University of Groningen

Syndromes of Thrombotic Microangiopathy

Koemhoff, Martin; Roofthoof, Marcus T.; van Spronsen, Francinus

Published in:
New England Journal of Medicine

DOI:
[10.1056/NEJMc1410951](https://doi.org/10.1056/NEJMc1410951)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2014

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Koemhoff, M., Roofthoof, M. T., & van Spronsen, F. (2014). Syndromes of Thrombotic Microangiopathy. *New England Journal of Medicine*, 371(19), 1846-1847. <https://doi.org/10.1056/NEJMc1410951>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

1. Food and Drug Administration. Medication guide for Triumeq (http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205551s000lbl.pdf).
2. Food and Drug Administration. September 10, 2014: Cardiovascular and Renal Drugs Advisory Committee meeting announcement (<http://www.fda.gov/AdvisoryCommittees/Calendar/ucm405489.htm>).

3. Mollan KR, Smurzynski M, Eron JJ, et al. Association between efavirenz as initial therapy for HIV-1 infection and increased risk for suicidal ideation or attempted or completed suicide: an analysis of trial data. *Ann Intern Med* 2014;161:1-10.

DOI: 10.1056/NEJMc1410930

Syndromes of Thrombotic Microangiopathy

TO THE EDITOR: In their review of the thrombotic microangiopathy syndromes, George and Nester (Aug. 14 issue)¹ do not mention the option of treating severe neurologic deficits in patients with shiga toxin–mediated hemolytic–uremic syndrome (ST-HUS) with IgG depletion through immunoadsorption.² In the 2011 outbreak in northern Germany, the delay in the onset of neurologic symptoms (5 to 12 days after the onset of diarrhea; mean and median, 8.0 days) strongly suggested antibody involvement in the pathogenesis of these symptoms. Consequently, all 12 patients had substantial improvement, and 10 of them fully recovered after IgG depletion through immunoadsorption, despite the failure of all other known treatments. This treatment option, although based on one prospective, uncontrolled study, may be a lifesaving treatment and should be considered in similar cases.

Shraga Aviner, M.D., Ph.D.
Haim Bibi, M.D.

Barzilai University Medical Center
Ashkelon, Israel
aviners@barzi.health.gov.il

No potential conflict of interest relevant to this letter was reported.

1. George JN, Nester CM. Syndromes of thrombotic microangiopathy. *N Engl J Med* 2014;371:654-66.
2. Greinacher A, Friessecke S, Abel P, et al. Treatment of severe neurological deficits with IgG depletion through immunoadsorption in patients with Escherichia coli O104:H4-associated haemolytic uraemic syndrome: a prospective trial. *Lancet* 2011;378:1166-73.

DOI: 10.1056/NEJMc1410951

plicates the binding of the Thomsen–Friedenreich antigen to preformed circulating IgM antibodies, owing to the neuraminidase-mediated cleavage of sialic acid residues from the membrane of glomerular capillary endothelial cells, red cells, and platelets.¹ Neuraminidase-associated thrombotic microangiopathy is generally observed in pediatric patients with pneumonia and meningitis and rarely in those with isolated pneumococcal infection.² The disease, frequently described as the hemolytic–uremic syndrome, has also been associated with group A beta-hemolytic streptococcus infection.³ Furthermore, the true incidence of neuraminidase-associated thrombotic microangiopathy could be underestimated.² Pneumococcal infection should be included among the causes of the thrombotic microangiopathy syndromes and considered especially in pediatric patients.

Fabio Villa, M.D.

Ente Ospedaliero Cantonale
Bellinzona, Switzerland
fabiovilla210486@gmail.com

No potential conflict of interest relevant to this letter was reported.

1. Ruggerenti P, Noris M, Remuzzi G. Thrombotic microangiopathy, hemolytic uremic syndrome, and thrombotic thrombocytopenic purpura. *Kidney Int* 2001;60:831-46.
2. Copelovitch L, Kaplan BS. Streptococcus pneumoniae-associated hemolytic uremic syndrome: classification and the emergence of serotype 19A. *Pediatrics* 2010;125(1):e174-e182.
3. Shepherd AB, Palmer AL, Bigler SA, Baliga R. Hemolytic uremic syndrome associated with group A beta-hemolytic streptococcus. *Pediatr Nephrol* 2003;18:949-51.

DOI: 10.1056/NEJMc1410951

TO THE EDITOR: George and Nester mention the main causes and pathological and clinical features of the thrombotic microangiopathy syndromes, disorders that can also be associated with pneumococcal infection. The pathogenesis of this rare but severe complication probably im-

TO THE EDITOR: George and Nester describe cobalamin C deficiency as one underlying cause of thrombotic microangiopathies. On the basis of our experience with cobalamin C deficiency in these syndromes¹ and the findings of other inves-

tigators,²⁻⁴ we would like to emphasize three clinically relevant aspects. First, although a majority of patients with cobalamin C deficiency present in infancy with neurologic problems,⁴ such deficiency in patients with thrombotic microangiopathies is observed throughout childhood and adolescence.¹⁻⁴ Second, since cobalamin C deficiency is treatable and occurs in combination with other causes of thrombotic microangiopathies (reported in four patients),^{1,2} we advocate routine measurement of blood levels of homocysteine in all patients with thrombotic microangiopathies, including those with complement defects. Homocysteine builds up as a result of renal failure,⁵ and values above 20 to 30 μmol per liter warrant further workup to exclude cobalamin C deficiency. Third, among the various coexisting clinical manifestations in cobalamin C deficiency, particular care should be taken to rule out pulmonary hypertension, which is associated with renal thrombotic microangiopathy¹ and has a dismal outcome, especially when treatment is delayed.

Martin Kömhoff, M.D., Ph.D.

Marcus T. Roofthoof, M.D., Ph.D.

Françjan Spronsen, M.D., Ph.D.

University Medical Center Groningen
Groningen, the Netherlands
m.komhoff@umcg.nl

No potential conflict of interest relevant to this letter was reported.

1. Kömhoff M, Roofthoof MT, Westra D, et al. Combined pulmonary hypertension and renal thrombotic microangiopathy in cobalamin C deficiency. *Pediatrics* 2013;132(2):e540-e544.
2. Sharma AP, Greenberg CR, Prasad AN, Prasad C. Hemolytic uremic syndrome (HUS) secondary to cobalamin C (cblC) disorder. *Pediatr Nephrol* 2007;22:2097-103.
3. Menni F, Testa S, Guez S, Chiarelli G, Alberti L, Esposito S. Neonatal atypical hemolytic uremic syndrome due to methylmalonic aciduria and homocystinuria. *Pediatr Nephrol* 2012;27:1401-5.
4. Fischer S, Huemer M, Baumgartner M, et al. Clinical presentation and outcome in a series of 88 patients with the cblC defect. *J Inher Metab Dis* 2014;37:831-40.
5. Herrmann W, Schorr H, Geisel J, Riegel W. Homocysteine, cystathionine, methylmalonic acid and B-vitamins in patients with renal disease. *Clin Chem* 2001;39:739-46.

DOI: 10.1056/NEJMc1410951

THE AUTHORS REPLY: Aviner and Bibi cite the report of Greinacher et al. in which IgG depletion by means of immunoadsorption was used to treat patients with ST-HUS who had severe neu-

rologic sequelae.¹ We agree that the recovery of the patients as described in their report was impressive. We also agree that patients with severe neurologic sequelae may warrant a trial of less proven treatments. We noted in our article that it is uncertain whether plasma exchange or anti-complement therapy is beneficial in patients with ST-HUS. We did not consider immunoadsorption because the existence of an antibody as the cause of neurologic sequelae in ST-HUS has not been documented.

Villa states that we should have considered thrombotic microangiopathy associated with severe pneumococcal sepsis as a primary syndrome. We had considered this because studies frequently describe pneumococcal sepsis-mediated thrombotic microangiopathy. However, we did not include it in our set of primary syndromes because of the limited mechanistic evidence that it is a distinct syndrome and because distinguishing this entity from the clinical manifestations of overwhelming sepsis is inherently difficult.

Kömhoff et al. advocate routine measurements of blood homocysteine levels in all patients presenting with thrombotic microangiopathy to determine whether cobalamin C deficiency could be the cause. We agree. In our article, we noted a recent case report in which cobalamin C deficiency was discovered to be the cause of thrombotic microangiopathy with severe kidney injury, which allowed for effective treatment.² However, discussion of the clinical evaluation of patients with thrombotic microangiopathy was beyond the scope of our review. Currently, many patients present with thrombotic microangiopathy and acute kidney injury without a clear cause. We believe that the wider use of routine laboratory assays (e.g., for plasma homocysteine and methionine and urine methylmalonic acid) may reveal a previously unsuspected diagnosis with minimal cost and no risk to the patient.

James N. George, M.D.

University of Oklahoma Health Sciences Center
Oklahoma City, OK
james-george@ouhsc.edu

Carla M. Nester, M.D.

University of Iowa
Iowa City, IA

Since publication of their article, the authors report no further potential conflict of interest.

1. Greinacher A, Friesecke S, Abel P, et al. Treatment of severe neurological deficits with IgG depletion through immunoadsorption in patients with Escherichia coli O104:H4-associated haemolytic uraemic syndrome: a prospective trial. *Lancet* 2011; 378:1166-73.

2. Cornec-Le Gall E, Delmas Y, De Parscau L, et al. Adult-onset eculizumab-resistant hemolytic uremic syndrome associated with cobalamin C deficiency. *Am J Kidney Dis* 2014;63:119-23.

DOI: 10.1056/NEJMc1410951

Case 25-2014: A Man with Ulcerative Colitis and Bloody Diarrhea

TO THE EDITOR: The Case Record contributed by Hohmann et al. (Aug. 14 issue),¹ regarding a man with ulcerative colitis in whom bloody diarrhea developed soon after fecal microbiota transplantation (FMT), highlights the difficulty in distinguishing cytomegalovirus (CMV) as a direct cause of disease from its being an “innocent bystander” in patients with CMV infection and active ulcerative colitis. However, the authors also reported an apparent case of diarrheal disease caused by *Blastocystis hominis* transmitted by means of FMT without describing the complex debate as to whether this organism is a true enteropathogen.

In developed countries, blastocystis is detectable in more than 50% of healthy persons with the use of polymerase-chain-reaction–based assays.² No difference in the prevalence of blastocystis exists between hosts with gastrointestinal symptoms and those without such symptoms,³ and symptoms that are attributed to blastocystis infection may not improve even after the elimination of the organism.⁴ The organism has been shown to be capable of both long-term colonization² and spontaneous disappearance without intervention.^{4,5} Physicians offering FMT should carefully monitor FMT recipients for infectious complications but must be aware that presence is not the same as causation.

Benjamin H. Mullish, M.B., B.Chir.

Imperial College London
London, United Kingdom
b.mullish@imperial.ac.uk

No potential conflict of interest relevant to this letter was reported.

1. Case Records of the Massachusetts General Hospital (Case 25-2014). *N Engl J Med* 2014;371:668-75.

2. Scanlan PD, Stensvold CR, Rajilić-Stojanović M, et al. The microbial eukaryote *Blastocystis* is a prevalent and diverse mem-

ber of the healthy human gut microbiota. *FEMS Microbiol Ecol* 2014 July 30 (Epub ahead of print).

3. Udkow MP, Markell EK. Blastocystis hominis: prevalence in asymptomatic versus symptomatic hosts. *J Infect Dis* 1993;168: 242-4.

4. Sun T, Katz S, Tanenbaum B, Schenone C. Questionable clinical significance of Blastocystis hominis infection. *Am J Gastroenterol* 1989;84:1543-7.

5. Grossman I, Weiss LM, Simon D, Tanowitz HB, Wittner M. Blastocystis hominis in hospital employees. *Am J Gastroenterol* 1992;87:729-32.

DOI: 10.1056/NEJMc1410949

THE DISCUSSANT REPLIES: We understand the controversy surrounding *B. hominis* (an anaerobic protozoan), and the case referenced in the discussion, reported by a Canadian physician, highlights it nicely. The patient had recurrent *Clostridium difficile* infection, and the spousal donor, who had no gastrointestinal symptoms, had stool that tested positive for *B. hominis* (no other donor was readily available). The FMT cured the *C. difficile* infection, but intermittent loose stools lasting months subsequently developed, with positive tests for blastocystis. A course of nitazoxanide cured the symptoms.

At a recent American Gastroenterological Association conference on FMT, physicians noted that blastocystis was a common finding in donor stool specimens (e.g., in 6 of 38 specimens that were screened in an Australian study).¹ The consensus of practitioners was that it would not be advisable to use such specimens for FMT. Attendees did not mention other cases of transmission of infectious agents by FMT. Representatives of the Food and Drug Administration highlighted the possibility of transmission of currently unknown infectious agents and the need for judicious use and careful follow-up of recipients of FMT.