European Journal of Clinical Microbiology & Infectious Diseases
https://doi.org/10.1007/s10096-018-3185-y

REVIEW

Risk factors of venous thrombo-embolism during cytomegalovirus infection in immunocompetent individuals. A systematic review

Manuela Ceccarelli[1] · Emmanuele Venanzi Rullo[1] · Giuseppe Nunnari[1]

Received: 24 November 2017 / Accepted: 3 January 2018

Abstract

Most of the effects and complications of cytomegalovirus (CMV) infection are still unknown, even though its tropism for the endothelium has been extensively investigated. In fact, CMV is suspected to be a cause of venous thrombo-embolism (VTE) since 1974, but there is still no consensus about the management of CMV-related thrombosis and how to prevent it. Cytomegalovirus-related thrombosis has been reported mostly in immunocompromised patients, rarely in immunocompetent individuals. In order to identify potential risk factors of CMV-related thrombosis, we performed a systematic review of the literature regarding immunocompetent patients with cytomegalovirus infection and thrombosis. We found 115 cases with a mean age of 37.36 years (SD ± 16.43 years). Almost half the female patients were assuming EP contraception at the time of the event, and almost half the patients were affected by a coagulation disorder. Interestingly, just two women and four men had no risk factor for thrombosis other than the CMV infection at the time of the event. In conclusion, coagulation disorders and EP contraception have to be taken into a great deal of consideration in patients with CMV infection, since they could be important risk factors for VTE. Knowing the correlation with coagulation disorders, the use of anticoagulation drugs cannot be considered overtreatment. It was not feasible to determine the usefulness of an antiviral treatment. Further studies, even randomized ones, are required to determine the usefulness of antiviral drugs and the real prevalence of CMV-related VTE.

Keywords Cytomegalovirus · CMV · Thrombosis · Infection · VTE · Venous thrombo-embolism

Introduction

Despite being one of the most widespread infections in the world, most of the effects and complications of cytomegalovirus (CMV) infection are still unknown [1]. Severe complications, such as pulmonary thromboembolism, in immunocompetent patients seem to be more frequent than thought [2]. However, pharmacological treatment of this infection is only available for immunocompromised patients, based on cost-effectiveness and the high prevalence of adverse effects in immunocompetent patients.

CMV infection is suspected to be a cause of venous thrombo-embolism (VTE) since 1974, when Vorlicky et al. hypothesized the connection existing between them [3], starting a series of study that brought us to knowledge of the connection between CMV infection and atherosclerosis. On the other hand, there are no certainties about risk factors or about which people most likely to develop a CMV-related VTE.

The aim of this systematic review was to identify potential risk factors of CMV-related thrombosis, and to evaluate whether and when anticoagulant and antiviral drugs need to be used.

Case report

A 35-year-old woman came to our attention complaining of fever, chills, and night sweats which had started a week before. She also complained of asthenia. She came back from her honeymoon, during which she visited Australia, 15 days before the medical examination. She had a similar symptomatology during travel, for which she was treated with NSAIDs with some relief. She had been taking a daily oestroprogestive

✉ Manuela Ceccarelli
manuela.ceccarelli86@gmail.com

[1] Department of Clinical and Experimental Medicine, Unit of Infectious Diseases, University of Messina, Via Consolare Valeria, 1, 98125 Messina, ME, Italy

Published online: 18 January 2018

birth control pill for almost 6 months. The clinical examination only revealed a spread lymphadenopathy, involving cervical, right axillary, and right inguinal nodes.

At admission, laboratory findings were of normal leukocyte count, normal alanine and aspartate amino-transferases (ALT and AST), and normal C reactive protein (CRP). CMV-IgG were positive, while IgM were negative, highlighting a previous infection. On a serological basis, we excluded HIV infection, EBV infection, and Brucella melitensis infection. We performed an intradermal reaction test with purified protein derivative (PPD), which resulted negative after 48 h. An abdominal ultrasound (US) identified a mild splenomegaly and a pericardial effusion, confirmed by an echocardiography (the patient had a familial history of recurrent pericarditis). Therapy for pericarditis with ibuprofen and colchicines was promptly started. Laboratory findings 5 days after admission resulted in a transaminase increase (both ALT and AST were over 100 IU/l, normal 0–50 IU/l) and high lactate dehydrogenase (LDH 947 IU/l, normal 150–460 IU/l). Three days after, the patient was still febrile. Suspecting a lymphoproliferative disorder, we decided to perform a total-body CT scan, highlighting a thrombosis localized in the inferior mesenteric vein, at the confluence with the splenic vein and pleuritis. We immediately started an anticoagulant therapy with fondaparinux. Three days after the CT scan we received results of a CMV-DNA polymerase chain reaction (PCR) test, performed on blood samples drawn in different days (before and after the CT-scan), highlighting the presence of CMV in both the samples with increasing values (385 cps/ml were found at the first determination, while 4941 cps/ml resulted at the second determination). We decided to start a 15-day course of ganciclovir, after which the patient's condition began to improve.

One month after the CT scan, an abdominal US with Doppler scan was performed, revealing a complete resolution of the thrombus. The anticoagulant was then stopped.

Materials and methods

On February 22nd, 2017, we performed a systematic review of the literature regarding the link existing between cytomegalovirus and thrombosis. We searched PubMed, Embase, and the Cochrane Library applying "cytomegalovirus" and "thrombosis" as search terms. References of the articles were also reviewed. We limited the inclusion only to articles written in English, French, Spanish, and German. No age-related exclusion was performed. We identified 1514 records and, after duplicates were removed, we screened 1235 of them. We excluded 1144 records by title and abstract, because they reported cytomegalovirus-related thrombosis in immunocompromised patients (HIV-positive patients, or patients who underwent transplantations, full-text not available online) and we assessed 91 full-text articles for eligibility. After assessment, we excluded 12 full-text articles because they reported about patients taking high-dose corticosteroids for rheumatological diseases or chronic IBDs, or they were case–control studies not defining their thrombosis cases one by one. At the end of the assessment, we included in our review 79 full-text articles reporting about immunocompetent patients affected by cytomegalovirus-related thrombosis, for a total of 114 cases (Fig. 1) [3–81]. We added one case we observed in our Infectious Diseases Unit in 2016, never reported elsewhere.

We performed a descriptive analysis of the data retrieved.

Results

Demographics and comorbidities [Table 1]

We found 115 cases, concerning 46 male patients (40%) and 69 female patients (60%). Their mean age was 37.36 years (SD ± 16.43 years).

Six patients were reportedly affected by hypertension and on treatment; five were obese, four patients had type 2 diabetes mellitus, five patients were pregnant at the moment the CMV infection occurred (there was no mention about the babies), three patients had history of venous thrombo-embolism, and two patients had history of cancer years before the event. In 15 cases, we found the patients were affected by health problems possibly predisposing them to thrombosis. Sixty-eight patients did not report having any health problem before their admission to hospital. Information about previous health status was missing in 14 cases.

Estrogen–progestogen (EP) contraception and other modifiable risk factors

Almost half (31 out of 69, 44,9%) of the female patients included in the review were taking EP contraception at the time of the event. The intake was oral in almost the totality of them (30/31). Curiously, one of the women was taking the drug intravaginally at the time of the thrombotic event [25]. Moreover, 15 out of 31 patients taking EP contraception were also affected by a coagulation disorder [9, 23, 37, 42, 46, 59, 61, 64, 65, 68, 76]. Ten patients reportedly did not assume estrogen–progestogen contraception, while the data was not available in 28 cases.

It is clearly stated that eight of the patients included, males and females, smoked at the time of the admission, while 15 of them did not. This data is not attainable in 92 cases.

Genetic and other non-modifiable risk factors

A heterozygotic Factor V Leiden mutation was found in 19 patients; nine patients had a heterozygotic factor VIII

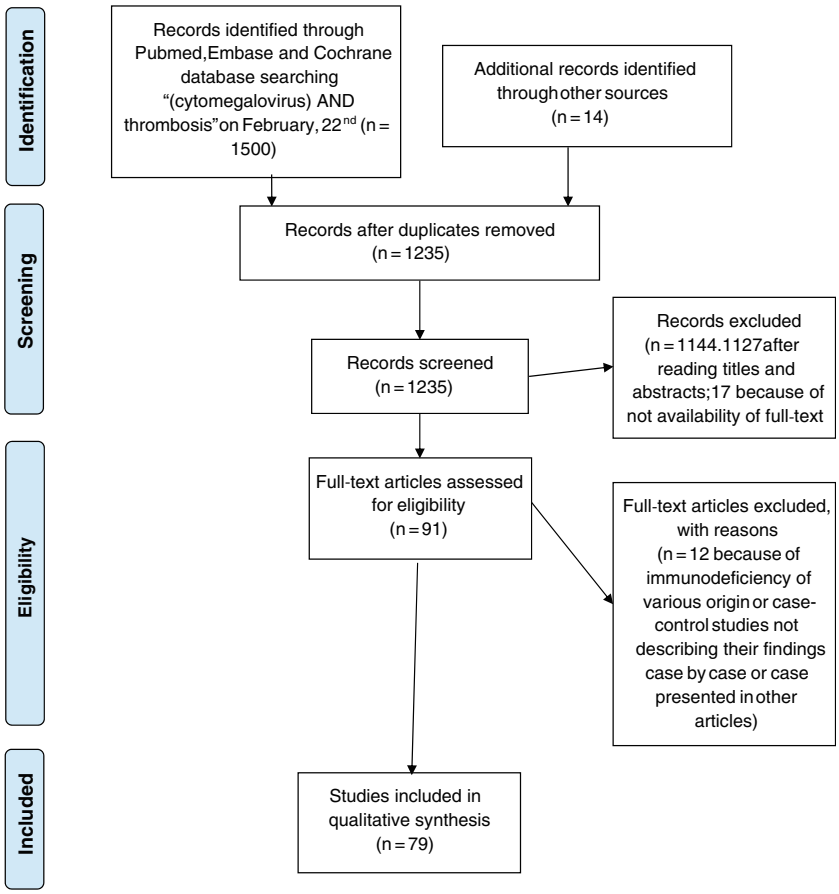

Fig. 1 Article assessment diagram

mutation, in seven patients a heterozygosis for the G20210A prothrombin mutation was highlighted, and three patients had a MTHFR mutation (two heterozygosis, one homozygosis). Five had a Protein C deficiency, while three lacked Protein S. One patient was affected by hyperhomocysteinemia. The blood samples of seven patients showed the presence of anti-phospholipids auto-antibodies, while four of them had anti-cardiolipin antibodies. In three cases, anti-nuclear antibodies were found, and two patients tested positive for lupus anticoagulant (LAC). It is reported that the positivity of auto-antibodies was only transient.

Twenty-eight patients had no coagulation disorder, while 34 of them were either not tested or the results were not disclosed in their reports.

Table 1 Population characteristics

	Total population	Age: mean (SD)	M: *n* (%)	F: *n* (%)
	115	37.36 (± 16.43)	46 (40%)	69 (60%)
Comorbidity	Number		Percentage	
- Hypertension	6		5.2%	
- Obesity	5		4.4%	
- Diabetes	4		3.5%	
- Pregnancy or puerperium	5		4.4%	
- History of VTE	3		2.6%	
- History of cancer	2		1.7%	
- Other	15		13.0%	
- None	68		59.1%	
- NA	14		12.2%	

VTE: venous thrombo-embolism, NA: not available; M: male; F: female; SD: standard deviation

Table 2 and Fig. 2a, b summarise our findings with regard to both modifiable and non-modifiable risk factors. Interestingly, two women (2.90% of the female population) and four men (8.70% of the male population) had no risk factor for thrombosis other than the CMV infection at the time of the event.

Symptoms

Data on fever were available in 78 cases; 71 patients had a fever, while seven had none. The information was not available for 37 patients.

Thirty-five patients complained of abdominal pain, four of arthralgia, five of chest pain, nine of headache, six of pain localized in lower limbs, four had no pain. Data about pain are not retrievable in 56 cases.

The most frequent symptoms were asthenia and anorexia, found in 23 patients, respiratory symptoms (cough, dyspnea) found in 18 patients, while gastrointestinal symptoms (nausea, vomit, diarrhea) and respiratory symptoms were found in 15 patients each. In addition, we had neurological signs (seven patients), hepatosplenomegaly (seven patients), lymphadenomegaly (six patients), rash (six patients), cardiological signs and symptoms (five patients), and other signs and symptoms, such as night sweats, sore throat, nycturia, itching (19 patients).

Thrombosis localization [Table 3]

The site most frequently affected by thrombosis was the pulmonary area, with 29 patients (25.7%) affected by pulmonary embolism, followed by portal vein (26 patients, 23.4%), splenic infarction (16 patients, 13.9%), superior mesenteric vein (15 patients, 13.5%), lower limbs (ten patients, 8.7%), other abdominal sites (nine patients, 7.8%), cerebral arteries and veins (five patients, 4.4%). The inferior mesenteric vein was affected in three patients (2.6%). Aortic arch was affected in two patients, both infants, both dead shortly after diagnosis. Notably, we included two cases of CMV-related thrombocytopenic thrombotic purpura (TTP). Interestingly, 76 patients had only one site involved, while 39 patients had more than one site involved in thrombosis.

Laboratory findings

A mild elevation of alanine transferase (ALT) was found in 18 patients, while moderate and severe elevation of ALT were respectively found in 24 and eight patients. Ten patients had normal ALT, while in 55 cases the data were not reported. As for aspartate transferase (AST), we found a mild elevation in 18 patients, a moderate one in 19 patients, and a severe elevation in ten patients. Normal AST were highlighted in 15 patients, while AST essay results were not reported in 55 cases.

CMV-IgM were positive in 87 patients, while they were negative in three patients. These data are not known for 25 patients. CMV-IgG were positive in 46 patients, negative in nine, and not available in 60 patients. CMV-DNA in blood or urine was positive in 38 patients, negative in one, and not performed or not declared in 76 patients. CMV pp65 antigen was found positive in 20 patients, negative in four patients. The test was not mentioned in 91 patients.

Therapies [Table 4]

Only 18 patients underwent an antiviral therapy (13 ganciclovir, three valganciclovir, one both ganciclovir

Table 2 Modifiable and non-modifiable risk factors (RF)

	EP contraception		Comorbidities		Smoker?		Coagulation disorders		Rheumatological disorders		No RF	
Females												
Total 69	Yes	31 (44.93%)	Yes	22 (31.88%)	Yes	6 (8.70%)	Yes	29 (42.03%)	Yes	8 (11.59%)	Do not have RF	2 (2.90%)
	None	10 (14.49%)	None	41 (59.42%)	No	7 (10.14%)	No	21 (30.43%)	None	42 (60.87%)	Have RF	64 (92.75%)
	NA	28 (40.58%)	NA	6 (8.70%)	NA	56 (81.16%)	NA	19 (27.54%)	NA	19 (27.54%)	NA	3 (4.35%)
Males												
Total 46			Yes	11 (23.91%)	Yes	2 (4.35%)	Yes	11 (23.91%)	Yes	5 (10.87%)	Do not have RF	4 (8.70%)
			None	27 (58.70%)	No	8 (17.39%)	No	20 (43.48%)	None	26 (56.52%)	Have RF	39 (84.78%)
			NA	8 (17.31%)	NA	36 (78.26%)	NA	15 (32.61%)	NA	15 (32.61%)	NA	3 (6.52%)

NA: not available

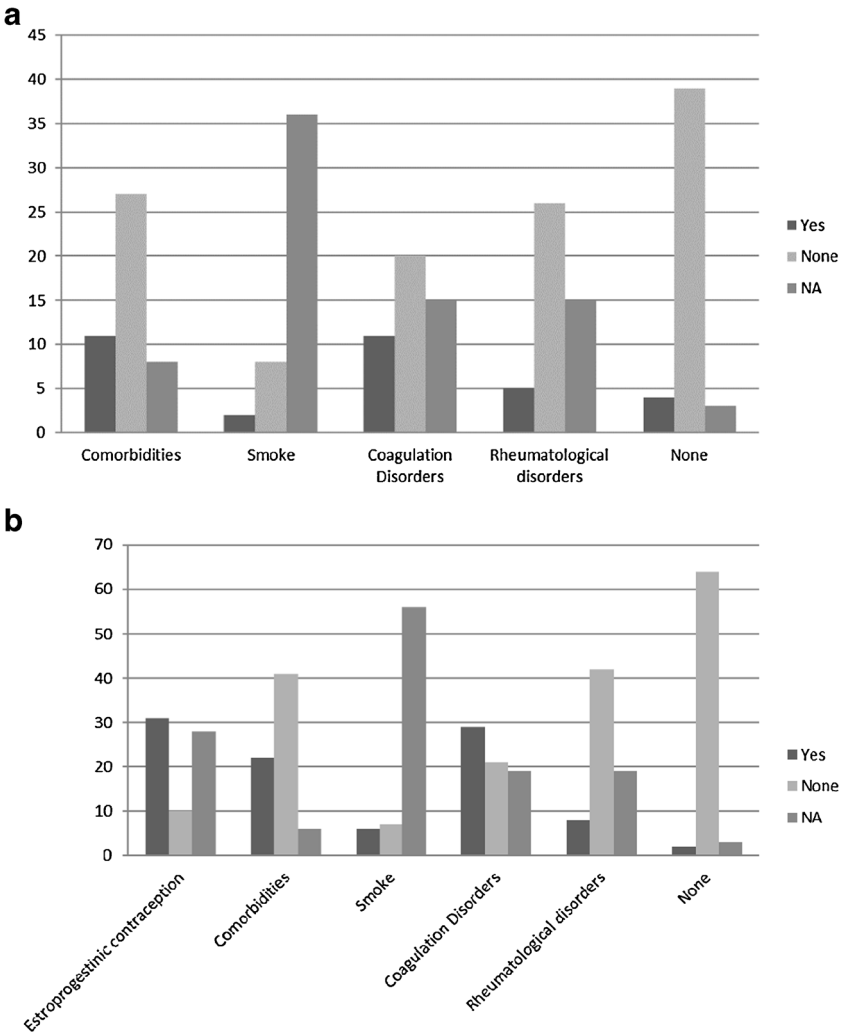

Fig. 2 **a** Modifiable and non-modifiable risk factors — males. **b** Modifiable and non-modifiable risk factors — females

Table 3 Sites involved

	1 site	> 1 site
Male	32	14
Female	44	25
Total	76	39
Location of site	*N* (%)	Comments
- Aortic arch	2 (1.7%)	Both infants, (outcome: death)
- Deep venous thrombosis	22 (19.1%)	
- Pulmonary embolism	29 (25.2%)	
- Portal vein	26 (22.6%)	
- Superior mesenteric vein	15 (13%)	
- Inferior mesenteric vein	3 (2.6%)	
- Splenic infarction	16 (13.9%)	
- Other abdominal	9 (7.8%)	
- Other lower limbs	10 (8.7%)	
- Other head	5 (4.4%)	
- Other	5 (4.4%)	

and valganciclovir, one foscarnet). In nine cases, it is clearly stated that the patient did not take the antiviral therapy. This information is not disclosed in 88 cases.

Seventy-eight patients took an anticoagulant therapy, while seven did not. Among the seven who did not undergo the therapy, there are three cases in which the diagnosis was made after their death. It is not known if the 30 remaining patients assumed any anticoagulant therapy.

Outcome

Complete resolution of the thrombus after a variable period was the outcome for 57 patients. In five cases, the outcome was only a partial resolution, while in five cases (three of which were newborns or infants) the outcome was death. We do not know the outcome for 48 out of 115 patients.

Table 4 Treatment

Treatment details	Number
Antiviral therapy	
Ganciclovir	14
Valganciclovir	4
Foscarnet	1
None	9
NA	88
Anticoagulant therapy	
Yes	78
None	7*
N/A	30
Anticoagulant (duration)	
None	7
20 days	1
1 month	1
3 month	6
5 months	2
6 months	23
7 months	1
9 months	2
12 months	1
21 months	1
144 months	1
N/A	65

* three patients were dead at the time of the diagnosis

Discussion

Despite being one of the most widespread infections in the world, most of the effects and complications of cytomegalovirus (CMV) infection are still unknown, and severe CMV disease is usually associated with infection in immunocompromised patients, with antiviral drugs only licensed for use in these patients [1]. However, severe CMV disease has poor prognosis both in immunocompromised and immunocompetent patients [2], and severe life-threatening complications, such as pulmonary thromboembolism, of CMV infection in immunocompetent patients may not be as rare as thought [82]. Crumpacker, writing about CMV disease associated complications in Mandell, Dolin and Bennett's Principles and Practice of Infectious Diseases, did not describe the causal association existing between the virus and coagulation, neither in immunocompetent nor in immunodeficient patients [83], despite it having been discussed since 1974, when, for the first time, Vorlicky et al. hypothesized the connection, reporting about a 3-day-old child with a major renal vein obstruction [3]. Since then, knowledge about CMV and its correlation with coagulation has improved, and in 1997 Sutherland et al. demonstrated that CMV and other herpesviruses can initiate the generation of thrombin by having essential phospholipid (pro-PL) and tissue factor (TF) activities on their surface [84]. In 2012, Gershom et al. published a study demonstrating that CMV and other herpesviruses also have a fibrinolysis-enhancing role, which may explain why they are only weak risk factors for vascular disease, despite having highly procoagulant activities on their surface [85].

Despite almost 50 years of experience exploring the tie linking CMV and thrombosis, there is still no consensus about the management of CMV-related thrombosis and how to prevent it. In this systematic review, we tried to identify potential risk factors to take into consideration for CMV-related thrombosis in immunocompetent patients, and to evaluate whether any recommendation can be reached regarding the use of anticoagulant and antiviral drugs.

The cohort of patients with CMV-related thrombosis had a mean age of 37 years, and almost 60 % were female.

CMV can be transmitted sexually; in fact, the titer of CMV in semen is the highest of that in any body secretion [86]. At the time of primary infection or reactivation, genetic predisposition, coagulation disorders, EP use, or other potential risk factors for VTE could contribute critically to the development of serious life-threatening events.

Hypertension, cancer, and previous venous thromboembolism (VTE) are well known for increasing the risk of a thromboembolic event. However, only 6 patients were affected by hypertension at the moment of the CMV infection, and previous cancer and VTE were respectively recorded as comorbidities in two patients each. While they can still increase the risk of a VTE together with CMV infection, they cannot be highlighted as the main risk factor.

Five women were affected by thrombosis during pregnancy or puerperium. Pregnancy alone increases the risk of VTE 4- to 5-fold over that in the non-pregnant state [87] (prevalence: 2.0 VTE per 1000 pregnancies), and a thromboembolic event is more common in the first half of the pregnancy than in the second half [88]. CMV infection prevalence is about 5–40 infections per 1000 pregnancies [89], but there are very few to no studies stating an accurate prevalence of CMV-related thrombosis. So, even though Schimanski et al. observed in their 2011 case–control study a 3.9% prevalence of CMV-DNA positive patients affected by VTE, they also stated the effectiveness of their study is limited by its retrospective design [76], and it remains difficult to establish the cumulative thrombosis risk for pregnant women affected by CMV infection.

Sixty-eight patients were reported as being healthy before the hospital admission, but half of them were also reported to be carriers of coagulative disorders such as heterozygosis for factor V Leiden mutation, protein C and S deficiency, MTFHR mutations, hyperhomocysteinemia, factor II and factor VIII mutations, or rheumatic disorders (presence of LAC, anti-phospholipids, anti-cardiolipin auto-antibodies). These disorders were largely unknown at the diagnosis of VTE.

Among them, there were 15 women taking EP contraception at the time of the event, despite the fact that women with thrombogenic mutations should not use combined hormonal contraceptives, as clearly stated in CDC guidelines "U.S. Selected Practice Recommendations for Contraceptive Use, 2013", and its previous editions. However, the same guidelines state that a universal screening for thrombogenic mutations is not cost-effective because of the rarity of the conditions and the high cost of screening [88].

Factor V Leiden has a 3–7% prevalence in the general population, increasing to 20% in a population affected by VTE, and constitutes a relative risk of a primary event of VTE of 3–5 fold more than the general population [89]. In our population, factor V Leiden has a total prevalence of 16.5%, which is slightly below the prevalence in a population affected by VTE, with a total prevalence of coagulation disorders of 40%, marking this risk factor as one of the most important in a CMV-related VTE.

Pain is a suggestive element in CMV-related VTE, being present in at least half the cases included in our study. Whenever patients present with CMV and they complain about a localized pain, VTE should be suspected.

Serology and polymerase chain reaction are obviously essential to the diagnosis. Our findings suggest a more common correlation between a primary infection and thrombosis, but relapses are related to thrombosis too. It is to be said that symptomatic CMV infection relapses in immunocompetent patients are usually less common than primary infections, and this fact alone can affect the prevalence of thrombosis during relapses.

It is important to highlight that the most commonly reported site involved was the pulmonary district, with or without primary localization. The second most involved site was the portal region. Interestingly, one of the patients suffering from portal vein thrombosis did not have any other risk factor, while others had one or two risk factors, with coagulation disorders being the most frequently reported. CMV-related thrombosis seems to involve both large and small vessels, and both arteries and veins, making it difficult to foresee where it will strike or the importance of the VTE.

There is no consensus about the use or not of an antiviral therapy in immunocompetent patients, and the use of such treatment is off-label in these patients. In addition, its usefulness is not demonstrated. Furthermore, there is no consensus about the use of an anticoagulant therapy. Atzmony et al. [72] and Protopapa et al. [51] reported that they did not use any anticoagulation in patients with splenic infarcts, where a CMV infection was considered the trigger of the VTE, because of the involvement of "small vessels only". However, their patients were also affected by coagulation disorders, one of them being heterozygous factor V Leiden. People affected by this condition are recommended to undergo an anticoagulant therapy for approximately 6–12 months after the first episode of VTE, especially if associated with transient risk factors like the CMV infection [90]. Despite being a serious complication of a CMV infection, CMV-related VTE seems to be a benign condition in the adult, complete resolution being the most frequent outcome. On the other hand, newborns and infants affected by CMV-related VTE seem to have a more unfortunate prognosis if the condition is not readily acknowledged and treated.

Conclusion

Our study is affected by the lack of data offered by some of the case-reports included.

We can offer some interesting conclusions:

- CMV-related VTE should be looked for especially in 30–50-year-old female patients currently undergoing EP contraception
- Coagulation disorders are an important additional risk factor. It is essential to know if the patients are affected by any of these conditions to determine the duration of the anticoagulant therapy
- Anticoagulation is not overtreatment. Even when only small vessels are involved, an anticoagulant therapy should be started, at least till thrombosis resolution
- Antiviral treatment was started only in a minority of patients included in the study, making it impossible to determine about the usefulness of a pharmacological treatment in reducing the symptoms and their duration in immunocompetent patients.

In conclusion, we suggest that CMV should be taken into consideration in all cases of thrombosis with no apparent cause, and that it would probably be reasonable to look for a thrombosis in all symptomatic CMV infections, even more if the patient has at least one other accountable risk factor or any localized pain.

Further studies, also randomized ones, are required to determine about the usefulness of antiviral drugs and the real prevalence of CMV-related VTE.

Acknowledgements MC and EVR searched literature and wrote the article; GN revised the manuscript.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interests The authors declare that they have no conflict of interests.

Ethical approval None required.

Informed consent None required.

References

1. Wreghitt TG, Teare EL, Sule O, Devi R, Rice P (2003) Cytomegalovirus infection in immunocompetent patients. Clin Infect Dis 37:1603–1606. https://doi.org/10.1086/379711
2. Eddleston M, Peacock S, Juniper M, Warrell DA (1997) Severe cytomegalovirus infection in immunocompetent patients. Clin Infect Dis 24:52–56
3. Vorlicky LN, Balfour HH (1974) Cytomegalovirus and renal vein thrombosis in a newborn infant. Am J Dis Child 127:742–744
4. Neau D, Bonnet F, Viallard JF, Longy-Boursier M, Le Bras M (1998) Thrombotic thrombocytopenic purpura and cytomegalovirus infection in an immunocompetent adult. Clin Infect Dis 25: 1495–1496
5. Lioger B, Debiais S, Lauvin MA, Bonnaud I, Maillot F, Ferreira-Maldent N (2013) Anticardiolipin antibodies-associated stroke in primary CMV infection. Eur J Neurol 20:e105–e106. https://doi.org/10.1111/ene.12179
6. Abgueguen P, Delbos V, Ducancelle A, Jomaa S, Fanello S, Pichard E (2009) Venous thrombosis in immunocompetent patients with acute cytomegalovirus infection: a complication that may be underestimated. Clin Microbiol Infect 16:851–854. https://doi.org/10.1111/j.1469-0691.2009.03022.x
7. Tanizawa K, Nakatsuka D, Tanaka E, Inoue T, Sakuramoto M, Minakuchi M, Hashimoto S, Noma S, Azuma T, Ishimaru H, Hatta K, Kohri Y, Taguchi Y (2009) Pulmonary thrombosis with transient antiphospholipid syndrome after mononucleosis-like illness. Int Med 48:1231–1234. https://doi.org/10.2169/internalmedicine.48.1949
8. Chou J-W, Cheng K-S (2016) Pulmonary embolism in an immunocompetent patient with acute cytomegalovirus colitis. Intest Res 14: 187–190. https://doi.org/10.5217/ir.2016.14.2.187
9. Ergas D, Herskovitz P, Skurnik Y, Mavor E, Sthoeger ZM (2008) Superior mesenteric vein thrombosis with pulmonary embolism: a rare presentation of acute cytomegalovirus infection. Isr Med Assoc J 10:235–236
10. Sánchez GR, Neches WH, Jaffe R (1982) Myocardial aneurysm in association with disseminated cytomegalovirus infection. Pediatr Cardiol 2:63–65. https://doi.org/10.1007/BF02265619
11. Lockwood MR, Liddle J, Kitsanta P (2006) Cytomegalovirus colitis—an unusual cause for diarrhoea in an elderly woman. Age Ageing 35:198–200. https://doi.org/10.1093/ageing/afj038
12. Abgueguen P, Delbos V, Chennebault JM, Payan C, Pichard E (2003) Vascular thrombosis and acute cytomegalovirus infection in immunocompetent patients: report of 2 cases and literature review. Clin Infect Dis 36:E134–E139. https://doi.org/10.1086/374664
13. Schreiner M, Barck T, Foroutan B, Baumgarten U (2011) A rare cause of portal vein thrombosis in a previously healthy young man with acute hepatitis. J Clin Virol 51:152–154. https://doi.org/10.1016/j.jcv.2011.03.002
14. Zamani F, Amiri A, Mohit M, Zolfaghari M, Jalaeefar A, Ranjbar M, Shakeri R (2009) CMV infection in a pregnant woman complicated by toxic megacolon and mesenteric vein thrombosis. Turk J Gastroenterol 20:234. https://doi.org/10.4318/tjg.2009.0016
15. Justo D, Danylesko A, Shvedov V, Katzir M, Paran Y, Atzmony L, Kemelman P, Lerman Y (2010) Cytomegalovirus colitis associated with arterial thromboembolism in an immunocompetent elderly man. J Am Geriatr Soc 58:405–406. https://doi.org/10.1111/j.1532-5415.2009.02710.x
16. Pichenot M, Morell-Dubois S, Flateau C, Deconinck L, Hatron PY, Lambert M (2013) Acute cytomegalovirus infection as a transient risk factor for thrombosis: report of three cases and focus on specific coagulation pathways. Thromb Res 132:145–147. https://doi.org/10.1016/j.thromres.2013.04.006
17. Kassem H, Khamadi K, Farrugia C, Hen NHH, Gharbi El T, Turner L (2017) Primary infection with cytomegalovirus: an infectious cause of splenic infarction. Rev Med Interne 38:555–557. https://doi.org/10.1016/j.revmed.2016.12.017sss
18. Ladd AM, Goyal R, Rosainz L, Baiocco P, DiFabrizio L (2008) Pulmonary embolism and portal vein thrombosis in an immunocompetent adolescent with acute cytomegalovirus hepatitis. J Thromb Thrombolysis 28:496–499. https://doi.org/10.1007/s11239-008-0303-1
19. Lanari M, Lazzarotto T, Papa I, Venturi V, Bronzetti G, Guerra B, Faldella G, Corvaglia L, Picchio FM, Landini MP, Salvioli GP (2001) Neonatal aortic arch thrombosis as a result of congenital cytomegalovirus infection. Pediatrics 108:e114
20. Spahr L, Cerny A, Morard I, Rubbia-Brandt L, Schrenzel J (2006) Acute partial Budd–Chiari syndrome and portal vein thrombosis in cytomegalovirus primary infection: a case report. BMC Gastroenterol 6:10. https://doi.org/10.1186/1471-230X-6-10
21. Belotti A, Doni E, Coccini V, Carpenedo M, Pogliani EM (2012) Splanchnic vein thrombosis in an immunocompetent patient with acute CMV infection: A case report. Haematologica 97(Suppl 1): haematol_97_s1
22. Vidal M, Corbin V, Chanet V, Ruivard M, Gourdon F, Laurichesse H, Beytout J, Lesens O (2005) Infections associated to severe thrombotic events and antiphospholipid antibodies. Med Mal Infect 35:552–555. https://doi.org/10.1016/j.medmal.2005.08.004
23. Viaene L, Nijs A, Ghillebert G (2008) Acute cytomegalovirus infection in patients with vena mesenterica superior thrombosis: coincidence or not? Tijdschr Geneeskd 64:514–519. https://doi.org/10.2143/TVG.64.10.2000319
24. Hashizume H, Hata M (2012) Deep venous thrombosis associated with cytomegalovirus reactivation in drug-induced hypersensitivity syndrome. J Eur Acad Dermatol Venereol 27:658–659. https://doi.org/10.1111/j.1468-3083.2012.04560.x
25. Rossetto V, Rossetto V, Senzolo M, Sartori MT, Gavasso S, Simioni P (2010) Intravaginal contraceptives and cytomegalovirus (CMV) infection associated to anti-protein C antibodies as risk factors for mesenteric vein thrombosis: a case report. Pathophysiol Haemos Thromb 37:247–288. https://doi.org/10.1159/000318098
26. Khater FJ, Myers JW, Moorman JP (2003) A 45-year-old woman with fever and splenic infarcts. Clin Infect Dis 37:1093. https://doi.org/10.1086/378295
27. Labarca JA, Rabaggliati RM, Radrigan FJ, Rojas PP, Perez CM, Ferrés MV, Acuna GG, Bertin PA (1997) Antiphospholipid syndrome associated with cytomegalovirus infection: case report and review. Clin Infect Dis 24:197–200
28. Ofotokun I, Carlson C, Gitlin SD, Elta G, Singleton TP, Markovitz DM (2001) Acute cytomegalovirus infection complicated by vascular thrombosis: a case report. Clin Infect Dis 32:983–986. https://doi.org/10.1086/319353
29. Inacio C, Hillaire S, Valla D, Denninger MH, Casadevall N, Erlinger S (1997) Case report: cytomegalovirus infection as a cause of acute portal vein thrombosis. J Gastroenterol Hepatol 12:287–288
30. Bensaid B, Pavic M, Estival JL, Rabar D, Dupin M, Combemale P (2007) Thrombose veineuse profonde révélée par une éruption cutanée au cours d'une primo-infection à cytomégalovirus. Ann Dermatol Venereol 134:779. https://doi.org/10.1016/s0151-9638(07)92538-7
31. Wirtz G, Federici L, Andrès E (2008) Embolie pulmonaire compliquant une infection à cytomégalovirus, infection mimant une maladie de Horton associée à une pseudopolyarthrite rhizomélique chez un sujet immunocompétent. Med Mal Infect 38:287. https://doi.org/10.1016/j.medmal.2007.12.002
32. Massoure M-P, Ezanno A-C, Millot I, Fixot K, Rey P, Sockeel P (2010) Acute portal vein thrombosis associated with acute cytomegalovirus infection in an immunocompetent adult and

complicated with an abdominal compartment syndrome. Gastroenterol Clin Biol 34:e3–e5. https://doi.org/10.1016/j.gcb.2010.01.003
33. Benoist S, Laisné M-J, Joly F, Boudiaf M, Panis Y, Valleur P (2003) Cytomegalovirus infection as a cause of acute superior mesenteric vein thrombosis with jejunal infarction. Surgery 133:222–223. https://doi.org/10.1067/msy.2003.8
34. Wang T, Kuttikat A, Pulsalkar P, Nanguzgambo A, Bhalara S (2015) Cytomegalovirus-associated portal vein thrombosis in an immunocompetent patient: an underestimated complication. Oxf Med Case Reports 2015:294–296. https://doi.org/10.1093/omcr/omv041
35. Paran Y, Shalev V, Steinvil A, Justo D, Zimmerman O, Finn T, Berliner S, Zeltser D, Weitzman D, Raz R, Chodick G (2013) Thrombosis following acute cytomegalovirus infection: a community prospective study. Ann Hematol 92:969–974. https://doi.org/10.1007/s00277-013-1715-3
36. Duenas C, Grande C, Martin A, Ceballos I, Sevil M, Fernandez A (2002) Trombosis mesentérica asociada a infección por citomegalovirus en paciente inmunocompetente. Enferm Infecc Microbiol Clin 20:96. https://doi.org/10.1016/s0213-005x(02)72754-7
37. Périsse A, Sahuc P, Wybrecht D, Joubert C, Gaillard T, Dagain A, Montcriol A, Alla P, Faivre A (2013) Cerebral venous thrombosis: an unusual complication of acute cytomegalovirus infection. Rev Med Interne 35:268–270. https://doi.org/10.1016/j.revmed.2013.04.001
38. Atzmony L, Halutz O, Avidor B, Finn T, Zimmerman O, Steinvil A, Zeltser D, Giladi M, Justo D (2010) Incidence of cytomegalovirus-associated thrombosis and its risk factors: a case-control study. Thromb Res 126:e439–e443. https://doi.org/10.1016/j.thromres.2010.09.006
39. Cañas CA, Cedeño SV, Carrascal E, Vélez JD (2009) Thrombotic diathesis in an immunocompetent patient with acute cytomegalovirus infection. Acta Med Colomb 34:136–139
40. Chelbi F, Huong DB-LT, Frigui M, Asli B, Hausfater P, Piette J-C (2005) Portal thrombosis complicating an acute cytomegalovirus infection in an immunocompetent patient. Rev Med Interne 27:54–58. https://doi.org/10.1016/j.revmed.2005.08.013
41. Sainte S, Suys B, Meyns B, Rega F (2013) Spontaneous aortic arch thrombosis in a neonate. J Thorac Cardiovasc Surg 146:e15–e16. https://doi.org/10.1016/j.jtcvs.2013.05.005
42. Tichelaar VYIG, Sprenger HG, Makelburg ABU, Niesters BGM, Kluin-Nelemans HC, Lijfering WM (2011) Active cytomegalovirus infection in patients with acute venous thrombosis: a case–control study. Am J Hematol 86:510–512. https://doi.org/10.1002/ajh.22006
43. Sherman S, Justo D, Engel T, Yossepowitch O, Bregman N, Gadoth A, Paran Y (2012) Cytomegalovirus-associated cerebral sinus vein thrombosis. J Med Virol 84:1934–1936. https://doi.org/10.1002/jmv.23424
44. Galloula A, Rossi A, Gautier V, Minozzi C, Messas E, Mirault T (2014) Portal vein thrombosis associated with an acute cytomegalovirus infection. J Mal Vasc 39:224–230. https://doi.org/10.1016/j.jmv.2014.03.005
45. Van Moerkercke W, Pauwelyn K, Brugman E, Verhamme M (2009) Cytomegalovirus-associated superior mesenteric vein thrombosis treated with systemic and in-situ thrombolysis. Eur J Gastroenterol Hepatol 21(5):587–592. https://doi.org/10.1097/MEG.0b013e3283196b15
46. Krähenmann P, Dürig R, Sendi P, Oestmann A (2011) Persistent fever in the elderly. Praxis (Bern 1994) 100:985–988. https://doi.org/10.1024/1661-8157/a000630
47. Paran Y, Halutz O, Swartzon M, Schein Y, Yeshurun D, Justo D (2007) Venous thromboembolism and cytomegalovirus infection in immunocompetent adults. Isr Med Assoc J 9:757–758
48. Snydman LK (2007) Persistent fever and splenic infarct due to cytomegalovirus (CMV) mononucleosis in an immunocompetent host. J Gen Intern Med 22:245–246. https://doi.org/10.1007/s11606-007-0176-6
49. Sridhara S, Ettinger NA, Vohsen D (2012) A case of cytomegalovirus (CMV) vasculitis presenting as deep venous thrombosis with pulmonary embolism (DVT/PE). Am J Respir Crit Care Med 185:A6165. https://doi.org/10.1164/ajrccm-conference.2012.185.1_meetingabstracts.a6165
50. Millán IFA, Fernández LP, Sánchez MIP, Quero JH (2009) Portal and mesenteric vein thrombosis secondary to cytomegalovirus hepatitis. Med Clin (Barc) 135:338–339. https://doi.org/10.1016/j.medcli.2009.06.003
51. Protopapa MN, Velissaris D, Mougiou A, Siagkris D (2014) Cytomegalovirus-associated splenic infarcts in an adult immunecompetent man: a case report and review of the literature. J Med Case Rep 8:85. https://doi.org/10.1186/1752-1947-8-85
52. Tavil B, Kuskonmaz B, Kiper N, Cetin M, Gumruk F, Gurgey A (2008) Pulmonary thromboembolism in childhood: a single-center experience from Turkey. Heart Lung 38:56–65. https://doi.org/10.1016/j.hrtlng.2007.06.004
53. Vandamme YM, Ducancelle A, Biere L, Viot N, Rouleau F, Delbos V, Abgueguen P (2014) Myopericarditis complicated by pulmonary embolism in an immunocompetent patient with acute cytomegalovirus infection: a case report. BMC Res Notes 7:193. https://doi.org/10.1186/1756-0500-7-193
54. Estival JL, Debourdeau P, Zammit C, Teixeira L, Guérard S, Colle B (2002) Spontaneous portal vein thrombosis associated with acute cytomegalovirus infection in an immunocompetent patient. Presse Med 30:1876–1878
55. Amitrano L, Guardascione MA, Scaglione M, Menchise A, Romano L, Balzano A (2006) Acute portal and mesenteric thrombosis: unusual presentation of cytomegalovirus infection. Eur J Gastroenterol Hepatol 18:443. https://doi.org/10.1097/00042737-200604000-00021
56. Lin CS, Penha PD, Krishnan MN, Zak FG (1981) Cytomegalic inclusion disease of the skin. Arch Dermatol 117:282–284
57. Catón B, de Otazu RD, Aldamiz-Echebarria M, Viguri A (1993) Haemolytic-uraemic syndrome with thrombotic microangiopathy of the retina following cytomegalovirus infection: postmortem findings. Postgrad Med J 69:653–655
58. Rojo-Alvaro J, Pérez-Ricarte S, Vicuna-Arregui M, Villar-Garcia I, Anniccherico-Sánchez FJ (2015) Mesenteric vein thrombosis associated with a cytomegalovirus infection. Rev Esp Enferm Dig 107:251–252
59. Fridlender ZG, Khamaisi M, Leitersdorf E (2007) Association between cytomegalovirus infection and venous thromboembolism. Am J Med Sci 334:111–114. https://doi.org/10.1097/MAJ.0b013e31812f5ba5
60. Girszyn N, Leport J, Baux N, Kahn JE, Blétry O (2006) Portal vein thrombosis associated with acute cytomegalovirus infection in an immunocompetent patient. Rev Med Interne 27:426–428. https://doi.org/10.1016/j.revmed.2005.12.008
61. Jeanneret C, Reutlinger C, Hirsch HH, Cathomas G, Rothen M, Martius F, Biedermann BC (2008) Multifocal thrombophlebitis and deep vein thrombosis in primary cytomegalovirus infection—a histopathological analysis. Thromb Haemost 99:445–447. https://doi.org/10.1160/TH07-06-0413
62. Arav-Boger R, Reif S, Bujanover Y (1995) Portal vein thrombosis caused by protein C and protein S deficiency associated with cytomegalovirus infection. J Pediatr 126:586–588
63. Bertoni M, Risaliti F, Giani A, Calabrese E, Di Natale ME (2015) Asymptomatic superior mesenteric vein thrombosis as unusual complication of acute cytomegalovirus infection: a case report. Ital J Med 10:147–150. https://doi.org/10.4081/itjm.2015.596

64. Yildiz H, Zech F, Hainaut P (2016) Venous thromboembolism associated with acute cytomegalovirus infection: epidemiology and predisposing conditions. Acta Clin Belg 71:231–234. https://doi.org/10.1080/17843286.2016.1177265
65. Slooter AJC, Ramos LMP, Kappelle LJ (2002) Migraine-like headache as the presenting symptom of cerebral venous sinus thrombosis. J Neurol 249:775–776. https://doi.org/10.1007/s00415-002-0682-8
66. de Celis G, Mir J, Casal J, Gomez D (1995) 31-year-old woman with an enlarged tender liver. Lancet 346:1270
67. Squizzato A, Ageno W, Cattaneo A, Brumana N (2006) A case report and literature review of portal vein thrombosis associated with cytomegalovirus infection in immunocompetent patients. Clin Infect Dis 44:e13–e16. https://doi.org/10.1086/509641
68. Bauduer F, Blanc A, Cordon B (2003) Deep vein thrombosis and acute cytomegalovirus infection: case report and review of the literature. Blood Coagul Fibrinolysis 14:489–491. https://doi.org/10.1097/01.mbc.0000061323.06975.bb
69. Youd P, Main J, Jackson E (2003) Cytomegalovirus infection and thrombosis: a causative association? J Inf Secur 46:141–142. https://doi.org/10.1053/jinf.2002.1035
70. Babyatsky MW, Keroack MD, Blake MA, Rosenberg ES, Mino-Kenudson M (2007) Case records of the Massachusetts General Hospital. Case 35-2007. A 30-year-old man with inflammatory bowel disease and recent onset of fever and bloody diarrhea. N Engl J Med 357:2068–2076. https://doi.org/10.1056/NEJMcpc079029
71. Lijfering WM, Sprenger HG, van Son WJ, van der Meer J (2007) Mesenteric vein thrombosis associated with primary cytomegalovirus infection: a case report. Blood Coagul Fibrinolysis 18:509–511. https://doi.org/10.1097/MBC.0b013e3281a3bef9
72. Atzmony L, Saar N, Chundadze T, Arbel Y, Justo D, Mashav N (2008) Cytomegalovirus-associated splenic infarcts in a female patient with factor V Leiden mutation: a case report. J Med Case Rep 2:385. https://doi.org/10.1186/1752-1947-2-385
73. Rinaldi F, Lissandrin R, Mojoli F, Baldanti F, Brunetti E, Pascarella M, Giordani MT (2014) Acute cytomegalovirus infection as a cause of venous thromboembolism. Mediterr J Hematol Infect Dis 6: e2014041. https://doi.org/10.4084/MJHID.2014.041
74. Nakayama T, Akahoshi M, Irino K, Kimoto Y, Arinobu Y, Niiro H, Tsukamoto H, Horiuchi T, Akashi K (2014) Transient antiphospholipid syndrome associated with primary cytomegalovirus infection: a case report and literature review. Case Rep Rheumatol 2014:271548. https://doi.org/10.1155/2014/271548
75. Jan F, Mehboob H, Qadir R, Jan A, Kanjwal K (2008) Splenic vascular thrombosis in an immunocompetent host due to cytomegalovirus infection. Internet J Cardiovasc Res 6:1–4
76. Schimanski S, Linnemann B, Luxembourg B, Seifried E, Jilg W, Lindhoff-Last E, Schambeck CM (2011) Cytomegalovirus infection is associated with venous thromboembolism of immunocompetent adults—a case–control study. Ann Hematol 91:597–604. https://doi.org/10.1007/s00277-011-1334-9
77. Rovery C, Granel B, Parola P, Foucault C, Brouqui P (2005) Acute cytomegalovirus infection complicated by venous thrombosis: a case report. Ann Clin Microbiol Antimicrob 4:11. https://doi.org/10.1186/1476-0711-4-11
78. Poon MLM, Tang JW, Chee YL (2011) Case report: cytomegalovirus-induced thrombosis in an immunocompetent patient. J Med Virol 84:116–118. https://doi.org/10.1002/jmv.22253
79. Uthman I, Tabbarah Z, Gharavi AE (1999) Hughes syndrome associated with cytomegalovirus infection. Lupus 8:775–777. https://doi.org/10.1191/096120399678841034
80. Kalaitzis J, Basioukas P, Karzi E, Markakis C, Liarmakopoulos E, Hadjimarkou A, Rizos S (2012) Small-bowel necrosis complicating a cytomegalovirus-induced superior mesenteric vein thrombosis in an immunocompetent patient: a case report. J Med Case Rep 6:118. https://doi.org/10.1186/1752-1947-6-118
81. Gueddi S, Righini M, Mezger N, Morard I, Kaiser L, Giostra E, Bounameaux H, Angelillo-Scherrer A (2006) Portal vein thrombosis following a primary cytomegalovirus infection in an immunocompetent adult. Thromb Haemost 95:199–201
82. Rafailidis PI, Mourtzoukou EG, Varbobitis IC, Falagas ME (2008) Severe cytomegalovirus infection in apparently immunocompetent patients: a systematic review. Virol J 5:47. https://doi.org/10.1186/1743-422X-5-47
83. Crumpacker CS II (2015) Cytomegalovirus (CMV). In: Mandell, Douglas and Bennett's principles and practice of infectious diseases, 8th edn. Elsevier Saunders, Philadelphia, pp 1738–1753
84. Sutherland MR, Raynor CM, Leenknegt H, Wright JF, Pryzdial EL (1998) Coagulation initiated on herpesviruses. Proc Natl Acad Sci U S A 94:13510–13514
85. Gershom ES, Vanden Hoek AL, Meixner SC, Sutherland MR, Pryzdial ELG (2012) Herpesviruses enhance fibrin clot lysis. Thromb Haemost 107:760–768. https://doi.org/10.1160/TH11-08-0601
86. Murray PR, Rosenthal KS, Pfaller MA (2016) Human herpesviruses. In: medical microbiology, 8th edn. Elsevier, Philadelphia, pp 425–446
87. Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton L (2005) Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. Ann Intern Med 143:697–706. https://doi.org/10.7326/0003-4819-143-10-200511150-00006
88. Center for Disease Control and Prevention (CDC) (2013) U.S. Selected Practice Recommendations for Contraceptive Use, 2013 Morbidity and Mortality Weekly Report (MMWR) 62. https://www.cdc.gov/mmwr/pdf/rr/rr6205.pdf Accessed 18 June 2017
89. Middeldorp S (2016) Inherited thrombophilia: a double-edged sword. ASH Education Program Book 2016:1–9
90. Campello E, Spiezia L, Simioni P (2016) Diagnosis and management of factor V Leiden. Exp Rev Hematol 9:1139–1149. https://doi.org/10.1080/17474086.2016.1249364