Anaemia of Prematurity
Epidemiology, Management and Costs

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Summary

Recombinant human erythropoietin (rHuEpo) has been increasingly used in preterm infants in the last 3 to 4 years. Recent studies have indicated a reduction in blood transfusion requirements in infants receiving rHuEpo. No significant adverse effects have emerged, apart from iron deficiency (if iron supplementation is inadequate), and the risk of transfusion-related infection is decreased.

Nevertheless, rHuEpo is relatively expensive (a 6-week course costs approximately the same as 2 blood transfusions), so its use requires careful consideration; it is logical to target rHuEpo therapy to those babies who are most likely to be transfused. Using this strategy, 1 study involving stable growing preterm infants has shown that direct costs of blood transfusion and rHuEpo were similar, and the use of rHuEpo was recommended. In addition, use of high-dosage rHuEpo early in the course of management on the neonatal intensive care unit has been shown to reduce direct treatment costs in ill preterm infants.

Further studies will continue to identify infants who are likely to benefit from rHuEpo therapy and to define its cost effectiveness in more detail.
Traditional management of anaemia of prematurity has included the use of red blood cell transfusions. In recent years, there has been much interest in the use of recombinant human erythropoietin (rHuEpo) as an alternative in this indication[1]. Use of the hormone should reduce the risk of transfusion-acquired infection. While there have been no major adverse effects attributable to rHuEpo, it is a relatively expensive treatment ($US30 to $US50 per week; a single blood transfusion cost $US145 at 1 institution in 1994[2]) and there is considerable debate as to which infants to treat.[1,3,4] In addition, it has become clear that use of rHuEpo should be regarded as part of an overall strategy to reduce the need for blood transfusion in preterm infants.[3]

This review focuses on the epidemiology of the anaemia of prematurity, its management and the costs of different treatment strategies.

1. Pathophysiology

All infants experience a decline in haemoglobin levels in the first 10 weeks of life.[5] The decrease is more marked in preterm infants, but is often well tolerated and the infants may be asymptomatic. The lowest haemoglobin levels reached differ with gestational age and birthweight.[5] In term infants, haemoglobin levels rarely drop below 90 g/L; for infants 1000g to 1500g, a nadir of 80 g/L may be attained, while the lower limit is 70 g/L for infants under 1000g.[5] The haematological picture is that of a normochromic normocytic anaemia with a low reticulocyte count (1 to 2%). Not all infants will tolerate these low haemoglobin levels, and symptoms of anaemia may develop. This condition has been termed the anaemia of prematurity. Small red blood cell transfusions (10 to 15 ml/kg) have been shown to ameliorate the clinical features of the condition.[6]

The causes of this type of anaemia are multifactorial and include iatrogenic losses as a result of blood sampling, a shortened red blood cell survival time, a relatively quiescent bone marrow and the need to expand the blood volume with growth.[5]

Erythropoiesis depends on the synthesis of erythropoietin, a 34kD glycoprotein, in the liver.[5] After birth, there is a switch in the major site of production to the peritubular cells of the kidney. Hypoxia induces erythropoietin secretion, and it is proposed that oxygen sensor cells containing a haem protein detect reduced arterial oxygen tension.

The liver sensor cells are less sensitive to hypoxia than the kidney, which may explain the low levels of circulating erythropoietin in preterm infants with anaemia (erythropoietin levels are low, relative to adults with an equivalent degree of anaemia).[5] Following stimulation of sensor cells, messenger RNA and then erythropoietin are produced. The latter enters the blood and binds to receptors on the surface of erythroid progenitor cells, known as burst-forming units–erythroid (BFU-E) and colony-forming units–erythroid (CFU-E). Proliferation and differentiation of these cells results in production of red blood cells. The ability of red blood cell precursors to respond to rHuEpo in preterm infants has been shown by the in vitro culture of circulating mononuclear cells (which include red blood cell progenitors) and bone marrow cells.[7,8]