Med Clin (Barc). 2017;xxx(xx):xxx–xxx

MEDICINA CLINICA

www.elsevier.es/medicinaclinica

Consensus conference

Practice guidelines for the emergency treatment of thrombotic microangiopathy☆,☆☆

Samuel Romero[a,*], Amparo Sempere[a,b], Inés Gómez-Seguí[a,b], Elena Román[c], Andrés Moret[a], Rosa Jannone[d], Iván Moreno[e], Santiago Mendizábal[c], Jordi Espí[f], Ana Peris[f], Rafael Carbonell[g], José Cervera[a,b], Javier Pemán[h], Santiago Bonanad[a], Javier de la Rubia[i,j], Isidro Jarque[a,b], Group of Microangiopatía Trombótica del Hospital Universitario y Politécnico La Fe de Valencia

[a] *Servicio de Hematología, Hospital Universitario y Politécnico La Fe, Valencia, Spain*
[b] *CIBERONC (Centro de Investigación Biomédica en Red de Cáncer), Spain*
[c] *Sección de Nefrología Pediátrica, Hospital Universitario y Politécnico La Fe, Valencia, Spain*
[d] *Servicio de Medicina Intensiva, Hospital Universitario y Politécnico La Fe, Valencia, Spain*
[e] *Servicio de Medicina Interna, Hospital Universitario y Politécnico La Fe, Valencia, Spain*
[f] *Servicio de Nefrología, Hospital Universitario y Politécnico La Fe, Valencia, Spain*
[g] *Servicio Orgánico de Urgencias, Hospital Universitario y Politécnico La Fe, Valencia, Spain*
[h] *Servicio de Microbiología, Hospital Universitario y Politécnico La Fe, Valencia, Spain*
[i] *Servicio de Hematología, Hospital Universitario Doctor Peset, Valencia, Spain*
[j] *Universidad Católica de Valencia "San Vicente Mártir", Valencia, Spain*

ARTICLE INFO

Article history:
Received 26 September 2017
Accepted 18 January 2018
Available online xxx

Keywords:
Thrombotic microangiopathy
Thrombocytopaenia
Microangiopathic haemolytic anaemia
Plasma exchange

ABSTRACT

Background and aim: The term thrombotic microangiopathy (TMA) involves a heterogeneous group of diseases that can be overwhelming or invalidating, with an acute development, characterized by microangiopathic haemolytic anaemia and thrombocytopaenia. Its management during its initial hours is essential to improving the prognostic of these patients. The aim of this review is to give recommendations about the optimization of TMA initial treatment and to accelerate the aetiological diagnosis.
Patients and methods: We provide a practice guideline based on four steps for the initial management of TMA: diagnosis of suspicion, syndromic confirmation, emergent treatment and complementary tests.
Results: The detection of microangiopathic haemolytic anaemia (characterized by elevated reticulocytes, LDH and indirect bilirubin, negative direct Coombs test and schistocytes in peripheral blood), and thrombocytopaenia not explained by other secondary aetiologies confirm the syndromic diagnosis of microangiopathic haemolytic anaemia and thrombocytopaenia (MAHAT). These patients require admission to an Intensive Care Unit to initiate plasma exchange therapy as soon as possible, ideally within the first 4–8 h. Prior to this, samples for ADAMTS13 and complement study should be obtained. Finally, it is important to request the complementary tests necessary to have a correct aetiological diagnosis.
Conclusions: Adherence to the agreed recommendations in this guideline will improve therapeutic results by facilitating cooperation between different specialists involved in TMA management.

Guía práctica de tratamiento urgente de la microangiopatía trombótica

Palabras clave:
Microangiopatía trombótica
Trombocitopenia

RESUMEN

Antecedentes y objetivo: El término microangiopatía trombótica (MAT) incluye un grupo heterogéneo de enfermedades potencialmente mortales o invalidantes, rápidamente evolutivas, caracterizadas por anemia hemolítica microangiopática y trombocitopenia. La actuación en las primeras horas es crucial

☆ Please cite this article as: Romero S, Sempere A, Gómez-Seguí I, Román E, Moret A, Jannone R, et al. Guía práctica de tratamiento urgente de la microangiopatía trombótica. Med Clin (Barc). 2018. https://doi.org/10.1016/j.medcli.2018.01.013

☆☆ Endorsed by the Valencian Association of Haematology and Hemotherapy (AVHH), the Internal Medicine Society of the Valencian Community (SMICV), the Valencian Society of Intensive and Critical Care Medicine and Coronary Units (SOVAMICYUC), the Valencian Society of Nephrology (SVN), the Spanish Society of Emergency Medicine, Comunidad Valenciana (SEMES-CV) and the Valencian Society of Clinical Microbiology (SVAMC).

* Corresponding author.
E-mail address: romero_sam@gva.es (S. Romero).

2387-0206/

Anemia hemolítica microangiopática
Recambio plasmático

para mejorar el pronóstico de los pacientes. El objetivo de esta revisión es proporcionar recomendaciones orientadas a optimizar el tratamiento inicial de la MAT y agilizar el diagnóstico etiológico.
Pacientes y métodos: Se diseña una guía práctica en la cual se diferencian cuatro apartados en el abordaje inicial de las MAT: sospecha diagnóstica, confirmación sindrómica, tratamiento urgente y estudios complementarios.
Resultados: La detección de anemia hemolítica microangiopática (caracterizada por aumento de reticulocitos, LDH y bilirrubina indirecta, Coombs directo negativo y esquistocitos en el frotis de sangre periférica) y trombocitopenia no justificable por otras causas secundarias confirma el diagnóstico sindrómico de anemia hemolítica microangiopática y trombocitopenia (AHMAT). Estos pacientes requieren ingreso en la unidad de cuidados intensivos para iniciar lo antes posible el recambio plasmático, preferiblemente en las primeras 4–8 h. Antes de realizar el recambio plasmático deben extraerse las muestras para el estudio de ADAMTS13 y de complemento. Finalmente, es importante solicitar las pruebas complementarias necesarias para obtener un correcto diagnóstico etiológico.
Conclusiones: La puesta en práctica de las recomendaciones consensuadas en esta guía permitirá mejorar los resultados terapéuticos al facilitar la cooperación de los distintos especialistas implicados en la atención de las MAT.

Introduction

Thrombotic microangiopathies (TMA) constitute a heterogeneous group of diseases of high diagnostic complexity whose common denominator is the endothelial lesion with formation of thrombi in microcirculation that leads to tissue ischaemia with systemic clinical consequences dependent on the organs involved. They can be potentially very serious and all of them have thrombocytopenia and microangiopathic haemolytic anaemia (MHA) in common. It is characterized by the detection of schistocytes (fragmented erythrocytes) in blood smear and a negative direct Coombs (DC) test.[1–3]

The classification of these processes is complex, since the diverse entities that present with TMA can be inherited or acquired, can affect children or adults, can begin acutely or subacutely and have different prognosis and treatment. Also, this classification has often been based on clinical and pathogenic criteria that may require specialized studies in reference laboratories with results that are not available until days or months after the initial suspicion. However, the overlapping of clinical and laboratory findings between the different entities that cause TMA, especially in the first hours of its development, makes it necessary to address these diseases jointly,[4] allowing a fast-therapeutic action that will, in most cases, determine the vital prognosis of the patient.[1,2,5,6]

According to the aetiology of the process, two groups have been identified, whose limits are not well defined:

- Primary TMA: of well-known pathophysiology on which the treatment is based and which include the different varieties of thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemic syndrome (HUS).
- Secondary TMA: associated with an identified etiological agent (drugs, infections, neoplasms, transplantation, nephropathies, autoimmune diseases, etc.) whose treatment consists mainly of controlling the underlying causes.

Guidelines rationale and objectives

TMA in general, but especially the primary one, is a vital emergency that requires rapid diagnosis and adequate treatment which determine the progression of patients. Given the difficulty of obtaining an established diagnosis in the first hours, to begin with, they must be globally addressed as a *microangiopathic haemolytic anaemia and thrombocytopenia* (MHAT) syndrome until an established diagnosis is available[3] (Fig. 1). One of the most common problems is the delay between the moment the patient starts receiving medical attention until diagnosis of TMA, which entails the delay of the treatment and sometimes irreversible microangiopathy complications. Given the clinical-biological suspicion of a severe MHAT syndrome, it is indicated to start plasma exchange (PE) as soon as possible, and it is advisable to carry it out in the first hours after the arrival of the patient in the emergency department, which improves the response and, therefore, the prognosis of this disease.[1–7]

There are guidelines focused on the study of diagnosis and treatment of TMA,[1,2,8] but there are no specific guidelines for emergency treatment during the first hours after being suspected. In this review we provide a series of recommendations aimed specifically at optimizing the initial approach to these conditions that serve as a basis for specialists regarding the diagnosis and urgent treatment of patients with TMA. Fig. 2 shows the steps to follow in the diagnosis and treatment of TMA that will serve as guidelines in this protocol.

Objectives

- Rapid and correct TMA study completion during the emergency period.
- Provide recommendation guidelines for the early identification and urgent treatment of patients with suspected TMA.
- Organize the extraction of samples that speed up the final etiological diagnosis.

Methodology

In order to tackle the TMA more agile and efficiently in our centre, the Thrombotic Microangiopathy Group of the La Fe University and Polytechnic Hospital was created. The working group initially involved in the preparation of the guidelines was composed of specialists in haematology, paediatrics, intensive medicine, internal medicine, nephrology, hospital emergency service physicians and microbiology. To develop and evaluate the methodological quality of this consensus document, the authors followed the criteria established in the AGREE II tool (Annex 1).[9] A literature search was carried out aimed at the emergency treatment of TMA in Pubmed using the key terms "thrombotic microangiopathy", selecting the most relevant literature published until September 2017. The authors analyzed all the information collected and established a series of recommendations based on the evidence obtained. To classify the quality of the literature reviewed, the *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) system was used (Table 1).[10,11] Of the areas in which no scientific