EPO are picked up by Medicare/Medicaid, the mean Hct of the more than 80% of US ESRD patients treated with rHuEPO remains around 32%, well below both the target level of the key clinical trials and the level at which maximum clinical benefits could be expected.

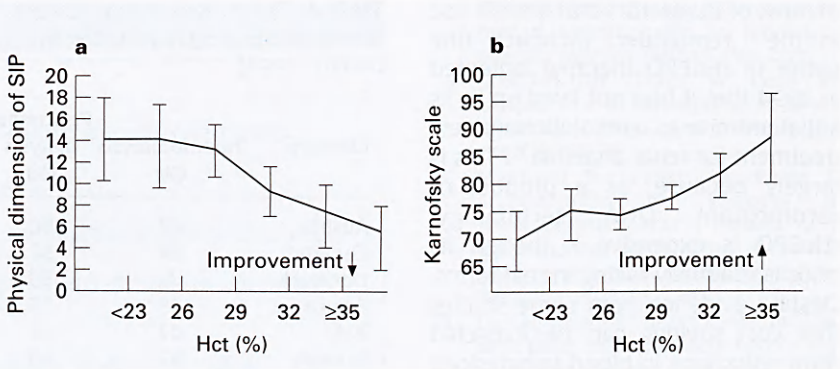


Figure 2(a). Sickness Impact Profile (SIP) versus haematocrit (Hct) in 86 patients on regular haemodialysis, 57 of them receiving recombinant human erythropoietin. *(Redrawn, with permission, of Oxford University Press, from Ref 18).* **(b)** Karnofsky Scale score in the same population as in (a). *Redrawn, with permission of Oxford University Press, from Ref 18.*

Inadequate response to recombinant human erythropoietin

Although only about 10% of patients in research studies fail to respond adequately to rHuEPO, a substantially larger proportion either do not reach target Hb or require excessive doses when the treatment is applied universally in clinical practice[20]. The causes, listed in Table 3[21], include the following:

- *Inadequate iron supplementation*, probably the commonest cause. Oral iron, with vitamin C to aid absorption, is often sufficient. If, however, an adequate serum ferritin is not maintained (due to poor compliance or absorption), parenteral iron therapy is required; this may result in a reduced requirement for rHuEPO[22]. It should be given initially in small doses (eg 10–40 mg iron saccharate) adjusted to the transferrin level to avoid oversaturation of transferrin[23].
- *Subclinical aluminium intoxication* can be sufficient to block the action of rHuEPO[24], and may require a course of desferrioxamine[25].
- *Infections* are another common cause (eg chronic sinusitis, dental abscesses, infected cysts), and may be revealed only by a careful search.
- *Parathyroidectomy* in CRF is often followed by a modest rise in Hb, and one study has shown an early rise in spontaneous EPO production[26], but the effectiveness of medical or surgical suppression of hyperparathyroidism in correcting unresponsiveness to exogenous rHuEPO is uncertain[21].
- Correction of *inadequate dialysis* (increase in urea reduction ratio from 61% to 72%) raised mean Hct from 26% to 32% on steady rHuEPO dosage in a controlled trial[20].
- *Malnutrition*, as judged by serum albumin, is a contributory factor[20].

Table 3. Causes of impaired response to recombinant human erythropoietin in chronic renal failure.

- Other causes of anaemia (Table 1)
- Infections
- Other inflammatory states
- Surgery
- Neoplastic diseases
- Malnutrition
- Under-dialysis
- Interaction with other drugs
- Inappropriate route of administration

In a few patients, none of these causes can be found. Interaction with other drugs has been suggested by the effect of withdrawal in a few case reports[27], but larger studies with angiotensin-converting enzyme inhibitors (which suppress spontaneous EPO production) have not shown an effect when rHuEPO is administered[21].

The route of administration affects the dose rather than the eventual Hb, but it is an important economic consideration. In most studies, the subcutaneous route achieves target Hb at a lower dose than IV administration – a dose reduction of 30–50%, at the cost of some pain at the injection site in about a third of the patients[28–30].

Audit of use

Despite the effectiveness of rHuEPO in most patients, and the reversibility

of most of the factors that limit its use in the remainder, Eschbach (the father of rHuEPO therapy) lamented in 1994 that it had not lived up to its initial promise as a revolutionary new treatment for renal anaemia[31]. This is largely because, as a product of recombinant DNA technology, rHuEPO is expensive – though its price is gradually falling in real terms. Despite evidence from some studies that cost savings can be expected from reductions in blood transfusions and hospitalisations, and that such cost savings may, for some populations, offset the costs of rHuEPO, this therapy is not widely available to all who need it (Table 4). Economics, rather than clinical considerations, are of paramount importance in many countries in determining who gets rHuEPO for renal anaemia.

For example, in Canada there are wide regional variations in rHuEPO utilisation that reflect provincial differences in reimbursement strategies[32]. In Ontario, where the government reimburses rHuEPO costs for all patients who meet certain clinical criteria, utilisation approaches US levels. In other provinces with less liberal reimbursement policies, utilisation lags behind because payment must come from patients or third-party payers (usually private health insurers).

In the US the situation is exacerbated by reimbursement practices. Medicare/Medicaid dictate the maximum acceptable Hct for US patients by linking Hct to reimbursement. US physicians could effect a substantial improvement in mean Hct for their patients by switching from the IV to the subcutaneous route, but at present over 80% of US haemodialysis patients receive their rHuEPO IV[33]. The present reimbursement system, with payment linked tightly to Hct, does not encourage the switch to a more cost-effective dosing schedule. Indeed, since many private dialysis providers make a profit on each vial of rHuEPO used and paid for by Medicare/Medicaid, the IV route is more remunerative.

Despite these shortcomings, there is no question that the availability of rHuEPO has had a significant impact on the life of many patients with ESRD. Patients no longer need to suffer the symptoms of severe anaemia and are permitted an improved level of exercise capacity and quality of life on dialysis, while perhaps benefiting in less obvious ways such as having less left ventricular hypertrophy and thus less cardiac risk. Although some of the benefits of rHuEPO in ESRD patients remain speculative, most ESRD patients achieve net benefit from rHuEPO therapy, despite its high cost.

Table 4. Comparison of recombinant human erythropoietin utilisation by country (1993).

Country	Haemodialysis (%)	Peritoneal dialysis (%)
Austria	77	60
Canada*	64	57
Denmark	72	55
France	45	25
Italy	47	33
Norway	93	40
Spain	57	39
Switzerland	74	55
United Kingdom	53	34
USA**	88	52

* Canadian figures from 1995.
** US figures from 1992.

Use of recombinant human erythropoietin in human immunodeficiency virus infection

A number of studies have detailed the beneficial effects of rHuEPO in correcting the anaemia associated with azidothymidine (AZT) therapy in patients with HIV infection or AIDS[34,35]. This has become an approved use for rHuEPO in most countries. Dose requirements are approximately double those in ESRD patients, and the drug is not recommended in patients with high endogenous EPO levels (>300 nmol/l). As the use of AZT has declined with the introduction of newer antiretroviral agents, so the need for rHuEPO in HIV/AIDS patients has somewhat declined.

Peri-surgical use of recombinant human erythropoietin

The use of rHuEPO as an adjunct to blood transfusion in patients undergoing elective cardiac or orthopaedic surgery has been the subject of a number of clinical trials. These studies have indicated that pre-operative rHuEPO therapy can both increase the number of units of blood that can be obtained through autologous blood donation and enhance pre-operative Hb levels, thus reducing dependence on transfusion of banked blood[36,37]. In some countries, rHuEPO is now approved for the routine preparation of patients coming for elective surgery, either as part of an autologous blood donation programme or as a means of avoiding or reducing blood transfusion.

While the use of rHuEPO is not applicable in all types of surgery, it has been estimated that it might be appropriate for as much as 30% of elective surgery, particularly cardiac and orthopaedic surgery where there are predictable blood losses and substantial blood transfusion requirements[38]. The cost-effectiveness of this therapy is highly dependent on avoiding the costs associated with blood transfusion, including those of transfusion-related illnesses such as viral infections. However, given public concern regarding the safety of the public blood supplies in some countries[39], it is likely that public pressure will force the use of pre-operative rHuEPO even if the cost-effectiveness is marginal. In jurisdictions where costs are picked up by private health insurance, such usage has already increased markedly.

Summary

The introduction of rHuEPO has certainly improved the general well-being of many patients with ESRD. Most nephrologists would agree that treatment with rHuEPO is an important aspect of the management of

Key Points

rHuEPO:

- Corrects renal anaemia in 90+% of patients in controlled trials
- Improves quality of life and exercise capacity
- Has not affected rate of decline of renal function in controlled trials
- Raises blood pressuure in a third of patients, less so if Hct is raised slowly
- May increase risk of occlusion of synthetic graft access sites
- Has non-renal indications including the anaemia of HIV infection and reducing postoperative transfusions

INADEQUATE RESPONSE (SUBOPTIMAL RISE IN Hct FOR DOSE):

- Is commoner when used universally than in controlled trials
- Calls for:
  - Review of iron supplements – change to parenteral iron if necessary
  - Search for occult infection, aluminium overload
  - Treatment of hyperparathyroidism
  - Correction of underdialysis or malnutrition
  - Change from IV to subcutaneous route

selected ESRD patients in the 1990s. Additional uses for rHuEPO are beginning to be defined, including perioperative use, treatment of AZT-associated anaemia, and in the anaemias associated with cancer chemotherapy or prematurity. The use of rHuEPO in preparation for elective surgery seems poised to be the most significant of these potential indications.

References

1 Winearls CG, Oliver DO, Pippard MJ, Reid C, *et al.* Effect of human erythropoietin derived from recombinant DNA on the anaemia of patients maintained by haemodialysis. *Lancet* 1986;**ii**:1175–7.

2 Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. *N Engl J Med* 1987;**316**:73–8.

3 Sundal E, Kaeser U. Correction of anaemia of chronic renal failure with recombinant human erythropoietin: safety and efficacy of one year's treatment in a European multicentre study of 150 haemodialysis patients. *Nephrol Dial Transplant* 1989;**4**:979–87.

4 Eschbach JW, Abdulhadi MH, Browne JK, Delano BG, *et al.* Recombinant human erythropoietin in anemic patients with end-stage renal disease: results of a phase III multicenter trial. *Ann Intern Med* 1989;**111**:992–1000.

5 Canadian Erythropoietin Study Group. Association between recombinant erythropoietin therapy and quality of life and exercise capacity of patients receiving haemodialysis. *Br Med J* 1990; **300**:573–8.

6 Nissenson AR, Korbet S, Faber M, Burkart J, *et al.* Multicenter trial of erythropoietin in patients on peritoneal dialysis. *J Am Soc Nephrol* 1995;**5**: 1517–29.

7 Nissenson AR. National cooperative rHu erythropoietin study in patients with chronic renal failure. A phase IV multicenter study. Report of National Cooperative rHu Erythropoietin Study Group. *Am J Kidney Dis* 1991;**18**:24–33.

8 Austrian multicentre study group of rHuEPO in predialysis patients. Effectiveness and safety of recombinant human erythropoietin in predialysis patients. *Nephron* 1992;**61**:399–403.

9 Churchill DN, Taylor W, Cook RJ, Laplante P, *et al.* Canadian hemodialysis morbidity study. *Am J Kidney Dis* 1992;**19**:214–34.

10 Muirhead N, Laupacis A, Wong C. Erythropoietin for anaemia in haemodialysis patients: results of a maintenance study (The Canadian Erythropoietin Study Group). *Nephrol Dial Transplant* 1992;**7**:811–6.

11 Dy GR, Bloom EJ, Ijelu GK, Merritts GW, *et al.* Effect of recombinant human erythropoietin on vascular access. *ASAIO Trans* 1991;**37**:M274–5.

12 Viron B, Chamma F, Jaar B, Michel C, Mignon F. Thrombosis of angioaccess in haemodialysed patients treated with human recombinant erythropoietin. *Nephrol Dial Transplant* 1997; **12**:368–9.

13 Jacobs C. Starting r-HuEPO in chronic renal failure: when, why and how? *Nephrol Dial Transplant* 1995:**10**(Suppl 2):43–7.

14 Roth D, Smith RD, Schulman G, Steinman TI. Effects of recombinant human erythropoietin on renal function in chronic renal failure predialysis patients. *Am J Kidney Dis* 1994;**24**: 777–84.

15 Evans RW, Rader B, Manninen DL. The quality of life of hemodialysis patients treated with recombinant human erythropoietin. *JAMA* 1990;**131**:55–60.

16 Mayer G, Thum J, Cada M, Stummvoll HK, Graf H. Working capacity is increased following recombinant human erythropoietin therapy. *Kidney Int* 1988;**34**:525–8.

17 Beusterien KM, Nissenson ART, Port FK, Kelly M, *et al.* The effects of recombinant human erythropoietin on functional health and well-being in chronic dialysis patients. *J Am Soc Nephrol* 1996;**7**: 763–73.

18 Walls J. Haemoglobin – is more better? *Nephrol Dial Transplant* 1995;**10**(Suppl 2):56–61.

19 The Renal Association. *Treatment of adult patients with renal failure: recommended standards and audit measures.* London: Royal College of Physicians of London, 1995.

20 Ifudu O, Feldman J, Friedman EA. The intensity of hemodialysis and the repsonse to erythropoietin in patients with end-stage renal disease. *N Engl J Med* 1996;**334**:420–5.

21 Drüeke T. R-HuEPO hyporesponsiveness – who and why? *Nephrol Dial Transplant* 1995;**10**(Suppl 2):62–8.

22 Fishbane S, Maesaka J. Reduction in recombinant human erythropoietin doses by the use of chronic intravenous iron supplementation. *Am J Kidney Dis* 1995;**26**:41–6.

23 Sunder-Plassman G, Hörl WH. Safety of injection of iron saccharate in

haemodialysis patients. *Nephrol Dial Transplant* 1996;**11**:1797–802.
24 Muirhead N, Hodsman AB, Hollomby DJ, Corby PE. The role of aluminium and parathyroid hormone in erythropoietin resistance in haemodialysis patients. *Nephrol Dial Transplant* 1991;**6**:342–5.
25 Altmann P. Aluminium toxicity in dialysis patients: no evidence for a threshold serum aluminium concentration. *Nephrol Dial Transplant* 1993; **8(Suppl 1)**:25–34.
26 Washio M, Iseki K, Oh Y, Nakamoto M, *et al.* Elevation of serum erythropoietin after subtotal parathyroidectomy in chronic haemodialysis patients. *Nephrol Dial Transplant* 1992;**7**:121–4.
27 Ikeda Y, Sakemi T, Ohtsuka Y, Kuwahra M, Fujisaki N. Drug-related low responsiveness to recombinant human erythropoietin therapy in three patients with end-stage renal disease. *Nephrol Dial Transplant* 1997;**12**:371–2.
28 Virot JS, Janin G, Guillaumie J, Michel P, *et al.* Must erythropoietin be injected by the subcutaneous route for every hemodialyzed patient? *Am J Kidney Dis* 1996;**28**:400–8.
29 Stevens ME, Summerfield GP, Hall AA, Beck CA, *et al.* Cost benefits of low dose subcutaneous erythropoietin in patients with anaemia of end-stage renal disease. *Br Med J* 1992;**304**:474–7.
30 Muirhead N, Churchill DN, Goldstein M, Nadler SP, *et al.* Comparison of subcutaneous and intravenous recombinant erythropoietin for anemia in hemodialysis patients with significant comorbid disease. *Am J Nephrol* 1992;**12**:303–10.
31 Eschbach JW. Recombinant human erythropoietin: the promise and the facts. *Kidney Int* 1994;**45** (Suppl 44):S70–6.
32 Canadian Organ Replacement Registry. *Annual report*. Ottawa, Ontario: Canadian Institute for Health Information, March 1996.
33 USRDS annual report. *Amer J Kidney Dis* 1994;**24**(Suppl 2)S57–75.
34 Henry DH, Beall GN, Benson CA, Carey J, *et al.* Recombinant human erythropoietin in the treatment of anemia associated with human immunodeficiency virus (HIV) infection and zidovudine therapy. Overview of four clinical trials. *Ann Intern Med* 1992;**117**:739–48.
35 Glaspy JA, Chap L. The clinical application of recombinant erythropoietin in the HIV-infected patient. *Hematol Oncol Clin North Am* 1994;**8**:945–59.
36 de Andrade JR, Jove M, Landon G, Frei D, *et al.* Baseline hemoglobin as a predictor of risk of transfusion and response to epoetin alfa in orthopedic surgery patients. *Am J Orth* 1996;**25**:533–42.
37 Price TH, Goodnough LT, Vogler WR, Sacher RA, *et al.* The effect of recombinant human erythropoietin on the efficacy of autologous blood donation in patients with low hematocrits: a multicenter, randomized, double-blind controlled trial. *Transfusion* 1996;**36**:29–36.
38 Goodnough LT. Clinical application of recombinant erythropoietin in the perioperative period. *Hematol Oncol Clin North Am* 1994;**8**:1011–20.
39 Krever Commission of Inquiry on the Blood System in Canada, Safety Hearings, 1994. Government of Canada, Ottawa, 1994.

Urinary tract infection in women

W R Cattell, MD, FRCP, FRCPE, *Consultant Physician and Nephrologist, Harley Street, London*

Urinary tract infection (UTI) is a major health problem, a cause both of considerable morbidity among women and of expense to the National Health Service. Most often an isolated event, it becomes recurrent in 10–20% of women and, in a small but significant number, life-threatening. All aspects of UTI have been recently reviewed[1], this brief synopsis is confined to its management in women.

Key Points

ISOLATED ATTACK OF CYSTITIS IN A WOMAN:

- Can be confirmed by a bacterial count of ≥100 organisms/ml if pyuria is present
- Can be treated without bacterial confirmation if dipstick test for pyuria is positive
- Does not require follow-up or imaging if cured symptomatically

RECURRENT CYSTITIS IN A WOMAN:

- Renal imaging: IVU is still the definitive test
- If the urinary tract is normal, should be treated with three-day courses of antibacterials
- Should be treated with an antibacterial which eliminates introital colonisation

CYSTITIS IN PREGNANCY:

- Trimethoprim and co-trimoxazole should be avoided in the first trimester
- Fluoroquinolones such as ciprofloxacin are contraindicated
- Nitrofurantoin and cephalosporins are suitable

IN ACUTE PYELONEPHRITIS:

- Initial treatment should be in hospital if vomiting
- The same drugs are used as in cystitis but for 10–14 days
- In the presence of vomiting, gentamicin is a reasonable first choice