Leading Article

Current views on aetiology and management of haemolytic uraemic syndrome

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The haemolytic uraemic syndromes (HUS) are a heterogeneous group of disorders characterized by haemolytic anaemia, thrombocytopenia and renal failure occurring predominantly in infants and young children. The disorder, which is acknowledged as the commonest cause of acute renal failure in children in Britain, is increasingly recognized in adults.^{2,3} Two broad subtypes are now recognized: the first is common in children and is associated with a diarrhoeal prodrome (D+), whereas the second is rare in childhood and not associated with antecedent diarrhoea (D-).⁴ D+ HUS is synonymous with typical, prototypic, epidemic or enteropathic HUS and D- with atypical or sporadic disease.

Many causes of D+ HUS, mainly infectious agents,^{5–8} have been proposed but a strong association has now been found between D+ HUS and enteric infection with verocytotoxin-producing *Escherichia coli* (VTEC).^{9,10} These organisms are associated with clinical conditions ranging from mild diarrhoea to haemorrhagic colitis and HUS.^{8,11} VTEC strains of several serotypes have been isolated from patients with HUS, but the majority of such isolates belong to the serotype 0157:H7.¹² VTEC produce 2 types of verocytotoxin (VT1 and VT2),¹³ which resemble Shiga toxin in structure and mode of action; linking D+ cases to the HUS which may complicate *Shigella dysenteriae* infections.¹⁴ The toxins consist of a biologically active subunit A, linked to B subunits,^{15,16} which bind to a specific cell surface glycoprotein GB3.¹⁷ Once attached to the cell surface subunit A enters the cell and inhibits protein synthesis by inactivating 60s ribosomal subunits, which leads to cell death.¹⁸

Karmali *et al.* found evidence of VTEC infection in an estimated 75% of Canadian children with D+ HUS using a combination of laboratory methods, involving recovery of VTEC or neut-

ralizable free verocytotoxin in faeces, and a rise in antibody titre to verocytotoxin.¹⁰ A collaborative study by the British Association for Paediatric Nephrology, the Communicable Disease Surveillance Centre, and the Division of Enteric Pathogens of the Public Health Laboratory, in which DNA probes were applied to faecal samples from children with HUS, confirmed the association between VTEC and D+ HUS in the United Kingdom.¹² Serological testing of patients with HUS for antibodies to the lipopolysaccharide of *E. coli* 0157 has been shown to be a valuable adjunct to established bacteriological techniques in providing evidence of infection for several weeks after the onset of the disease.¹⁹

Predisposing or aetiological factors for the development of D- HUS and other subgroups include autosomal recessive and autosomal dominant inheritance, drugs such as cyclosporin A and mitomycin-C and other agents.⁷ The ability to injure the vascular endothelium appears to be the primary requisite for an agent to cause HUS. Endothelial cells carry the VT receptor and are damaged by VT in culture.^{20,21} The endothelial lesions of HUS can also be caused by the intra-arterial injection of mitomycin-C in the rat²² and there are now numerous case reports of mitomycin C-associated HUS in the literature.^{23,24} Neuraminidase, lipopolysaccharides, phospholipase C and cyclosporin A can all produce a HUS with consequent endothelial cell damage. The neuraminidase-producing organisms, including pneumococci,^{25,26} Clostridia,²⁷ and some viruses, produce the enzyme neuraminidase. This cleaves sialic acid from the cell membranes of red blood cells, platelets and endothelial cells, so exposing the Thomsen-Friedenreich antigen that is normally hidden. Antibodies against this antigen are normally present in human sera, probably in response to cross reacting intestinal bacterial polysaccharide antigens. These antibodies agglutinate red blood cells with exposed antigens and possibly bind to endothelial and platelet membranes leading to haemolysis, thrombocytopenia and renal failure.

The cornerstone of treatment for all subgroups

of HUS is vigorous and early control of renal failure and hypertension with careful correction of electrolyte disturbances and anaemia. Inappropriate rehydration in a situation where renal function is compromised may produce significant morbidity with hyponatraemia and pulmonary oedema. Once the diagnosis has been made early dialysis should be commenced to prevent such complications if the patients are oligoanuric. The haemoglobin level should be maintained above 8 g/dl, and the institution of early dialysis allows blood transfusions to be given with less risk of volume overload and hyperkalaemia. Should hypertension persist after the control of volume overload then antihypertensive agents should be given. Labetalol or sodium nitroprusside may be infused initially and once oral therapy can be tolerated captopril, hydralazine or propranolol are usually effective agents. Gastrointestinal involvement in D + HUS may be severe with profuse diarrhoea, haemorrhagic colitis, ileitis, abdominal distension and rectal prolapse. In such cases intravenous alimentation should be given until the gastrointestinal symptoms resolve and oral feeding be contemplated.

Central nervous system involvement may complicate both D + and D - HUS.^{28,29} The risk of such involvement is reduced by control of hypertension and the correction of electrolyte imbalance; however, severe cerebral dysfunction may still occur. Anticonvulsants should be given if required and elective ventilation instituted should the patient be comatose or the level of consciousness become impaired. Computed tomography and cerebral perfusion scanning with intracranial pressure monitoring may be important adjuncts to effective treatment as either cerebral oedema and elevated intracranial pressure or vascular involvement with normal intracranial pressure may be present. Hyperventilation, mannitol, to be given cautiously if the child is anuric, and fluid restriction should be instituted in the presence of raised intracranial pressure whereas such measures may impair cerebral perfusion should a cerebral vasculopathy be present. Plasma exchange and/or prostacyclin infusion have been used in the management of patients with presumed central nervous system vascular disease.³⁰

The outcome of the majority of cases of D + HUS is good with supportive treatment and appropriate renal failure management. A few children with D + HUS die in the acute phase of the illness with complications of acute renal failure, fulminant colitis or central nervous system involvement. Most recover renal function with only a minority having residual impairment.^{31,32} Numerous specific treatments of D + HUS have been attempted including anticoagulation therapy, fibrinolytic

agents, antiplatelet drugs, prostacyclin, vitamin E, plasma exchange and fresh frozen plasma infusions. Controlled trials of anticoagulation and fibrinolytic agents have failed to demonstrate any significant improvement in D + HUS^{33,34} and uncontrolled trials or reports on the other forms of treatment are difficult to evaluate in the face of the improvement seen in most cases of D + HUS with supportive treatment alone. However, two controlled clinical trials of plasma infusion therapy in children with D + HUS produced conflicting results.^{35,36} Both studies failed to show any beneficial effect on acute mortality and renal outcome 1–2 years later. Loirat *et al.*,³⁶ however, reported a greater incidence of cortical necrosis in the early renal biopsies in the untreated group. Thus the indications for plasma therapy remain controversial. Until evidence from controlled trials supporting the use of plasma exchange and prostacyclin infusion becomes available, such treatments should be restricted to the minority of patients with severe complications associated with a poor prognosis such as those with cerebral or severe gastrointestinal involvement and a high polymorphonuclear count at presentation.³⁷

Patients with D - HUS have a poor prognosis; there is a significant mortality and morbidity with the majority developing some degree of renal impairment and hypertension.^{38,39} Renal failure controlled with early dialysis and hypertension with volume depletion if necessary, and captopril or a prostacyclin infusion if required. On the basis of the observed deficiency of prostacyclin in some cases and experience in the management of thrombotic thrombocytopenic purpura many centres treat D - HUS with fresh plasma.⁴⁰ Some cases appear to respond to plasma exchange but not fresh plasma alone. We treat children with D - HUS with plasma exchange using an infusion of fresh frozen plasma at the end of the procedure. Relapsing D - HUS is managed by a programme of intermittent plasma exchange at increasing intervals for a few months after the last relapse. The cases are too few, however, for a controlled clinical trial to be instigated, but empirically we have found that acute renal failure may be reversed but that there remains a probability of relapse several months after the last plasma exchange.

Treatment of patients with neuraminidase-associated HUS may be problematic. Most adult plasma contains antibodies against the Thomsen-Freidenreich antibody and plasma infusion or whole blood transfusion in such patients may be deleterious, accentuating the polyagglutination and haemolysis. These patients should receive washed red cells and albumin solutions thus avoiding additional agglutinating antibody, and exchange transfusion should be considered.

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