Task force for the diagnosis of thrombotic microangiopathy

Força-tarefa para o diagnóstico de microangiopatia trombótica

DOI:10.34117/bjdv7n12-315

Recebimento dos originais: 12/11/2021
Aceitação para publicação: 09/12/2021

Renata Oliveira Santos
Residente em Clínica Médica (Hospital Santa Casa de Misericórdia de Maceió)
Universidade Estadual de Ciências da Saúde de Alagoas (UNCISAL)
R. Dr. Jorge de Lima, 113 - Trapiche da Barra, Maceió - AL, 57010-300
E-mail: renataoliveira216@gmail.com

Andrea Vanessa da Cunha Lima
Bacharel em Medicina pela UNCISAL
UNCISAL
R. Dr. Jorge de Lima, 113 - Trapiche da Barra, Maceió - AL, 57010-300
E-mail: andrealima392@gmail.com

Attie Dalbony França
Bacharel em Medicina pela Universidade Federal de Alagoas (UFAL)
UFAL
Campus A.C. Simões, Av. Lourival Melo Mota, s/n - Tabuleiro do Martins, AL, 57072-900
E-mail: daboniattie@gmail.com

Julia Matida de Melo Silvestre
Bacharel em Medicina pela UFAL
UFAL
Campus A.C. Simões, Av. Lourival Melo Mota, s/n - Tabuleiro do Martins, AL, 57072-900
E-mail: juliammsilvestre@gmail.com

Thiago Araujo Pontes
Acadêmico em Medicina pelo Centro Universitário CESMAC
CESMAC
R. da Harmonia - Farol, Maceió - AL, 57081-350
E-mail: thiagoapontes@gmail.com

André Falcão Pedrosa Costa
Doutor em Nefrologia pela Universidade de São Paulo (USP)
UNCISAL, UFAL e CESMAC
R. da Harmonia - Farol, Maceió - AL, 57081-350
E-mail: falcaopedrosa@uol.com.br

ABSTRACT
Background: Thrombotic microangiopathy triggers microangiopathic hemolytic anemia, thrombocytopenia, and organic injuries. It is a rare and serious condition that demands specific approaches and strategies to recognize it promptly, especially in critically ill patients. The task force could be an effective model. Methods: An evaluative study of the impact of a task force in establishing a routine for the diagnosis of TMA in ICUs. A standard flowchart was used for 90 consecutive days and a low platelet count was the driver for the collection of epidemiological and laboratory data. Suspicion of typical HUS was proven after analyzing haptoglobin, LDH, creatinine, ADAMTS-13 enzyme, and Shiga toxin levels. Meetings were also held with ICU personnel and the self-explanatory flowchart was fine tuned. Results: There were 490 patients (55.9% male and 44.1% female) aged 59.5 ± 21.13 years. Forty-two percent of patients in the sample had thrombocytopenia. Out of the 42 patients, five (1.02%) had TTP, three (0.6%) were presumed to have atypical HUS, and none had typical HUS. The task force remained in touch with researchers to assess diagnoses and three other suspected cases of atypical HUS underwent specific treatment.Discussion: Only 1.62% of the sampled patients had TMA. Despite its complexity, the task force model is useful in situations in which higher technology is the norm. Conclusion: The use of a task force has proven to be effective in establishing a diagnostic practice for a health condition deemed rare or exceedingly rare.

Keywords: Thrombotic microangiopathy; task force, microangiopathic hemolytic anemia, intensive care unit.

RESUMO
Antecedentes: A microangiopatia trombótica desencadeia anemia hemolítica microangiopática, trombocitopenia, e lesões orgânicas. É uma condição rara e grave que exige abordagens e estratégias específicas para a reconhecer prontamente, especialmente em doentes críticos. A task force poderia ser um modelo eficaz. Métodos: Um estudo avaliativo do impacto de uma task force no estabelecimento de uma rotina para o diagnóstico de TMA em UCI. Um fluxograma padrão foi utilizado durante 90 dias consecutivos e uma baixa contagem de plaquetas foi o condutor para a recolha de dados epidemiológicos e laboratoriais. A suspeita de HUS típico foi provada após análise da haptoglobina, LDH, creatinina, enzima ADAMTS-13, e níveis de toxina Shiga. Foram também realizadas reuniões com o pessoal da UCI e o fluxograma auto-explicativo foi bem afinado. Resultados: Havia 490 pacientes (55,9% homens e 44,1% mulheres) com 59,5 ± 21,13 anos. Quarenta e dois por cento dos doentes da amostra apresentavam trombocitopenia. Dos 42 pacientes, cinco (1,02%) tinham TTP, três (0,6%) presumivelmente tinham HUS atípicas, e nenhum tinha HUS típicas. A task force permaneceu em contacto com investigadores para avaliar diagnósticos e três outros casos suspeitos de HUS atípicas foram submetidos a tratamento específico.
Discussão: Apenas 1,62% dos pacientes amostrados tinham TMA. Apesar da sua complexidade, o modelo da task force é útil em situações em que a tecnologia superior é a norma. Conclusão: A utilização de um grupo de trabalho provou ser eficaz no estabelecimento de uma prática de diagnóstico para uma condição de saúde considerada rara ou excessivamente rara.

Palavras-chave: Microangiopatia trombótica, task force, anemia hemolítica microangiopática, unidade de cuidados intensivos.

1 INTRODUCTION

Thrombotic microangiopathies (TMAs) are hereditary or acquired syndromes of a sudden or gradual onset and that can affect all age groups. The most common phenotypic manifestation is Thrombotic Thrombocytopenic Purpura (TTP) – which may be congenital or acquired and is caused by the reduction in the activity of the ADAMTS13 enzyme, a metalloprotease that cleaves the von Willebrand Factor (vWF). This then leads to disseminated platelet aggregation, causing severe manifestations of TMAs – ischemia of organs and tissues. Typical Hemolytic-Uremic Syndrome (STEC-HUS) is linked to the presence of Shiga Toxin, which is mainly produced by the E. coli strain O157:H7. It is generally a self-limiting condition that starts with diarrhea and may evolve to systemic complications such as renal failure. Atypical Uremic Hemolytic Syndrome (HUS) is related to the uncontrolled activation of the complement system resulting from genetic alterations to the inhibitory factors of this system such as factor H. or even by increased activation of certain components of this system. TMAs may also be triggered by drugs such as calcineurin inhibitors, by infections such as HIV, by malignant hypertension, or they may even be linked to changes in coagulation factors. Despite the pathophysiologic peculiarities of TMAs, the diagnosis and treatment have one element in common: they are rare diseases that affect only about 0.5% of the population and that require a specific therapeutic approach. TMAs provide the substrate for the thickening of the endothelium, edema, and the detachment of its underlying membrane. Molecular analysis showed an increase in the expression of vWF – responsible for attracting platelets and causing microthrombi, which occlude the microvasculature and cause ischemia in several organs[2,6-8,13,19,20].

Lab testing confirms TMA when hemolytic anemia is detected (reduction and elevation of haptoglobin and indirect bilirubin levels, respectively) using the negative direct Coombs test. Microangiopathic-type anemia (presence of schistocytes in peripheral blood) also points to TMA. Another universal finding is thrombocytopenia, with more pronounced levels generally in TTP cases. Target organ damage completes the textbook triad of TMAs. The signs are elevated levels of lactate dehydrogenase (LDH) and creatinine, neurological symptoms, or acute symptoms in the cardiovascular, gastrointestinal, and other systems. For the differential diagnosis, the ADAMTS13 level is useful because its activity is greatly reduced in cases of TTP and it is normal in other cases. In typical HUS, stool analysis reveals the presence of Shiga toxin. Since the genetic analysis of the regulatory factors of the complement cascade has no predictive power, the

diagnosis of aHUS in the presence of irrefutable evidence of TMA is made by excluding other entities. Greater involvement of the nervous system in TTP and higher prevalence of renal injury in aHUS cannot be definitive elements in the differential diagnosis since many patients have similar features for both conditions. In patients affected by TMA associated with other diseases such as Hypertensive Disease of Pregnancy and Malignant Hypertension, or patients taking calcineurin inhibitors, there is greater complexity because these conditions are known as complement amplifiers[2,8,9,13,20]. Clinical evolution data are usually useful for the correct differential diagnosis.

Regardless of different pathophysiological bases and elevated morbidity and mortality, TMAs require specific therapeutic approaches: plasmapheresis associated with corticosteroids is effective in the treatment of most TTP patients; cases of typical HUS are only managed with clinical support, which includes dialysis when severe acute kidney injury occurs. However, aHUS does not respond adequately to such approaches and the recommended therapy is the use of eculizumab, a monoclonal antibody that irreversibly inhibits C5a. Thus, given the great diagnostic challenges and the rarity of its incidence, a project was designed along the lines of a task force with the main objective of introducing routine diagnosis of TMAs among critically ill patients.

We know that the method of employing a research model based on a task force has already been used in several prospective studies in order to define in a flowchart the criteria for the diagnosis of certain diseases in their early stages, thus contributing directly to a more accurate prognosis and a better therapeutic response. The task forces were initially built around evidence-based strategies. As the need arose, they became more refined to better recognize the growing number of rare and unknown diseases and were adapted to the reality of each healthcare service[14,15].

2 METHODS

The project received approval from the Research Ethics Committee (CEP) of the State University of Health Sciences of Alagoas – UNCISAL. (CAAE: 42263815.0.0000.5011).

The task force model study was carried out for ninety consecutive days and the primary data were derived from the investigation of the presence of thrombocytopenia (defined by a platelet count below 150,000 / mm³ or by a reduction greater than 25% from its previous basal levels, either sporadic or sustained). Diagnostic exams followed a standardized flowchart (Figure 1). After confirmation of non-immune microangiopathic

hemolysis (reduction of haptoglobin, presence of schistocytes, and negative indirect Coombs test), a blood sample was collected for measurement of ADAMTS13 activity (equal to or lower than 5% was indicative of TTP). Stool analysis to detect the presence of Shiga-toxin was carried out if the clinical status was suggestive of STEC-HUS. Laboratory data were analyzed at each hospital; the ADAMTS13 and Shiga-toxin analyses were performed on blood samples sent to the Mayo Clinic Laboratory, USA.

All patients admitted to general adult ICUs in the city of Maceió were evaluated daily for a period of ninety consecutive days. All inpatients were included because exclusion criteria were not proposed for a prevalence study about a rare clinical condition.

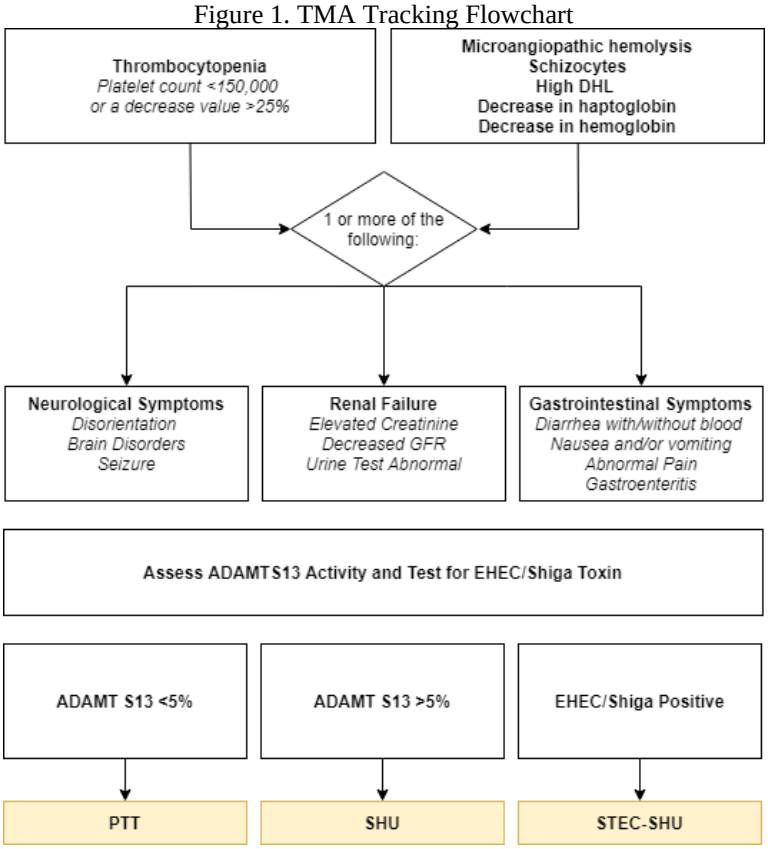
The daily presence of assistant researchers in the ICUs was an important element for the screening of suspected cases. To confirm the diagnosis of TMA, a specialist was contacted whenever suspected cases were identified. In case of a positive diagnosis, the specialist took the blood samples that were to be sent to the Mayo Clinic in the USA for analysis of ADAMTS13 or Shiga-toxin. The specialist was also responsible for assisting the attending physician in diagnosing TMA and for holding academic conferences to promote a routine for the diagnosis of TMA in ICUs.

The researchers had access only to the patients' medical records. The applicability of the flowchart (Figure 1) for identifying suspected cases of TMA was assessed through the collection of daily laboratory data. Sociodemographic data, such as sex, age, and race were collected. Also recorded were clinical data, such as primary diagnosis, associated diseases, use of mechanical ventilation (MV), vasoactive drugs (VAD), dialysis, urinary volume, and outcomes (discharge, transfer, or death). The laboratory data collected were platelet count and levels of hemoglobin, urea, creatinine, sodium, potassium, calcium, phosphorus, albumin, pH, pO2, and pCO2. Analyzed data were recorded as the mean or the median.

Thus, the task force came up with a clinical model that included longitudinal and prospective prevalence. A diagnostic flowchart was applied to help detect cases. The task force was also engaged in the training of professionals from the participating units with classes and educational posters. The specialist (researcher in charge) provided ongoing consulting and assistance in the differential diagnosis of suspected cases.

The program used to analyze the data was Microsoft Excel® version 2013. Prevalence was estimated using the traditional formula. The number of TMA cases diagnosed before and after the arrival of the task force gave a measure of the introduction of routine diagnosis of TMA.

Figure 1. TMA Tracking Flowchart



Font: made by the authors.

3 RESULTS

A total of 490 medical records were evaluated. They came from the general adult ICUs in the following health care facilities – Hospital Helvio Auto (HEHA), Hospital Geral do Estado de Alagoas (HGE – State General Hospital), Santa Casa de Misericordia de Maceio (SCMM), Hospital Universitario Professor Alberto Antunes, Hospital Unimed Maceio, Hospital Sanatório, Hospital Memorial Arthur Ramos (HMAR), Hospital Vida, and Hospital do Açucar.

Males (55.92%) were more predominant than females (44.08%). The mean age was 59.5 years (± 21.13), ranging from 13 to 97 years. Most patients were between the ages of 64 and 80.

The bulk of the patients were discharged from the ICU (69.59%) and 24.28% of them died. Patients whose hospital stay was extended or who were transferred to other facilities accounted for 4.48% and 1.63% of the total, respectively. Other clinical data are shown in Table 1 and 2.

The leading causes of hospitalization were sepsis and stroke (8% each), postoperative complications and lung disease (7% each), and traumatic brain injury – TBI (6%). A prevalence of comorbidities was observed in 29% of cases: diabetes mellitus –

DM (19%), chronic kidney disease – CKD (11%) and heart disease (10%) were the most common comorbidities. The least frequent comorbidities were obesity and Alzheimer's Disease – AD (2% each), and dyslipidemia (DLP) (1%).

Laboratory test results are detailed in Table 1. Mean platelet count was 233.9 ± 124.79 x10³ / mm³ (lowest at 5 x10³ / mm³ and highest at 774 x10³ / mm³). Mean hemoglobin was 10.37 ± 2.12 g / dL, ranging from 5.4 to 17.5 g / dL. Serum creatinine level was 2.12 ± 2.36 mg / dL (0.2 - 17.08 mg / dL).

Thrombocytopenia was observed in 206 patients, i.e., 42.04% of the study population. It was also more commonly seen in male (60.68%) than in female patients (39.32%). Mean age was 60.23 ± 20.1 years.

The bulk of the patients were discharged (65.53%) and 30.58% of them died. Patients whose hospital stay was extended or who were transferred to other facilities accounted for 3.4% and 0.49% of the total, respectively. Other clinical data are shown in Table 1.

The leading causes of hospitalization for patients presenting with thrombocytopenia are stroke and pulmonary diseases (10% of cases each), sepsis (9%), TBI (8%), and postoperative complications and other infectious diseases (7% each). The leading comorbidities in patients with thrombocytopenia are hypertension (28%), DM (22%), CKD (11%), sequelae of heart disease (7%) and sequelae of stroke (7%).

Laboratory test results showed a mean platelet volume of 149.46 ± 77.02 x10³ / mm³ (lowest at 5 x10³ / mm³ and highest at 413 x10³ / mm³). Mean hemoglobin was 10.23 ± 2.05 g / dL, ranging from 5.4 to 17.2 g / dL. Serum creatinine level was 2.15 ± 2.21 mg / dL (minimum of 0.31 mg / dL and maximum of 16.97 mg / dL). Other laboratory results can be found in Table 2.

Three patients (2 women and 1 man) with presumptive diagnosis of HUS were identified during the time of the study, which constituted 0.61% of the sample and 1.45% of patients with thrombocytopenia. They were using mechanical ventilation – (MV) and undergoing stereotactic radiation therapy (SRT). One of them was using some form of deep vein arterialization – (vasoactive medication – VM). Hypoalbuminemia and elevation of nitrogenous slags were observed in all three patients, who eventually died.

The diagnosis of TTP was established in five patients (1.02% of the total sample or 2.42% of the patients with thrombocytopenia), all of whom had ADAMTS13 activity lower than 5%. Patients from the other group underwent plasmapheresis and required MV. Of these, only one did not need DVA and three underwent hemodialysis. In addition

to hyperkalemia, hypoalbuminemia, and sodium disturbances, elevations were seen in serum urea and creatinine levels.

During the study we did not find patients with a presumptive diagnosis of typical hemolytic uremic syndrome (STEC-HUS).

We observed a general prevalence of Thrombotic Microangiopathy (TMA) in 1.63% of the patients evaluated. Its prevalence among patients with thrombocytopenia was 3.88%.

Table 1. Leading causes of hospitalization and the prevalence of comorbidities.

Comorbidities	%	Causes	%
Hypertension	28%	Stroke	8%
Diabetes mellitus	19%	Sepsis	10%
Chronic kidney disease	11%	Postoperative complications	7%
Sequelae of Heart disease	10%	Lung disease	7%
Sequelae of Stroke	7%	Traumatic brain injury	6%
Obesity	2%	Other infectious diseases	7%
Alzheimer's Disease	2%		
Dyslipidemia	1%		

Font: made by the authors.

Table 2. Leading causes of hospitalization and the prevalence of comorbidities for patients with thrombocytopenia.

Causes	%	Comorbidities	%
Stroke	10%	Hypertension	28%
Pulmonary diseases	10%	Diabetes mellitus	22%
Sepsis	9%	Chronic kidney disease	11%
Traumatic brain injury	8%	Sequelae of Heart disease	7%
Postoperative complications	7%	Sequelae of Stroke	7%
Other infectious diseases	7%		

Font: made by the authors.

4 DISCUSSION

The present study was aimed at assessing the prevalence of TMA in a population of critically ill patients who had been hospitalized in the various ICUs in the city of Maceio during the data collection period set in a task force format.

The use of the standard flowchart (Figure 1) in the detection of TMA was of fundamental importance for the resolution of suspicious cases, as well as for spreading the idea of routine diagnosis concerning this disease. Studies carried out by task forces have long been used to promote strategies that strengthen the association between an early diagnosis and a good therapeutic approach in order to reduce the rate of fatal outcomes in conditions with high lethality and with persistent diagnostic hurdles[14,20].

Indeed, as seen in the literature, TMAs are rare, rapidly evolving, and often fulminating conditions that require both an early and accurate diagnosis. Thus, it is also fundamental to establish the differential diagnosis, since each malady has its very specific treatment[4,5,20,22,24]. Current literature shows diagnoses of thrombocytopenia, hemolytic anemia, fever, renal failure, and neurological changes[2,8,13,20], which were found in patients who had had a presumptive diagnosis.

The prevalence of TMA places it among rare clinical conditions, which is consistent with our findings: prevalence of 1.63%. Concurrently, there was a higher prevalence of TTP (1.02%) in relation to aHUS (0.61%). The former, predominant among men, is an overall condition that affects the activity of the ADAMTS13 enzyme and that culminates in a defect in the cleavage of Von Willebrand multimers, thus leading to the formation of thrombi (predominantly platelets) and vascular occlusion. The most effective therapy in cases of acquired TTP 6,7 is plasmapheresis associated with immunosuppression. The latter leads to greater renal involvement, which increases the need for SRT, and is slightly more predominant in females. The currently recommended therapy is anti-C3b monoclonal antibody, eculizumab[9,19,23]. In those cases with a strong suspicion of aHUS, death came before a diagnosis was confirmed, which suggested a possible delay in the clinical diagnosis in spite of the goals defined in the flowchart. However, within the first year after the end of the study, three patients were diagnosed in time and eculizumab was used to treat them.

5 CONCLUSION

Despite being an extremely rare clinical entity, the use of a task force protocol helped to elucidate cases of TMA by taking thrombocytopenia as the initial diagnostic finding and following the steps defined in a specific flowchart.

Those cases diagnosed and still undergoing treatment after completion of our study demonstrate that this proposed task force model is, in fact, effective in implementing a routine for the diagnosis of TMAs.

6 IMAGE AND TABLES DESCRIPTIONS

IMAGE 1. TMA Tracking Flowchart

Diagnosis of TMA requires certain laboratory signs, along with evidence of involvement of at least one organ system. Three of these organ systems are presented here, but all tissues are susceptible to injury with the development of clinical cases related

to microthrombosis and ischemia (the only potential exception is the lungs, which are rarely affected by TTP). In some of the hematological parameters, thrombocytopenia is characteristically severe in TTP, while in Hemolytic Uremic Syndrome, the percentage of platelets is higher and may be almost normal at presentation.

TABLE 1. Clinical data (sampling and thrombocytopenic)

A comparative clinical data between sampling and the thrombocytopenic group.

TABLE 2. Laboratory tests results (sampling and thrombocytopenic)

An estimated average of laboratory tests results between sampling and thrombocytopenic patients' group.

REFERENCES

1. Barbour T. et al. (2012). Thrombotic microangiopathy and associated renal disorders. *Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association*, *27*(7), 2673–2685.

2. Campo Y. et al. (2000). Síndrome hemolítico urémico: Aspectos epidemiológicos y patogénicos. *Revista Cubana de Pediatría*, *72*(3), 203–213.

3. Caprioli J. et al. (2006). Genetics of HUS: the impact of MCP, CFH, and IF mutations on clinical presentation, response to treatment, and outcome. *Blood*, *108*(4), 1267–1279.

4. Celis M., Salas P. & Ostaiza, P. (2015). Microalbuminuria en pacientes pediátricos con diagnóstico de síndrome hemolítico urémico. *Revista Chilena de Pediatría*, *86*(2), 92–96.

5. Domingues R.B. et al. (2003). Disseminated cerebral thrombotic microangiopathy in a patient with adult's still disease. *Arquivos de neuro-psiquiatria*, *61*(2A), 259–261.

6. Fagundo J.C. et al. (2003). Síndrome hemolítico urémico. *Revista Cubana de Hematología, Inmunología y Hemoterapia*, *19*(2-3).

7. George J.N. & Nester C.M. (2014). Syndromes of thrombotic microangiopathy. *The New England journal of medicine*, *371*(7), 654–666.

8. Goldraich N.P. (1997). Síndrome hemolítico-urêmica e suas diferentes formas de apresentação: uma patologia atual na Nefrologia. *Jornal Brasileiro de Nefrologia*, Comentário Editorial. 19(3), 294–300.

9. Gupta M., Feinberg B.B. & Burwick R.M. (2018). Thrombotic microangiopathies of pregnancy: Differential diagnosis. *Pregnancy hypertension*, *12*, 29–34.

10. Ikeda T. et al. (2016). Two cases of kidney transplantation-associated thrombotic microangiopathy successfully treated with eculizumab. *Nephrology (Carlton, Vic.)*, *21 Suppl 1*, 35–40.

11. Joly B.S., Coppo P. & Veyradier A. (2017). Thrombotic thrombocytopenic purpura. *Blood*, *129*(21), 2836–2846.

12. Laurence J. (2012). Atypical hemolytic uremic syndrome (aHUS): making the diagnosis. *Clinical advances in hematology & oncology: H&O*, *10*(10 Suppl 17), 1–12.

13. Morales M.F. & Castro M.M. (2013). Púrpura trombocitopénica trombótica: Informe de un caso y revisión de la fisiopatología. *Revista de la Facultad de Medicina (México)*, *56*(1), 30–38.

14. North Carolina Institute of Medicine (2012). Task force on Chronic Kidney Disease: Addressing Chronic Kidney Disease in North Caroline. NCIOM Chronic Kidney Disease Update.

15. North Carolina Institute of Medicine (2016). Task force on Evidence-Based Strategies. 2016 Updates to recommendations.

16. Román E. et al. (2017). Secondary thrombotic microangiopathy and eculizumab: A reasonable therapeutic option. Microangiopatía trombótica secundaria y eculizumab: una opción terapéutica razonable. *Nefrologia : publicacion oficial de la Sociedad Espanola Nefrologia*, *37*(5), 478–491.

17. Saha M., McDaniel J.K. & Zheng X.L. (2017). Thrombotic thrombocytopenic purpura: pathogenesis, diagnosis and potential novel therapeutics. *Journal of thrombosis and haemostasis: JTH*, *15*(10), 1889–1900.

18. Scully M. et al. (2012). Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. British Journal of Haematology, 158: 323–335.

19. Shatzel J.J. & Taylor J.A. (2017). Syndromes of Thrombotic Microangiopathy. *The Medical clinics of North America*, *101*(2), 395–415.

20. Silvariño R. et al. (2014). Síndrome urémico hemolítico atípico: ¿una entidad subdiagnosticada? Características clínicas y analíticas a propósito de dos casos. *Revista Médica del Uruguay*, *30*(1), 56–64.

21. Skerka C. et al. (2013). Complement factor H related proteins (CFHRs). *Molecular immunology*, *56*(3), 170–180.

22. Song D. et al. (2013). The spectrum of renal thrombotic microangiopathy in lupus nephritis. *Arthritis research & therapy*, *15*(1), R12.

23. Vaisbich M.H. (2014). Hemolytic-Uremic Syndrome in childhood. *Jornal brasileiro de nefrologia : 'orgao oficial de Sociedades Brasileira e Latino-Americana de Nefrologia*, *36*(2), 208–220.