Introduction

Patient management decisions in medicine depend to an ever-increasing degree on objective—evidence based—diagnostic guidelines. This is particularly true for neurocritical care, where many patients are unconscious or unable to communicate adequately. Therefore, the diagnostic procedures underlying the guidelines must not only be correctly applied, but must also be legally and scientifically testable, to justify the management decisions.

Recently, concern has been raised that about 99% of more than 3000 laboratories participating in two independent US surveys (1,2) relied on visual assessment of the cerebrospinal fluid (CSF) for xanthochromia. Xanthochromia assessment is used to help decide whether or not an intracranial bleed has occurred, which is important for diagnosing a subarachnoid hemorrhage (SAH). Because a SAH is associated with a high mortality (50–60%), which increases significantly (to ~80%) if the initial diagnosis is missed and a rebleed occurs, a meticulous diagnostic approach is essential for rapid and appropriate treatment.

In this review, we argue for abandoning the visual assessment of the CSF for xanthochromia, because new evidence suggests that it is perceptually impossible or unreliable in approximately 80% of critical cases (3,4). Instead, we argue for relying on the more sensitive and more specific spectrophotometry (5), which is also documentable and therefore legally testable. First, we review the clinical relevance of CSF pigment analysis. Second, we summarize why the human visual system is unreliable for detecting xanthochromia. Third, we review the laboratory techniques available for CSF analysis. Fourth, we review the UK experience with...
spectrophotometric-based national guidelines and the current US recommendations for CSF pigment analysis. We conclude with an evidence based diagnostic flowchart.

**The Clinical Relevance of CSF Pigment Analysis**

The normal CSF is clear and colorless, as shown by the roughly flat spectrophotometric trace depicted in Figure 1A. It consists of 99% water and has a much lower protein concentration (~350 mg/L) than the serum (~70,000 mg/L). The color changes when additional substances such as bilirubin (yellow) or hemoglobin (Hb) (red) enter the CSF. The correct identification of CSF pigments allows one to draw pertinent conclusions about pathology in the patient under examination. Although the major concern for the neurocritical care physician will be to correctly identify SAH, there are confounding factors and other conditions that need to be considered when making the diagnosis (for review see ref. 6 and references therein).

The color changes associated with blood pigments released into the CSF, as the result of potentially life-threatening conditions such as an aneurysmal SAH, are very rapid. Erythrocytes are hemolyzed and release Hb (red colored) which dissociates into heme and globin. The heme groups are, in turn, converted by heme oxygenase to biliverdin (bile green) and further by biliverdin reductase to bilirubin (canary yellow) (7). Bilirubin arises only in vivo, which makes it the most specific metabolite for distinguishing a true bleed from a traumatic tap (7–14). In fact, the presence of bilirubin in the CSF taken 6–12 hours after ictus in a patient with suspected SAH is virtually a fail-proof diagnostic (10,12,15,16).

**Subarachnoid Hemorrhage**

Cerebral aneurysms are estimated to be present in approximately 5 million North Americans, of whom approximately 30,000 are likely to experience an aneurysmal SAH (17,18). For these, the mortality from a SAH rises to approximately 80% if a rebleed occurs (19). The risk of a rebleed can be minimized by protection of the aneurysm either surgically (“clipping”) or radiologically (“coiling”) (19,20). Clearly, sensitive diagnostic tools are crucial for determining if an aneurysmal hemorrhage has occurred and enabling rapid and adequate patient management. At present, the diagnosis of a SAH is predominantly made on the basis of non-enhancing computed tomography (CT) of the brain (6,19). There are, however, two situations under which the CT can be unreliable. First, it may occur when the CT is performed some time after the bleed; Van Gijn et al. reported that the sensitivity of the CT falls from 97% in the first day after the bleed to less than 10% after three weeks (21). Others have reported a negative CT in 14.6–20% of patients with a proven SAH (22,23), which presumably must also be caused in part by lack of prompt scanning. Second, a caudally-located bleed or small bleed adjacent to bony structures (i.e., above the orbits) can be difficult to detect because of imaging artifacts. Third, the scan may be technically suboptimal; being difficult because of severe anemia or movement artifacts (6). Even when optimally timed, using modern scanners, and in the best of hands the CT still has a false negative rate of approximately 2–3% and confidence intervals are wide (24,25). Not surprisingly, therefore, a body of literature provides

![Fig. 1](image-url) Examples for (A) a spectrophotometric scan showing a normal CSF; (B) a spectrophotometric scan showing the presence of oxyhemoglobin in the CSF; The highest peak for oxyhemoglobin (OxyHb) is observed at 415 nm and secondary, much smaller peaks are observed between 525–600 nm; (C) a spectrophotometric scan showing the presence of bilirubin and oxyhemoglobin in the CSF. This scan is consistent with a SAH. For practical reasons, the absorbance for bilirubin will be read at 476 nm, which is outside the absorbance for oxyhemoglobin. It should be noted that the maximum of the broad bilirubin peak lies within 450–460 nm.