



# Primary thrombophilia XV: antithrombotic treatment of sticky platelet syndrome worldwide

Yarely Itzayana García-Navarrete<sup>1,2</sup>, María Fernanda Vallejo-Villalobos<sup>2,3</sup>, Jesús Mauricio Olivares-Gazca<sup>1,2</sup>, Yahveth Cantero-Fortiz<sup>1,4</sup>, Andrés A. León-Peña<sup>1,5</sup>, Juan Carlos Olivares-Gazca<sup>1,2</sup>, Iván Murrieta-Álvarez<sup>1,2</sup>, Guillermo J. Ruiz-Delgado<sup>1,2</sup>, Guillermo J. Ruiz-Argüelles<sup>1,2,5</sup>

<sup>1</sup>Centro de Hematología y Medicina Interna de Puebla, Puebla, México; <sup>2</sup>Universidad Popular Autónoma del Estado de Puebla, Puebla, México; <sup>3</sup>Christus Muguerza Hospital Betania, Puebla, México; <sup>4</sup>Universidad de las Américas Puebla, Puebla, México; <sup>5</sup>Laboratorios Clínicos de Puebla, Puebla, México

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**Correspondence to:** Guillermo J. Ruiz-Argüelles, MD, FRCP (Glasg), MACP, DSc (hon). Centro de Hematología y Medicina Interna de Puebla, 8B Sur 3710, 72530 Puebla, Mexico. Email: gruiz1@clinicaruiz.com

**Background:** Sticky platelet syndrome (SPS) is a common but under-recognized cause of thrombosis. Treatment with antiplatelet drugs results in a low re-thrombosis rate. The aim of this study is to analyze the treatment of persons with SPS in different parts of the world.

**Methods:** Data from 43 publications describing 1,494 patients with SPS worldwide were analyzed. Data concerning treatment was available in 16 of these papers, and involving 332 patients.

**Results:** Three hundred thirty two patients were treated with antiplatelet drugs; 303 were given solely aspirin and 29 received combinations with aspirin (heparin or coumadin), whereas two persons did not receive aspirin. The re-thrombosis rate for patients given antiplatelet drugs was 5/332 (1.5%) and only 3 patients died.

**Conclusions:** Most patients with SPS are treated with antiplatelet drugs worldwide, the re-thrombosis rate is very low. Physicians worldwide are aware of the fact that the best treatment for persons with the SPS is the use of antiplatelet drugs.

**Keywords:** Sticky platelet syndrome (SPS); thrombophilia; antithrombotic; thrombosis; antiplatelets

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## Introduction

The condition known as sticky platelet syndrome (SPS) was first described in 1983; however, its prevalence did not receive substantial recognition in medical literature until much later (1-25). SPS is a relatively common cause of thrombosis (20,26-31), and is associated with both unexplained arterial and venous thrombotic events (32-34). Three forms of the SPS have been identified: Types I, II and III are defined by platelet hyperaggregability with both epinephrine and adenosine-diphosphate (ADP), type II with

only epinephrine and type III with only ADP (13,31,35-39). The platelet abnormality appears to be congenital, based on familial occurrence, but the precise nature of the defect has not been defined. Treatment of SPS relies on diminishing the inherent platelet hyperaggregability by means of antiplatelet drugs; in most cases, aspirin appears adequate but there are situations in which other anti-platelet drugs must be employed (27,33,36,40-43) (see *Table 1*). Only one paper has described a prospective study of SPS treatment (40), and it proved that by using antiplatelet drugs, mainly aspirin, the platelet hyperreactivity of patients can be reverted and that

**Table 1** Salient features of the treatment of patients with sticky platelet syndrome according to our literature review

Author	Country	Year	Cases	Location of thrombosis	Treatment	Follow-up
Mammen <i>et al.</i> (3)	USA	1988	Unknown	MI	Aspirin	Article not found
Berg-Dammer <i>et al.</i> (4)	Germany	1997	2	Superior sagittal sinus/middle cerebral artery/left subclavian/left vertebral artery	Heparin/catheter/thrombolysis. Aspirin 100 mg/daily	Nineteen months after the failed attempt to treat the aneurysms, the patient had regained full working capability. At that time she was taking ASA (Aspirin) daily. A follow-up laboratory examination confirmed thrombocytosis as well as chronic intravascular activation of platelets, coagulation and fibrinolysis
Baker; Bick (6)	USA	1999	153	DVT/stroke/MI/retinal vein	Aspirin	-
Chaturvedi, Dzieczkowski (8)	USA	1999	1	Acute stroke	Heparin/Warfarin	-
Bick (10)	USA	2000	21	Recurrent miscarriage	Aspirin 81 mg/d	Immediately post-conception, fixed low dose subcutaneous heparin at 5,000 U (anti-Xa) every 12 hours was added to the daily ASA regimen 81 mg/d. The heparin used was Fuji porcine mucosal heparin (20,000 U/mL concentration). Two patients suffered loss on ASA plus heparin, and placental thrombi and infarcts were present; thus, there were two losses that clearly represented treatment failure
Weber <i>et al.</i> (12)	Germany	2002	34	DVT/retinal vein thrombosis/portal vein thrombosis/pulmonary embolism	Heparin/Aspirin	-
Frenkel <i>et al.</i> (15)	USA	2003	200	Acute stroke, DVT	Aspirin 81 mg/day	Treatment with low-dose aspirin reverses clinical symptoms and hyperaggregability in the laboratory
Lewerenz <i>et al.</i> (17)	Germany	2004	1	Acute stroke/MI	Aspirin	-
Kahles <i>et al.</i> (21)	Germany	2006	1	Acute myocardial infarction/pulmonary embolism	Abciximab/stent/antiplatelet therapy/t-PA/heparin	Despite intravenous full heparinization and platelet aggregation inhibition with acetylsalicylic acid 100 mg and ticlopidine 2x250 mg, the patient unexpectedly developed a cardiogenic shock after two days
Kubisz (20)	Slovakia	2006	128	Acute stroke/MI/DVT/recurrent miscarriage	-	-
Fodor <i>et al.</i> (23)	Hungary	2007	1	Left temporal-superior branch retinal artery occlusion	Aspirin 300 mg/day	Four years after the event, her best-corrected visual acuity is stabilized at 20/20, without any further episodes of visual loss or any other neurological symptoms. The patient is under antiplatelet therapy (ASA: 100 mg/day) and undergoes imaging annually

**Table 1** (continued)

Table 1 (continued)

Author	Country	Year	Cases	Location of thrombosis	Treatment	Follow-up
Muhfeld (25)	USA	2007	3	Renal allograft rejection/ colonic microinfarctions/ pulmonary embolism/DVT	Heparin/Aspirin 100 mg	In two cases, the patients and the affected family members were placed on low-dose acetylsalicylic acid therapy and platelet function tests normalized in successive testing. The other patient still developed vascular events while on therapy with acetylsalicylic acid
Randhawa et al. (26)	New Zealand	2007	1	Ischemic optic neuropathy	Aspirin 81 mg/day	At 3-month follow up, his right optic disco edema had resolved
Ruiz-Argüelles et al. (24)	Mexico	2007	46	Thrombosis at younger than 40/recurrent thrombosis/thrombosis in unusual sites	Aspirin	-
El-Amm et al. (27)	USA	2008	3	Renal allograft rejection	Aspirin	-
Mears, Van Stavern (29)	USA	2009	1	Ischemic optic neuropathy	Aspirin 81 mg/day	-
Sand et al. (28)	Germany	2009	1	Cutaneous microembolism on fingers	Heparin (does not mention the dose)	Despite heparin therapy <i>in vivo</i> adrenaline release triggered by the stress of the operation lead to increased platelet clumping with occlusion of small vessels. Unfortunately, soon afterwards the patient developed cardiovascular failure and died
Bojalian et al. (44)	USA	2010	1	Popliteal artery/renal and splenic infarction/left axillar artery/left subclavian artery/left internal jugular vein	Heparin/embolectomy/Aspirin	-
Loeffelbein et al. (30)	Germany	2010	1	Venous and arterial flap thrombosis	Aspirin 81 mg/day	The treatment was well-tolerated, with no further thromboembolic events or problems
Alexandra et al. (45)	USA	2011	1	Retinal vein	Aspirin (80–100 mg)	Given the possibility of recurrent thrombosis with oral anticoagulant therapy alone in patients with sticky platelet syndrome, she was concurrently maintained on low-dose aspirin therapy. On initial follow-up examination, the patient's intraretinal hemorrhages remained stable, and there was no evidence of macular edema. She continues to deny any new visual symptoms or any decrease in visual acuity since that time.
Gehoff et al. (46)	Germany	2011	1	Acute stroke, PFO	Aspirin (100 mg/day)	The analysis at 1 month demonstrated a therapeutic effect of the low-dose acetylsalicylic acid medication

Table 1 (continued)

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Author	Country	Year	Cases	Location of thrombosis	Treatment	Follow -up
Rac <i>et al.</i> (34)	USA	2011	1	Recurrent miscarriage	Aspirin 325 mg/daily	She was subsequently started with ASA daily and has had no further clotting episodes. No treatment strategy, however, has been conclusively demonstrated to increase the chance of pregnancy success in patients with sticky platelet syndrome
Kotulicova <i>et al.</i> (47)	Slovakia	2012	77	Pulmonary embolism/DVT/MI/ Acute stroke	-	-
Kubisz <i>et al.</i> (48)	Slovakia	2012	9	2 DVT/4 arterial (acute stroke, MI, arterial thrombosis)/3 both	-	-
Sokol <i>et al.</i> (49)	Slovakia	2012	27	Recurrent miscarriage	Aspirin	-
Darulova <i>et al.</i> (50)	USA	2013	1	Pulmonary embolism	Alteplase/heparin was started with an intravenous bolus of alteplase 10 mg and then 40 mg intravenously during the first hour and 50 mg intravenously during the second hour. Intravenous anticoagulation with heparin was initiated after alteplase treatment to complete the treatment (heparin 10,000 U bolus and consequently 1,000 units/hour intravenously). This therapy was administrated with a positive effect and led to the stabilization of patient's condition	This therapy was administrated with a positive effect and led to the stabilization of patient's condition. After stabilization of patient's condition, the cause of pulmonary embolism was investigated, but there was nothing in the history suggesting a cause
Ruiz-Argüelles <i>et al.</i> (42)	Mexico	2013	100	Thrombosis at younger than 40/recurrent thrombosis/thrombosis in unusual sites	Aspirin	-
Simonova <i>et al.</i> (51)	Slovakia	2013	9	Cerebral venous thrombosis/DVT/pulmonary embolism/acute stroke/MI	Heparin/Aspirin	-
Tekgunduz <i>et al.</i> (52)	Turkey	2013	6	History of thrombosis	Aspirin 100 mg/day	-
Vasil'ev <i>et al.</i> (53)	Russia	2013	70	Thrombosis	Heparin/Aspirin	Article not found
Castillo-Martinez <i>et al.</i> (54)	Mexico	2014	1	Cutaneous limb veins	Aspirin 81 mg/day	She got a full recovery after four months

Table 1 (continued)

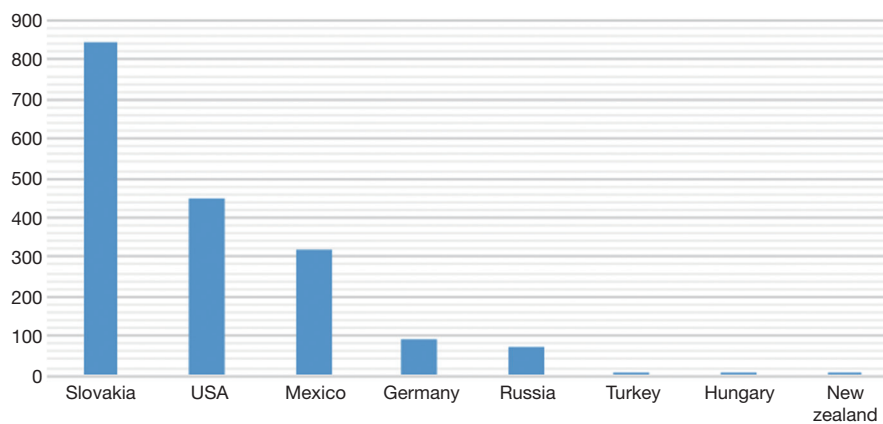
Table 1 (continued)

Author	Country	Year	Cases	Location of thrombosis	Treatment	Follow-up
Hayes <i>et al.</i> (55)	USA	2014	64	Acute stroke/DVT/MI	Aspirin	-
Kubisz (37)	Slovakia	2014	71	Acute stroke	-	-
Ruiz-Arguelles (39)	Mexico	2014	95	Thrombosis at younger than 40/recurrent thrombosis/thrombosis in unusual sites	Aspirin 81 mg/day	The platelet aggregation response to adenosine diphosphate and epinephrine significantly diminished after treatment and only two individuals developed another thrombosis, 52 and 129 months after starting therapy; interestingly, these two episodes were located in the retinal central artery and neither individual was identified to have any additional associated thrombophilic conditions
Alsheekh <i>et al.</i> (56)	USA	2015	1	Carotid artery	Abciximab/thrombectomy (does not mention the dose)	A repeat duplex ultrasound was performed on postoperative day six and demonstrated a patent artery without a hemodynamically significant stenosis. At three year follow up the patient remained on dual antiplatelet therapy and without evidence of carotid occlusion. On follow-up at 7 years, patient remains well with no further neurologic events
Sokol <i>et al.</i> (57)	Slovakia	2015	23	Recurrent miscarriage	Aspirin	-
Sokol <i>et al.</i> (58)	Slovakia	2015	27	Recurrent miscarriage	Aspirin	-
Yagmur <i>et al.</i> (59)	Germany	2015	48	TIA/DVT/pulmonary embolism/renal infarction	Heparin/Aspirin	-
Ruiz-Delgado <i>et al.</i> (32)	Mexico	2017	77	Recurrent miscarriage	Aspirin	-
Skerenova <i>et al.</i> (60)	Slovakia	2018	37	Recurrent miscarriage	Aspirin	-
Sokol <i>et al.</i> (61)	Slovakia	2018	64	Recurrent miscarriage	Aspirin	-
Sokol <i>et al.</i> (62)	Slovakia	2018	84	DVT	-	-
Solis-Jimenez <i>et al.</i> (63)	Mexico	2018	1	Renal allograft rejection (renal infarction)	Nephrectomy/Aspirin	-

MI, myocardial infarction; ASA, acetylsalicylic acid; DVT, deep vein thrombosis; TIA, transient ischemic attack; PFO, patent foramen oval.



**Figure 1** Countries in which patients with sticky platelet syndrome have been identified.



**Figure 2** Number of patients with sticky platelet syndrome that have been described in some countries.

this translates into a low re-thrombosis rate (36,40). Herein, we analyze the salient features of treatment of persons with SPS who have been identified in different parts of the world.

## Methods

We employed the PubMed database to search for all entries with the term “Sticky Platelet”, either in the title and/or the abstract. The relevant features of all publications were further analyzed, focusing in the treatment features and the re-thrombosis rate.

## Results

The initial search identified 108 papers in total. However,

although 41 of these included the search terms, they were discarded as they did not actually describe SPS. Twenty-four papers comprised reviews on SPS and 43 papers described either cases or series of patients. These latter 43 papers (*Table 1*) were further assessed. The country with the greatest number of papers published on SPS was the United States (fourteen publications), followed by Slovakia (eleven publications), Germany (eight publications), and México (six publications), with Hungary, Turkey, Russia and New Zealand having only a single publication each (23,26,52,53) (see *Figure 1*). In these publications, a total of 1783 patients with SPS were identified over the past 30 years [1988–2019] (see *Figure 2*). The thromboses identified were both venous or arterial; in some patients, SPS was identified together with another thrombophilic condition, either acquired or inherited (10,25,39) (see *Table 1*). Three hundred thirty two

patients were treated with antiplatelet drugs; 303 were given solely aspirin and 29 received combinations with aspirin (heparin or coumadin), whereas two persons did not receive aspirin (heparin + alteplase; abciximab) (see *Figures 3* and *4*).

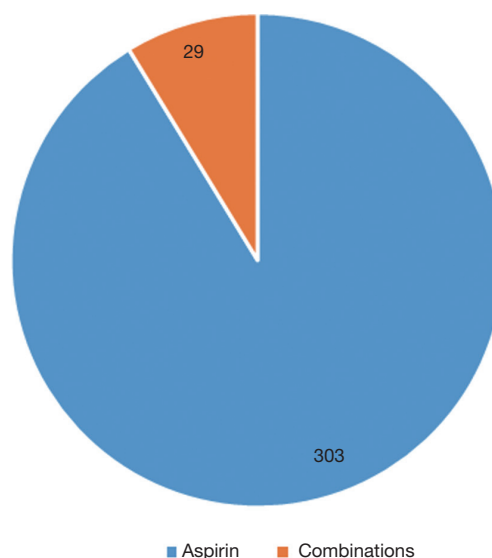
The doses of aspirin employed ranged between 80 and 325 mg/day (see *Table 1*); information about the use of enteric-coated *versus* non-coated aspirin is unavailable. The re-thrombosis rate for patients given antiplatelet drugs was 5/325 (1.5%); two of these patients were given subsequently direct oral anticoagulants. In only two papers were platelet aggregometry studies repeated after the treatment, as a way to control the efficacy of the treatment (4,40).

## Discussion

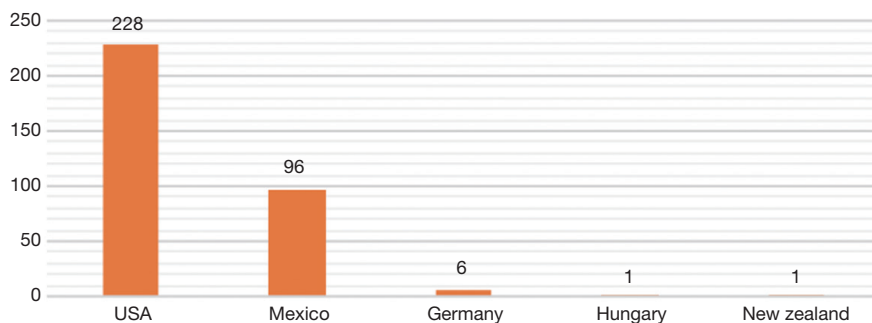
Over past years, we have been interested in analyzing the changes in the hemostatic system of Mexican Mestizos which can result in thrombophilia (40,42). In our studies, SPS was found to be the second most frequent thrombophilic condition identified in Mexican mestizos who expressed any clinical marker of thrombophilia (42), only exceeded by the MTHFR gene 677 C->T mutation. In México, we (11,19,24,42) and others (64) have found that approximately 50% of Mexican mestizo patients with a clinical marker of thrombophilia display the SPS phenotype. Most patients with SPS display other thrombosis-prone conditions, but there are also instances which SPS is identified as the single thrombophilia marker. Thus, SPS likely contributes to so-called “multifactorial thrombophilia” (19).

There are limited papers dealing with SPS treatment (*Table 1*); and most experiences stem from small series of patients or reviews (6,10,12,15,20,24,32,37,39,42,47-49,51,53,55,57-62,65-67) or case reports (4,8,17,21,23,25-30,34,44-46,50,52,54,56,63,68). Persons with the SPS

phenotype but no history of thrombosis may not need treatment at all, but it is not irrational to prescribe them low doses of aspirin. For patients with history of thrombosis and the SPS phenotype, in a prospective study (40), we found that the platelet hyperaggregability can be reverted by means of aspirin in most cases (75%), whereas other/additional antiplatelet drugs were needed in the remaining 25% (with clopidogrel employed in our experience). Use of antiplatelet drugs enabled a low re-thrombosis rate at 129 months of 3.6%, thereby permitting freedom from re-thrombosis of 96.4% of the whole group of 55 patients at 129 months (40). The re-thrombosis rate that we found in our previous prospective study (3.6%), contrasts with that observed in the whole group of patients which we are presenting here (1.5%);



**Figure 3** Of the 332 patients with the sticky platelet syndrome, 303 were treated solely with aspirin, whereas 29 were given aspirin plus other anticoagulant drugs.



**Figure 4** Number of patients worldwide with the sticky platelet syndrome in which their treatment has been described.





**Figure 5** Proposed algorithm of the treatment of persons with a history of thrombosis and the sticky platelet syndrome phenotype.

this may stem from the fact that the data collection period in our group is substantially longer. In our prospective study (40), we analyzed the platelet hyperreactivity before and after the delivery of the antiplatelet drug and switched from aspirin to clopidogrel if the laboratory abnormally did not revert with aspirin (i.e., ‘aspirin resistance’ or ‘high on treatment aspirin activity’) (40). In another papers, we have suggested that pregnant women with the SPS phenotype should be given aspirin during all the pregnancy, mainly if they have experienced previous miscarriages (32,69,70). In the studies which we have now analyzed, only two (4,40) refer to repeating the platelet aggregation studies after

starting antiplatelet drug therapy and then switching to another drug based on such testing; interestingly, despite the lack of any laboratory control of the treatment of persons with SPS, the re-thrombosis rate was very low (1.5%). This finding could militate against the recommendation of controlling the SPS treatment by means of platelet aggregometry studies but needs further investigation. There is no information available on the re-thrombosis rate in SPS patients not given antiplatelet drugs. *Figure 5* refers to the algorithm that we suggest to treat patients with SPS, based on our experience and that stemming from the papers herein analyzed (19).



## Conclusions

In summary, we have found that physicians worldwide are aware of the fact that the best treatment for persons with the SPS is the use of antiplatelet drugs. The rethrombosis rate is very low. Additional research on the SPS may be needed to better understand the pathophysiology of the condition; in the meanwhile, offering antiplatelet drugs to persons displaying the SPS phenotype seems adequate.

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