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9 April 2026

Subject: Royal College of Physicians response to Regulation 28 report to prevent future deaths

Dear Emma Brown,

The Royal College of Physicians (RCP) notes the matters of concern contained within the Regulation 28 Prevention of Future Deaths report related to the death of Miss Chloe Angela Ulett. We send our sincere condolences to the family of Miss Chloe Angela Ulett.

To ensure an informed and comprehensive response to this case, we have consulted the RCP's Patient safety committee, which comprises a number of our national stakeholders including NHSE, as well as acute medicine colleagues, including the Society of Acute Medicine and those with a special interest in metabolic disorders.

This regulation 28 report raises the concerns around the diagnosis of hyperammonaemia. Hyperammonaemia is characterised by the rise of ammonia within the blood stream which can result in patients becoming confused, drowsy and have headaches.

Severe hyperammonaemia is well recognised as a metabolic emergency. Its main causes can be split into the following subsections:

a) Overproduction of anaemia - caused by increased protein load, increased catabolism and urinary issues (for example, urease-producing infections)
b) Reduced elimination due to liver failure, drugs and toxins and metabolic disorders.

The majority of patients who present with high ammonia levels in the blood have acute or chronic liver failure, but other causes of raised ammonia need to be considered as this is a diagnosis which has fatal consequences, as this case sadly demonstrates. Many of the inherited causes of hyperammonaemia are recognised in infancy. Indeed, urea cycle disorders are rare, affecting 1:35,000-50,000 infants. The point prevalence in adults is significantly lower.

Whilst guidelines in the Investigation of Hyperammonaemia in children and adults are available from NHS Scotland, there are currently no formal guidelines on investigation of hyperammonaemia in adults in England, although advice is available from the British Inherited Metabolic Disease Group. There is reference to the investigation of high ammonia in confused patients within the Royal College of Emergency Medicine (RCEM) best practice guideline 'Acute Behavioural Disturbance in the Emergency Departments' (October 2023) as stated in this Regulation 28 report. This guideline advises doing 'other tests as clinically indicated e.g. … appropriate metabolic screen (including ammonia level)' in those with acute behavioural disturbance. The Royal College of Paediatrics and

Child Health (RCPCH) has also produced a clinical guideline document for the management of children and young people with an acute decreased in conscious level. The RCP is aware that the NHS England National Patient Safety Team have undertaken work with the Royal College of Pathologists (RCPath) on the specific issue of hyperammonaemia and ammonia testing and that as a result, a national Patient Safety Bulletin was issued. The RCP supports the highlighted need for 'prompt measurement of ammonia and action in the event of hyperammonaemia'. The RCP notes a gap in best practices guidelines as neither NICE nor the BMJ currently recommend the testing of ammonia levels for undifferentiated acutely presenting confused patients, as stated within the Regulation 28.

While RCEM guidance exists, this case illustrates opportunities for enhanced awareness regarding the possibility of hyperammonaemia in patients presenting with acute behavioral changes and seeking urgent advice if the cause of acute deterioration is unclear particularly in someone with no other underlying health disorder. Over the past decade, additional cases associated with metabolic disease have been noted at inquests, which highlights the importance of continuing to increase recognition of this disorder which is treatable.

The RCP recognises that physicians are working in very busy environments, but training should emphasise the importance of early intervention and advise, particularly for acute deterioration without cause in someone with no other health issues. Those physicians working in acute medicine as well as those in other medical specialities should be aware of these potential rare diagnoses, such as hyperammonaemia presenting acutely in adults. The RCP also advocates for urgent specialist reviews where diagnostic uncertainty exists, for example, assessment by a neurologist to help identify the diagnosis, ensuring management is not delayed. The RCP acknowledges that the available guidance is not well embedded and the triggers for the condition described are not well known by the majority of clinicians. At the RCP, the concerns of hyperammonaemia have been discussed at the Patient Safety Committee and the RCP has committed to raising the profile by sharing this issue with their members via the RCP website within the coming months.

Hyperammonaemia is rare but the presentation of those with confusion due to any cause is high in the acute setting. 10-20% of all admissions present with confusion due to a wide variety of issues (National Institute for Health and Care Excellence: Delirium, prevention, diagnosis and management (CG103). London: NICE; 2010 (updated 2019)). Hyperammonaemia remains a diagnosis of exclusion and as such, ammonia levels are not usually in the first bloods sent for a patient, as the primary aim in someone presenting with confusion is to ensure they do not have sepsis. As highlighted by this challenging case, hyperammonaemia remains a diagnosis that should be carefully considered when the cause of acute confusion is unclear. Awareness of this condition varies among clinicians, and our review of this regulation 28 report underscores the value of developing clearer guidance on the investigation and management of hyperammonaemia, particularly in Trusts without access to metabolic medicine specialists.

We suggest that any guidance produced would need to be created with the RCP, RCEM and the Society of Acute Medicine to ensure practical implementation. Guidance would need to be realistic and deliverable, especially given metabolic diseases are rare. There is also a risk that a significant number of patients would be over-investigated (given numbers who present with confusion vs those with metabolic disorders which result in hyperammonaemia) and thus may cause harm to patients. Any guidance would need to balance this risk with the risk of not identifying a potentially reversible/treatable condition which without intervention, has devastating consequences. At the RCP, we would be happy to contribute to the development of such guidance this should be shared nationally to enable systems learning. At the RCP, we could support by facilitating information and guidance sharing with our physician members and fellows as well as other stakeholders and we urge UHB to share this information with the RCP for this purpose. Furthermore, it would be valuable for the stakeholders and specialties regularly involved in these scenarios to collate available evidence including success stories and examples of efficient management of these rare events. In preventing future deaths, as a profession we have a duty to consider how such rare disorders (many of which

have serious, even fatal, consequences) are recognised and how information is disseminated to physicians who will see such a case perhaps only once in their career, if at all.

Furthermore, we acknowledge that the window of opportunity to make such a diagnosis is relatively small, 24 to 48 hours from commencement of symptoms and therefore it should be a condition which should be considered in those presenting with symptoms. There are practical considerations and one of the recognised barriers is believed to be the measurement of ammonia. Indeed, the false positive rates of this test are high. This is because ammonia rises rapidly in the blood unless specific precautions are taken, and in some centres, the physical transporting of the blood to the laboratory precludes any chance of accurate levels being measured. The sample also needs to be kept on ice, which is no longer readily available in NHS Trusts, therefore causing challenges in completion of this investigation. NHS Trusts should have clear pathways for medical and nursing staff to follow in cases where a test for ammonia is required and appropriate.

Our review of the case underscores the value of considering urea cycle disorders in pregnant or postpartum individuals experiencing unexplained confusion or critical illness and highlights the importance of awareness of the benefit of involving the regional maternal network in such instances. All regions have access to these networks, and increasing awareness of this resource is vital to optimal care of pregnant and postpartum women.

The benefit of referring a patient where there is concern is that the network would have convened a multidisciplinary team including obstetrics, obstetric physicians and select specialist physicians and anaesthetists at short notice, who would then have been able to advise on investigation, diagnosis and management. The awareness of the networks and how to access them needs to be reinforced to all those who are involved in the assessment of pregnant and postpartum women. In any future communication to our members and fellows we will aim to emphasise this point so people are aware of the networks that would be useful, particularly in supporting postpartum or pregnant patients.

Once again, our sincere condolences to Miss Ulett's family at this difficult time.

Yours sincerely,

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Clinical Director for Patient Safety and Clinical Standards