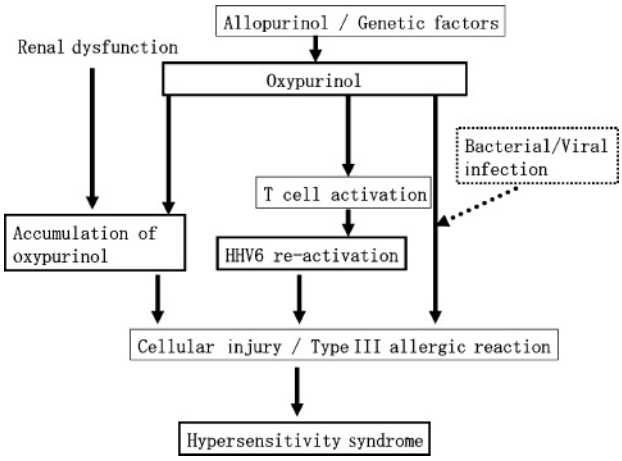

Fig. 1. Possible mechanism for the onset of allopurinol hypersensitivity syndrome. In addition to established pathways (direct cellular injury and inactivation of viruses), community infection may accelerate the cascade.

IgG, Epstein-Barr virus, measles and rubella were positive but within the normal range, we suspected that the AHS may have been induced by influenza virus infection. Her symptoms diminished following withdrawal of allopurinol and administration of predonisolone. Current hypotheses for mechanisms of the AHS onset include two pathways Fig. 1. First, storage of allopurinol and its metabolite, oxypurinol, may directly inflict cell damage, especially in patients with renal dysfunction. A second possible pathway suggests that a type III allergic reaction caused by allopurinol may induce the re-activation of HHV-6, or activation of other opportunistic viruses, such as cytomegalovirus [2] and Epstein-Barr virus [3], through the activation of T-lymphocytes. Recently, CD46 was identified as a receptor for HHV-6, and it was therefore suggested that this reactivated virus damages cells, including epidermal cells and lymphocytes, via CD46 binding [4]. In the present case, the influenza virus titre was elevated in parallel with the clinical symptoms of AHS, and it is possible that this virus exacerbated the cascade reaction in the same way as do other viruses. We suggest that such community-acquired bacterial and viral infections may also accelerate these cascade reactions and that genetic factors may interact with these events.

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A case of lethal enteroviral haemolytic uraemic syndrome?

Sir,

In the recent years much has been learnt about haemolytic uraemic syndrome (HUS), which is defined by symptomatic or bloody diarrhoea, acute nephropathy, thrombocytopenia and microangiopathic haemolytic anaemia. Often HUS is complicated by neurological symptoms in children [1]. The main aetiological culprit is Shiga-like toxin-producing *E. coli* (STEC) accounting for ∼85% of HUS cases. Recently the aetiological role of enteroviruses in HUS has been studied and rejected as being an aetiological agent [3] even though earlier case reports suggested a role (see references in [3]). We present a case of HUS, which was probably due to enteroviral infection.

A 17-month-old girl, who was previously healthy, was admitted with bloody diarrhoea preceded by vomiting for a day or two. A few hours into the admission the girl developed a seizure and was transferred to an ICU. Extensive clinical and laboratory testing was carried out (Table 1). Tests showed uraemia, thrombocytopenia, haemolytic anaemia, leucocytosis and anuria. The patient developed cardiac arrest at 8 h into the admission. Resuscitation with concurrent peritoneal dialysis was attempted for an hour without success.

On autopsy we found a normally developed girl without any deformities. The autopsy revealed a thickened haemorrhagic colon, stasis and oedema in the lungs, hydrothorax and hydroperitoneum. The CNS was without lesions (vascular or any other). There were no signs of iatrogenic injury.

On histopathological examination we found signs of endothelial damage in the small vessels of the kidneys (Figure 1) and the intestine (with thrombosis), fragments of thrombi in the small lung vessels and a necrotic colon with submucosal haemorrhage and leukocyte infiltration. No thrombi were found in the brain.

Concurrent to the autopsy we requested several tests expecting to find a STEC infection but instead we found an enteroviral infection (Table 1).

Our case indicates that enteroviral infections may be able to inflict HUS, and contradicts other studies of HUS [3].

It is clear from the above-mentioned findings that the case presented as HUS, with all of its cardinal findings, uraemia, thrombocytopenia, haemolytic anaemia, and endothelial damage in the kidney and intestine. We used stool and tissue cultures for the bacterial tests whereas viral tests included PCR, serology and cultures. Sadly subtyping (using cell cultures) was unsuccessful after several attempts.

A weakness in our report is that we do not have multiple tests (i.e. serology) to exclude a STEC infection, only a standard stool culture. Furthermore, one could speculate that the finding of enteroviral RNA is coincidental or from "leakage" of colonic virus into blood.

In support of our conclusion, enteroviruses are known to be able to infect colonic cells and endothelial cells, and damage both by either lytic or immunological mechanisms, the prerequisites for inducing HUS [4,5]. Furthermore our detection techniques are more sensitive [6,7] than the ones used earlier in studies [3].

Our case underlines the need for a large-scale epidemiological investigation of STEC-negative HUS cases using the most recent sensitive diagnostic tests especially considering the poorer prognosis of STEC-negative cases [3].

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A proposal of the simple guide regarding the conversion ratio from epoetin to darbepoetin alpha in treating haemodialysis patients with renal anaemia

Sir,

Darbepoetin alpha (darbepoetin), which has the longest half-time of all the erythropoiesis-stimulating agents (ESAs), is now used world-wide with many advantages for both the patient and the healthcare worker [1,2]. Several recent observations have suggested that in treating renal anaemia the conversion ratio from epoetin to darbepoetin according to the theoretically calculated '1 μg darbepoetin = 200 U epoetin' rule (1:200 rule) leads to an overestimate of the required darbepoetin dose [1]. In particular, in a large-scale multicentre prospective study of 100 haemodialysis (HD) patients, Bock *et al.* concluded that, although the 1:200 rule is appropriate for lower epoetin doses (<5000 IU/week), a 1:250 to 1:350 conversion rule could be applied to the darbepoetin dose for patients converting from ≥5000 IU of epoetin per week [1]. I almost agree with their conclusion. But I think that a simpler guide regarding the conversion ratio according to the proceeding epoetin dose could be obtained from my experience of treating HD patients with darbepoetin for over 7 months in our clinic and I will attempt to propose the guide here.

In our clinic, 32 chronic HD patients underwent HD treatment two to three times a week in September 2007 and I took charge of all the patients at that time and remained in charge of them thereafter. Out of these patients 26 had been treated with between 750 and 9000 IU of epoetin alpha (epoetin) weekly for renal anaemia. I changed all these patients to darbepoetin from October, the 40th week in 2007. I estimated adequate initial dose of darbepoetin according to the 1:200 rule and 10, 15, 20, 30 or 40 μg of darbepoetin was given once a week or every two weeks to these patients. My policy to treat renal anaemia is basically by the combination of ESAs and iron repletion without other medication, and the target level of haemoglobin (Hb) of the patients is almost between 10 and 11 g/dL according to the guidelines in 2004 of the Japanese Society for Dialysis Therapy [3]. Though several changes in the doses were required in many patients during about the first 12 weeks, almost adequate doses of darbepoetin needed to keep Hb stable could be obtained after that.

Those HD patients who developed anaemia from other causes than renal failure, such as intestinal bleeding, during the previous 12 weeks, were excluded for the evaluation.

Finally, 23 out of the 26 patients were eligible for this inquiry. I reviewed their clinical records and found the total epoetin doses of each individual patient from the 4 weeks between week 32 and 35 in 2007 as well as the Hb levels from weeks 32 and 36. In the same way, I got the total darbepoetin doses from the 13th to the 16th week in 2008 and got Hbs at the 15th and the 17th week. From these data, I calculated individual patient's weekly doses of epoetin per 1.0 g/dL of Hb during the former 4 weeks and also calculated weekly darbepoetin doses per 1.0 g/dL of Hb during the latter 4 weeks. Then, I compared the doses of epoetin with the ones of darbepoetin for 1.0 g/dL of Hb in each individual patient to get the darbepoetin:epoetin conversion ratio.

Only one patient belonging to the epoetin > 6000 IU/week group showed darbepoetin:epoetin = 1:631, five patients in the 6000 IU/week ≥ epoetin > 4500 IU/week group showed a mean ratio of 1:303 (1:401, 318, 289, 282, 227), nine patients in the 4500 IU ≥ epoetin > 3000 IU group showed 1:251 (1:379, 356, 274, 260, 248, 243, 209, 151, 139) and eight patients in the 3000 IU ≥ epoetin group showed 1:169 (1:305, 265, 211, 146, 133, 113, 97, 81).

From these results, I think the individual difference in the adequate conversion ratio is very noticeable in the lower