Acute Porphyria Screening Protocol in the Emergency Department: A Strategy for Early Diagnosis

Protocolo de Rastreio de Porfiria Aguda no Serviços de Urgência: Estratégia para Diagnóstico Precoce

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Abstract:

Acute porphyrias are a group of rare metabolic diseases, arise from defects in the heme biosynthesis pathway. These conditions are clinically characterized by acute neurovisceral attacks, chronic symptoms, and long-term complications. Given the non-specific presentation and the typically low index of clinical suspicion, diagnostic delays are recurrent and result in significant preventable morbimortality. To address and mitigate this clinical impact, a structured and clinically feasible screening protocol for the early detection of acute porphyria is herein proposed for implementation in the Emergency Department (ED), as this setting represents the principal point of care for patients experiencing an acute attack. The target population encompasses patients presenting to the ED with unexplained acute abdominal pain, acute or subacute polyneuropathy, or acute psychosis (specifically first episodes, atypical presentations, or treatment-refractory cases). Given the lack of immediate access to quantitative biochemical testing of porphyrins in the emergency setting, the Hoesch test emerges as a crucial tool. This method is a rapid, low-cost qualitative assay for detecting elevated urinary porphobilinogen (PBG), a hallmark of most acute porphyria attacks. Notwithstanding its inherent limitations, such as the potential for false negatives in the rarest subtype of acute porphyria and its reliance on operator proficiency, the systematic implementation of this Hoesch-based screening protocol offers an essential strategic approach to optimize the early recognition of acute porphyria and ultimately reduce the associated morbimortality stemming from delayed diagnosis.

Keywords: Abdominal Pain; Emergency Service, Hospital; Heme; Porphyria, Acute Intermittent/diagnosis.

Resumo:

As porfirias agudas são doenças metabólicas raras, resultantes de defeitos na via de biossíntese do heme. Estas condições são clinicamente caracterizadas por crises neurovisceral agudas, sintomas crónicos e complicações a longo prazo. Perante a apresentação clínica inespecífica e o baixo índice de suspeição clínica, os atrasos no diagnóstico são recorrentes, resultando em morbimortalidade evitáveis. Para mitigar este impacto clínico, propõe-se um protocolo de rastreio estruturado e clinicamente exequível para a deteção precoce das porfirias agudas, a ser implementado no Serviço de Urgência (SU), uma vez que existe elevada probabilidade de o doente em crise necessitar de cuidados hospitalares urgentes. A população-alvo para este rastreio inclui doentes que se apresentem no SU com dor abdominal aguda inexplicada, polineuropatia aguda ou subaguda, ou psicose aguda (especificamente, primeiros episódios, apresentações atípicas ou casos refratários ao tratamento). Dada a frequente indisponibilidade de acesso imediato a testes bioquímicos quantitativos no contexto do SU, o teste de Hoesch emerge como uma ferramenta crucial por ser um método qualitativo rápido e de baixo custo para detetar as elevações de porfobilinogénio (PBG) urinário, um achado característico da maioria das crises de porfiria aguda. Apesar das suas limitações inerentes, incluindo o potencial para resultados falso negativo no subtipo mais raro de porfiria aguda e a sua natureza operador-dependente, a implementação sistemática deste protocolo, oferece uma estratégia essencial para otimizar o reconhecimento precoce da porfiria aguda e, consequentemente, reduzir a morbimortalidade associada ao diagnóstico tardio.

Palavras-chave: Dor Abdominal; Heme; Porfiria Aguda Intermitente/diagnóstico; Serviço de Urgência Hospitalar.

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Introduction

Acute porphyrias are rare inherited metabolic disorders that result from enzyme deficiencies within the heme biosynthesis pathway (Table 1). These include acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP), and aminolevulinic acid dehydratase porphyria (ALADP).[1,2] Patients with acute porphyria face a persistent risk of life-threatening neurovisceral crises and debilitating long-term complications, significantly impacting their quality of life (Fig. 1).[1,3]

In European countries, the prevalence of acute porphyria is 1-2 per 100 000 inhabitants.[4] Reported penetrance ranges from 10% to 52%, associated with genetic and personal high-susceptibility risk factors, such as cytochrome P450-coding genes and their polymorphisms.[5,6] Symptomatic AIP exhibits a consistent incidence across most European countries. However, for Portugal, European epidemiological studies estimate approximately 150 symptomatic patients, contrasting with the less than 30 patients currently monitored in our Reference Centers for Metabolic Inherited Disorders (unpublished data). This significant discrepancy raises questions about a genuinely low prevalence or, most likely, reflects severe underdiagnosis. This highlights the critical need for a standardized strategy for acute porphyria diagnosis.

Clinical manifestations during acute attacks include a broad array of nonspecific signs and symptoms (Fig. 1). As reported in the EXPLORE study, 99% of patients reported pain during attacks, mostly abdominal pain (92%), arm or leg pain (77%), and back pain (72%).[3] Common signs and symptoms, observed in over 80% of patients, included nausea and light-induced urine discoloration to a brownish-red hue.[3,7] Psychiatric symptoms range from anxiety, depression, irritability, and insomnia to psychosis. Peripheral neuropathy, typically manifesting as an acute or subacute axonal motor neuropathy (acute flaccid paralysis), results in muscle weakness, diminished tendon reflexes, and variable sensory impairment. Furthermore, cranial nerve involvement and the potential for life-threatening respiratory or bulbar paralysis are recognized complications.[8] Distinguishing acute porphyria from Guillain-Barré syndrome is essential; proximal muscle weakness, early autonomic instability, and the lack of albumin-cytological dissociation in the cerebrospinal fluid are more suggestive of porphyria. Finally, encephalopathy, seizures, and hyponatremia have also been reported.[9-11]

In acute porphyria attacks, circulating levels of the heme precursors δ-aminolevulinic acid (ALA) and porphobilinogen (PBG) are significantly elevated, except for ALADP, which exhibits only increased ALA levels. This elevation is attributed to the increased activity of hepatic ALA synthase 1 (ALAS1), the rate-limiting enzyme in heme biosynthesis. Up-regulation of ALAS1 can be induced by a wide range of triggers, including intracellular heme depletion, prolonged fasting, low-carbohydrate diet, smoking, alcohol consumption, psychological stress, female sex hormones, infections, surgery, and porphyrinogenic drugs (a comprehensive list is available from sources such as www.drugs-porphyria.org and the Porphyria Foundation drug database). Identifying and eliminating these triggers is essential for reversing acute attacks.[1]

Table 1: Main clinical presentation, relevant biochemical markers and genetic features of acute porphyrias.

	Acute Intermittent Porphyria (AIP)	Variegate Porphyria (VP)	Hereditary Coproporphyria (HCP)	Aminolevulinic Acid Dehydratase Deficiency Porphyria (ALADP)
Affected enzyme	Hydroxymethylbilane synthase (HMBS)	PROTOgen oxidase (PPOX)	COPROgen oxidase (CPOX)	ALA dehydratase (ALAD)
Acute neurovisceral symptoms	+++	++	++	+++
Cutaneous symptoms	-	+	+	-
Hoesch test result in acute attacks	Positive	Positive	Positive	Negative
Metabolites in urine[a]	PBG ↑↑ ALA ↑ Uro (I+III) ↑↑↑ Copro III ↑	PBG ↑ ALA ↑ - Copro III	PBG ↑ ALA ↑ - Copro III ↑↑↑	PBG ↓ or N ALA ↑↑ - -
Accumulated metabolites in faeces	-	Proto ↑↑ Copro III ↑ Proto>>CoproIII (Copro III / Copro I >2)	Copro III ↑↑↑ (Copro III/ Copro I >2	-
Plasma porphyrin fluorescence peak	618-623 nm	624-627 nm	618-623 nm	618-623 nm

ALA: δ-aminolevulinic acid; Copro: coproporphyrin; PBG: porphobilinogen; Uro: uroporphyrin; Proto: protoporphyrin.
[a]The excretion of urinary precursors can be normal during an acute attack.

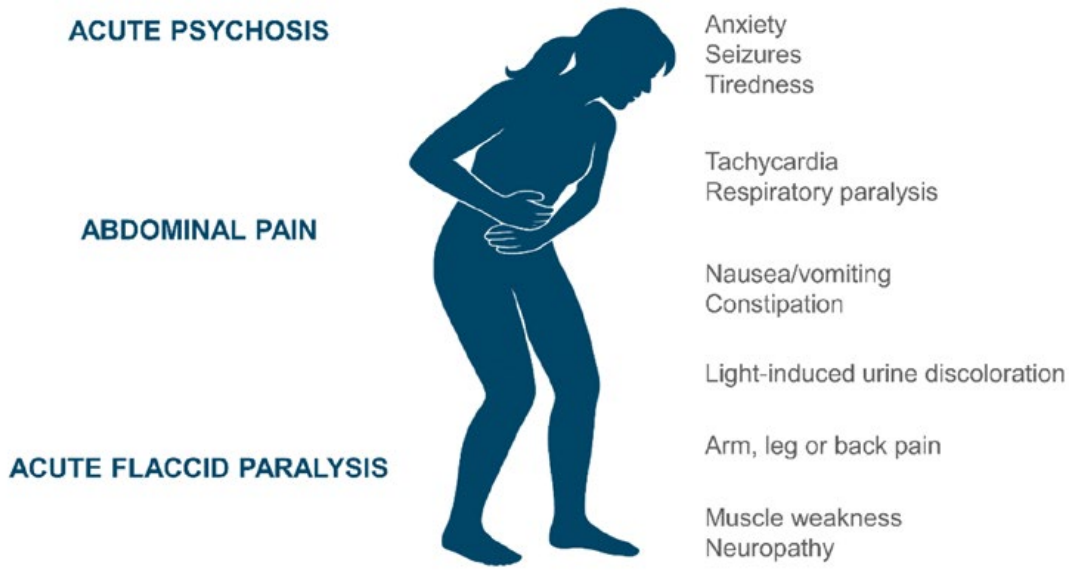

Figure 1: Common signs and symptoms of acute porphyria attacks requiring hospitalization, urgent care, or increased medication use.

Because of the nonspecific nature of symptoms, patients are commonly undiagnosed or misdiagnosed, which can result in untreated attacks and subsequent permanent neurological sequelae, severe life-threatening complications, or fatal outcomes. A population-based study reported a delay of up to 15 years between the onset of symptoms and the diagnosis of acute porphyria.[11] Given this critical delay, the Emergency Department (ED) provides an ideal opportunity for diagnosis, as patients experiencing acute porphyria attacks are highly likely to present in this setting.[12] In these cases, the combination of severe symptoms and predictable porphyrin precursor elevation leads to a more straightforward diagnostic workup if proper tools are available. Nonetheless, effective patient screening protocols are imperative to optimize ED efficiency, considering their demanding workloads. Therefore, this article aims to present a feasible screening protocol for the early detection of acute porphyrias in patients presenting to the ED with clinical manifestations, such as, acute abdominal pain, polyneuropathy, or acute psychosis.

ACUTE PORPHYRIA SCREENING PROTOCOL: COMPONENTS AND IMPLEMENTATION

Methodology

The screening protocol was developed through a non-systematic literature review, encompassing international guidelines and expert opinion articles on acute porphyrias. This evidence served as the foundation for a subsequent multi-disciplinary expert consensus to ensure clinical applicability. The expert panel was assembled from national reference centers for inherited metabolic disorders and recognized specialized laboratories. The panel composition included diverse specialties critical to the management of acute porphyria, such as Internal Medicine, Neurology, Psychiatry, Clinical Pathology, and a specialized laboratory analyst. The clinicians involved maintained active clinical practice in the ED at the time of the protocol's development. This requirement ensured that the resulting protocol was not only evidence-based but also feasible and resource-sensitive for implementation within a Portuguese ED setting with limited resources. As the described protocol constitutes a clinical quality improvement and management strategy designed for implementation within the ED, rather than a prospective clinical research study, it is exempt from formal ethics committee review.

Inclusion and Exclusion Criteria for Screening

The protocol targets specific groups of patients presenting to the ED (as depicted in Fig. 2). Patient should be included for screening if they present with:

- **Acute abdominal pain** with moderate to severe intensity, with an unclear etiology following the initial workup.
- **Acute polyneuropathy,** especially when differential diagnoses include conditions like Guillain-Barré syndrome.
- **Acute psychosis,** especially in a first psychotic episode or when clinical manifestations are atypical and/or treatment resistant.

The presence of concomitant systemic arterial hypertension, tachycardia, encephalopathy, seizures, hyponatremia, brown-reddish urine, and previous episodes of abdominal pain of unclear etiology should be considered red flags that significantly increase suspicion for acute porphyria.[7]

The screening protocol should be routinely applied to adult patients from puberty up to 65 years of age, reflecting the typical onset of symptoms.[11] However, we emphasize the importance

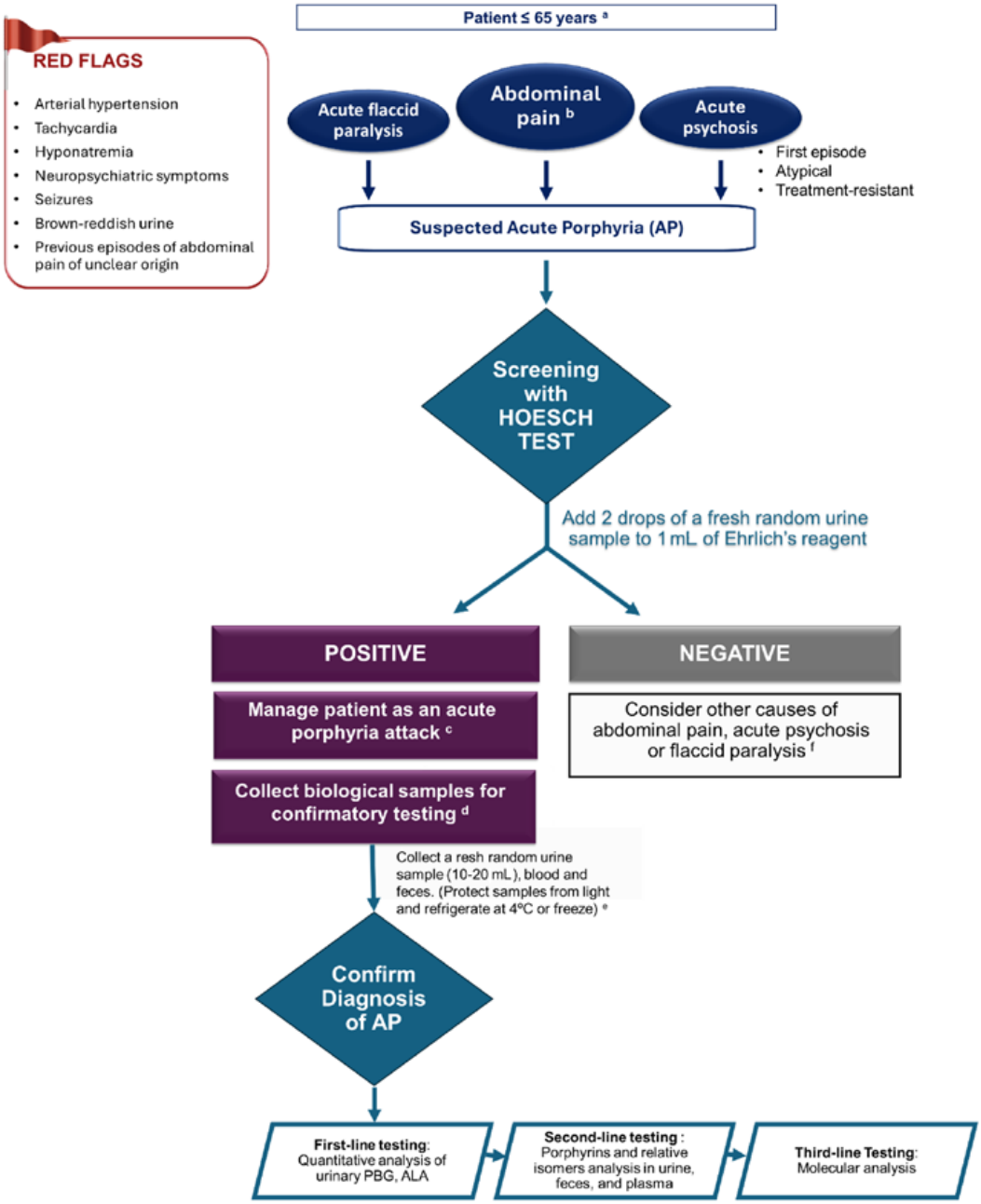

Figure 2: **Acute Porphyria Screening Algorithm for Emergency Departments (ED)**.
This algorithm outlines the screening process for acute porphyria in patients presenting to the ED. Initial assessment includes considering specific clinical presentations (acute flaccid paralysis, acute abdominal pain, or acute psychosis (first episode, atypical, or treatment-resistant) and "Red Flags" (e.g., arterial hypertension, tachycardia, neuropsychiatric symptoms, brown-reddish urine). The screening begins with the collection of a fresh random urine sample in a plain container, protected from light, for a Hoesch test. A positive Hoesch test suggests "possible acute porphyria," leading to immediate management of the patient as an acute porphyria attack and the collection of biological samples for confirmatory testing.

[a]Screening may also be considered in patients older than 65 years who present with unexplained nonspecific neurovisceral, neurologic, and/or psychiatric conditions.
[b]For patients presenting with acute abdominal pain, other associated surgical and medical conditions (e.g., peritonitis, appendicitis, acute cholecystitis, pancreatitis, intestinal occlusion, acute gastroenteritis, acute drepanocytic crisis, and acute hemolysis) should be ruled out before initiating screening for acute porphyria.
[c]Management of an acute porphyria attack should follow established institutional or expert guidelines. See Fig. 4 for details on urgent treatment protocols
[d]Samples for the initial Hoesch test, and subsequent confirmatory tests, should be collected while symptoms are present and preferably before specific treatment for porphyria is started, but collection should not delay any urgent therapeutic measures.
[e]Biological samples (urine, blood, feces) collected for confirmatory testing must be protected from light and refrigerated at 4°C. Urine samples for porphyrin precursor analysis are stable under these conditions for up to 48 hours.[22-24]
[f]It is important to note that a negative Hoesch test, which primarily detects PBG, does not exclude ALADP, as this condition is characterized by isolated ALA elevation.
ALA: δ-aminolevulinic acid; ALADP: ALA dehydratase deficiency porphyria; AP: acute porphyria; ED: Emergency Department; PBG: porphobilinogen

of considering the diagnosis even in younger or older patients with nonspecific neurovisceral symptoms or with unexplained neurologic and psychiatric conditions.

Exclusion of common and critical surgical and medical conditions is mandatory prior to implementing the screening protocol. For patients presenting with abdominal pain, these exclusion criteria include, but are not limited to, peritonitis, appendicitis, acute cholecystitis, pancreatitis, intestinal occlusion, acute gastroenteritis, acute drepanocytic crisis, and acute hemolysis.

Screening Test

Screening for acute porphyria in the ED setting is feasible with the Hoesch test. A 4-dimethylaminobenzaldehyde (DMAB) in acid (Ehrlich's reagent) is used as a reagent. When PBG reacts with the DMAB, a pink or red chromophore is formed (Fig. 3). Ehrlich's reagent exhibits good stability, requires no special conditioning, is cost-effective, and yields immediate results.[13,14] Patients selected for screening, collect 10-20 mL of fresh random urine sample in a plain container protected from light. Add two drops of this urine to 1 mL of Ehrlich's reagent; if the resulting mixture turns reddish (or pink), the test is considered positive. This result needs confirmation by first-line and second-line tests, preferably using a portion of the same urine sample.[15] Confirmation of an acute porphyria attack should not delay the patient's management.

Management Algorithm

Confirmation of an acute porphyria attack should not delay the patient's management.[16,17] As soon as possible, initiate appropriate supportive treatments using safe drugs for acute porphyria.[2,17-19] These resources are essential for both selecting appropriate symptomatic therapies and avoiding porphyrinogenic drugs mentioned as triggers. Review prescribed and over-the-counter medication, as well as illegal drugs, and search for other triggering factors and possible complications associated with acute attacks (Fig. 4). Given the complexity and specific management requirements of acute porphyria, it is crucial to promptly contact a specialized metabolic or porphyria center for expert guidance and to coordinate ongoing patient care.

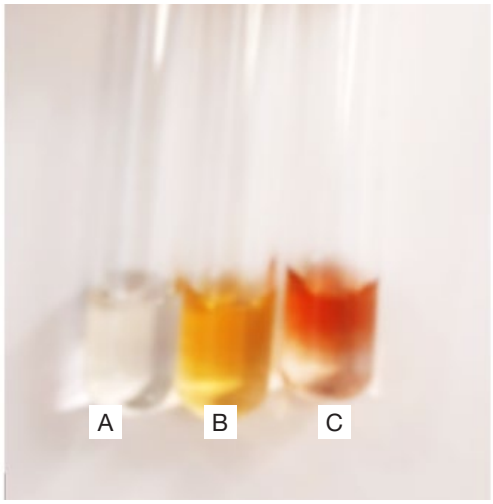

Figure 3: The Hoesch Test for qualitative detection of porphobilinogen (PBG). Tube (A) displays Ehrlich's reagent alone (4-dimethylaminobenzaldehyde in acid), serving as a baseline control. Tube (B) demonstrates a negative result, typically a yellowish or orange color, after the addition of normal urine (or urine without elevated PBG). Tube (C) illustrates a positive result, characterized by a distinct change to a pink-red color, indicating the presence of elevated PBG in the urine of a patient during an acute porphyria attack.

LABORATORY DIAGNOSIS OF ACUTE PORPHYRIA

After a positive screening result, a definitive diagnosis of acute porphyria requires biochemical testing performed in appropriate and certified laboratories. The biochemical workup typically involves the analysis of three sample types: random (spot) urine, blood (specifically plasma), and feces. Levels of PBG and ALA are determined in urine. Total porphyrins and their fractionation (speciation of isomers) are assessed in both urine and feces. Blood samples are used to determine plasma porphyrin levels and total erythrocyte protoporphyrin concentration.[14,15,20] To prevent misleading results, samples should be collected as soon as possible after symptom onset.

Sample requirements and stability

Porphyrins (e.g., protoporphyrin) and porphyrin precursors (e.g., PBG) are light-sensitive, and improper sample handling or storage can lead to false-negative results. Samples are generally stable for up to 48 hours at 4°C when protected from light, and for at least one month at -20°C. PBG quantification should be performed promptly, as a 20% decrease in PBG has been observed after 2 days at room temperature, even when samples were protected from light.[20,21] Collection of a 24-hour urine specimen is discouraged because it: 1) unnecessarily delays diagnosis; 2) offers little, if any, advantage over a spot urine sample; 3) increases the risk of analyte degradation or loss during the collection period; 4) increases the risk of light exposure; and 5) increases the risk of incorrect storage conditions.[15] It is crucial to ensure that these biological samples are protected from light and appropriately refrigerated or frozen according to laboratory protocols.[21]

First-line tests: ALA and PBG quantitation

First-line laboratory testing for acute porphyria includes the measurement of ALA and PBG in a fresh random (spot) urine sample, protected from light and normalized to creatinine concentration (refer to Fig. 2). Although reference intervals are not fully harmonized between laboratories, many apply an upper reference limit for urinary PBG of approximately 1.5 μmol /mmol creatinine. Nevertheless, the hallmark of an acute porphyria attack is a significant elevation of PBG and ALA in urine (or plasma in anuric patients), typically at least four-fold above the upper

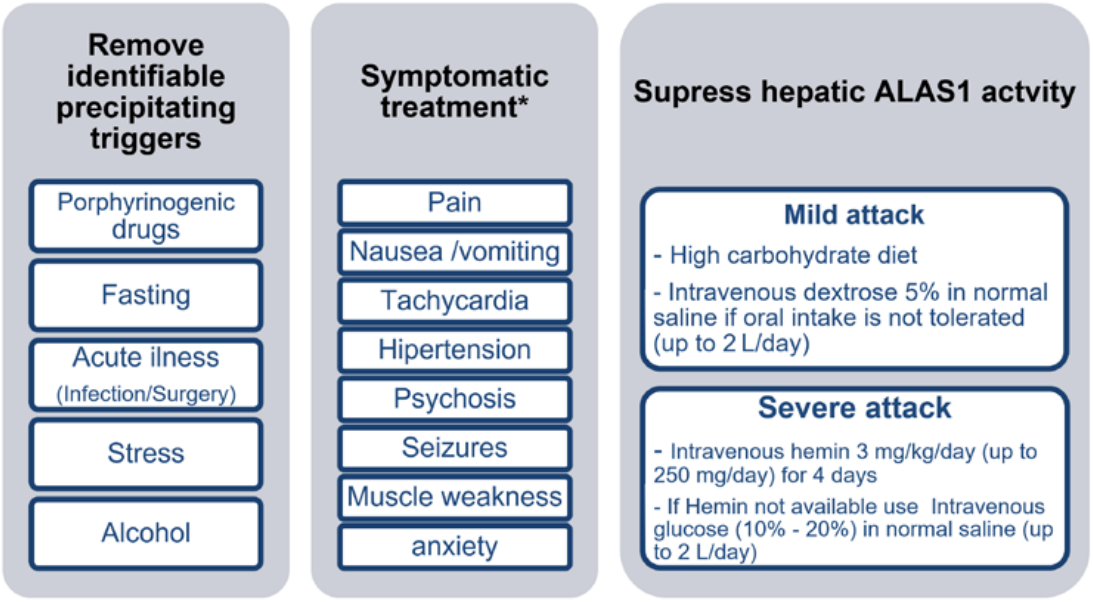

Figure 3: The three main pillars for acute porphyria attack management. This figure outlines the multifaceted approach to treating acute porphyria attacks, focusing on: 1) removing identifiable precipitating triggers; 2) providing symptomatic treatment; and 3) suppressing hepatic ALAS1 activity, with specific strategies tailored for mild and severe attacks.* Symptomatic relief must be achieved using appropriate supportive treatments with drugs confirmed to be safe for acute porphyria. Comprehensive databases listing safe drugs are available at www.drugs-porphyria.org and https://porphyriafoundation.org/drugdatabase/.

limit of normal.[9] A common pitfall in the diagnostic workup is to screen only for total urinary porphyrins without including the porphyrin precursors ALA and PBG. In most patients with an acute attack, PBG is increased to a greater extent than ALA. Isolated ALA elevations or an increased ALA to PBG ratio can be found in tyrosinemia type I, lead intoxication or ALA dehydratase deficiency porphyria (ALADP), an extremely rare form of porphyria. If urinary PBG and ALA levels are normal, an acute porphyric attack can generally be ruled out. Note that dilute urine samples (e.g., following administration of large volumes of intravenous fluids) can yield false-negative results if PBG concentration is expressed per unit volume. Therefore, results should always be reported as a ratio to urinary creatinine concentration.[9] A new urine sample should be requested if the creatinine level is below 2 mmol/L, indicating a very dilute sample.

Second-line tests: Differential diagnosis of acute porphyria

To further differentiate between the types of acute porphyrias, additional second-line testing is necessary. This differential diagnosis relies on measurements of total porphyrins and their specific isomer patterns in urine, feces, and plasma. Plasma porphyrin analysis (including fluorescence scanning) is particularly useful for variegate porphyria (VP) and has practical application in patients with renal failure where urine excretion is compromised.

In a normal urinary porphyrin excretion pattern, coproporphyrin predominates, with coproporphyrin isomer III being the most abundant; only traces of uroporphyrin are typically detected.[15,20] In patients with porphyria, urinary porphyrin excretion varies depending on the specific enzymatic defect underlying the type of porphyria and the stage of the disease. In AIP, a pattern of markedly elevated uroporphyrin (isomers I and III) and less pronounced elevations of coproporphyrin (predominantly isomer III, but also isomer I) is often observed, sometimes with a slight increase in heptacarboxylporphyrin. The urinary porphyrin profile in HCP is characterized by highly elevated excretion of coproporphyrin III, often with a moderate increase in uroporphyrin (both isomers I and III). However, the definitive differentiation of HCP typically requires fecal porphyrin analysis. In ALADP, urinary coproporphyrin III and ALA are significantly increased (refer to Table 1).[20]

Mild to moderate increases in total urinary porphyrins (often referred to as secondary porphyrinuria) are not specific for acute porphyria and can be observed in a wide range of other clinical conditions. These include hepatobiliary diseases (e.g., hyperbilirubinemia, Dubin-Johnson syndrome, Gilbert syndrome, Rotor syndrome), toxic exposures, alcoholism, and infections.[20,9] The finding of isolated secondary coproporphyrinuria is rarely indicative of an acute porphyria. It is important to recognize these secondary causes of porphyrin overproduction, as a lack of awareness can lead to misdiagnosis of porphyria.[20,22]

Regarding fecal porphyrins, a normal profile is characterized by relatively small amounts of protoporphyrin and coproporphyrin, with coproporphyrin III typically being the major

coproporphyrin isomer.[23] In AIP, fecal porphyrins are usually normal or only slightly elevated, but in HCP, there is a characteristic accumulation of coproporphyrin III in feces, leading to an increased coproporphyrin III / coproporphyrin I ratio (often >2, whereas normally it is <0.8).[24] In VP, both protoporphyrin and coproporphyrin (especially protoporphyrin) are typically elevated in feces. Additionally, a plasma porphyrin fluorescence emission peak at 626-628 nm is a hallmark of VP (Table 1).[25]

Given the potential for variability in the performance and interpretation of urine and fecal porphyrin fractionation, these analyses should ideally be performed in centers with an adequate workload to maintain analytical expertise. Measuring porphyrins in both urine and feces can be important to ensure that VP or HCP is not missed, particularly since urinary PBG excretion can return to normal levels within a few days of the clinical presentation of an acute attack.[20]

Third-line Tests: molecular analysis

Once the biochemical testing indicates acute porphyria, genetic testing should be performed in a laboratory experienced in distinguishing pathogenic mutations from incidental polymorphisms (Table 1).[14,23]

Discussion

The nonspecific nature of acute porphyria's clinical manifestations presents a significant diagnostic challenge, frequently resulting in misdiagnosis and delayed treatment, leading to considerable morbidity and mortality.[11,14] To address this critical challenge, this manuscript proposes a structured screening protocol targeting three high-risk patient groups in the Emergency Department (ED), patients presenting with acute abdominal pain, acute flaccid paralysis, and/or acute psychosis (particularly first episodes, atypical presentations, or treatment-resistant). The suspicion for acute porphyria in any of these groups is substantially increased by the presence of red flags, such as unexplained hyponatremia, hypertension, tachycardia, or urine color darkening upon light exposure. Biochemical testing is crucial for diagnosing acute porphyria attacks, specifically the measurement of the porphyrin precursors ALA and PBG, and the analysis of porphyrin profiles. The restricted availability of specialized biochemical tests for diagnosing acute porphyria often causes diagnostic delays of several days. The present discussion aims to analyse the practical impact of implementing this Hoesch-based protocol, evaluate potential barriers in the national context, and delineate its inherent limitations.

The primary practical impact of this protocol lies in optimizing the diagnostic and treatment workflow in the ED. By enabling ED physicians to rapidly screen suspected patients using the Hoesch test, a low-cost and easy-to-use tool, the protocol reduces the time to clinical decision-making. This allows for the prompt initiation of crisis management based on high clinical suspicion and a positive screening test. By expediting this process, the protocol significantly mitigates the risk of permanent neurological sequelae and fatal complications associated with delayed diagnosis. Furthermore, standardizing screening in the ED facilitates more efficient communication with reference laboratories, ensuring that samples for definitive confirmation are collected in crisis, maximizing result reliability, without delaying treatment initiation. Samples should be sent to experienced centers, namely those associated with International Porphyria Network (IPNET), as is the Instituto Nacional Ricardo Jorge in Porto.

Acute abdominal pain is one of the most common presenting complaints in the ED, accounting for approximately 10% of all ED admissions.[26] Due to its heterogeneous presentation and broad differential diagnosis, abdominal pain poses a significant clinical challenge in this setting. While common and life-threatening surgical and medical conditions must be diligently ruled out first, it is equally crucial not to overlook less frequent conditions.[26] Particularly when initial investigations are inconclusive or if the clinical picture presents with atypical features, clinicians must actively consider and investigate rarer causes, such as acute porphyrias. Diehl-Wiesenecker et al published a multicenter prospective screening project for acute porphyria in a real-life emergency department setting, demonstrating the feasibility of implementing a screening protocol for this rare disease.[27] In the study, over 653 patients aged 18 to 75 years with abdominal pain were screened, but only 68 patients met the inclusion criteria for porphyrin analysis due to restrictive criteria. During the first 15 months, patients had to present with severe abdominal pain (intensity on the visual analog scale ≥ 7) and prolonged abdominal pain (duration ≥ 4 hours), potentially missing those with moderate pain intensity or pain onset of less than 4 hours. Plasma fluorescence analysis was used for screening; however, this required sample shipment, as it is not widely accessible in most hospitals, leading to delays in obtaining results. Screening tools need to be widely available, easy to use, and cost-effective, and in an ED environment, the rapid delivery of test results is crucial for effective patient management.[23] The Hoesch test largely fulfils these essential criteria for ED screening. While the Hoesch test offers clear advantages for rapid screening, it also has a major limitation. The primary limitation stems from the nature of the Hoesch Test itself. As a qualitative screening method, it requires visual color assessment, making it operator-dependent and susceptible to false positives due to possibleinterference.[13,29] Crucially, the protocol will fail to identify patients with ALADP, who present with an increase only in ALA without a corresponding increase in PBG, the substrate detected by the Hoesch Test. Thus, while the protocol acts as a high-sensitivity tool for the most common acute porphyrias, it does not negate the need for a high index of clinical suspicion in atypical cases. All borderline situations still necessitate immediate sample collection for quantitative confirmatory testing.

Transposing this protocol into routine clinical practice is likely to encounter several barriers in Portugal. The first is the requirement for sufficient availability of the Hoesch Test, and standardized staff training, which may not be standard across all emergency laboratory settings. Secondly, while initial therapeutic decisions can be made in the ED, access to quantitative confirmatory biochemical tests still relies on sample shipment to national reference centers. Therefore, successful implementation of the protocol requires an initial investment in personnel training to raise the index of suspicion and ensure adequate hospitals implementation of this first-line screening.

Conclusion

Emergency departments play a pivotal role in establishing effective screening strategies for rare diseases, including acute porphyrias. This is essential for optimizing awareness and diagnostic acumen among physicians. Initiating the diagnostic work-up in the ED is the ideal setting when clinical suspicion arises, given that patients presenting during an acute crisis typically exhibit significantly elevated levels of porphyrinogenic intermediates, thereby maximizing the sensitivity and yield of immediate screening tools. The implementation of robust screening protocols will support a national and standardized diagnostic pathway, ultimately improving patient outcomes, especially with the emergence of prognosis-modifying therapies. Therefore, this protocol strongly advocates for the immediate, routine implementation of the Hoesch test as the critical initial screening tool in the ED. This approach provides a feasible, rapid, and cost-effective means to overcome diagnostic delays, enabling timely confirmation and the prompt initiation of appropriate therapeutic management. ■

Apresentações Anteriores/Previews Presentations

A poster with this protocol was presented and discussed at the International Congress of Porphyrins and Porphyrias (ICPP), September 21-25, 2024; Pamplona, Spain

Contributorship Statement

SM, FF - Conception, drafting, critical review and final approval.

AG, JD, CL, MB - Critical review and final approval.

AO - Conception, critical review and final approval.

All authors approved the final draft.

Declaração de Contribuição

SM, FF - Concepção, redação, revisão crítica e aprovação final.

AG, JD, CL, MB - Revisão crítica e aprovação final.

AO - Concepção, revisão crítica e aprovação final.

Todos os autores aprovaram a versão final a ser publicada.

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