# Antiphospholipid syndrome update

### Jerry Scott Day

June 15, 2024

Dr. Chieh Min (Benjamin) Lai

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## Antiphospholipid Syndrome

Duarte-Garcia 2019 Arth Rheum; Dabit 2022 Curr Rheum Rep; Cervera 2002 Arth Rheum; Kearon 2018 Blood; Miranda 2019 JTH; Andreoli 2013 Arth Care Res; Kutteh 2014 Curr Op Ob Gyn

## Agenda

## 1. Diagnosis & classification

### 2. Treatment

## Problems with Sydney criteria





Manning 2024 JTH; Schreiber 2018 Nat Rev Dis Primers; Knight 2023 BMJ

## Other APS manifestations

### **PREVALENCE OF APS MANIFESTATIONS**



Cervera 2015 Ann Rheum Dis; Guidon 2022 Arth Res Ther; Pires da Rosa 2022 Scan J Rheum Found; Stojanovich 2013 Clin Exp Rheum

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### 2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria

Medha Barbhaiya,<sup>1\*</sup> <sup>(D)</sup> Stephane Zuily,<sup>2\*</sup> <sup>(D)</sup> Ray Naden,<sup>3†</sup> Alison Hendry,<sup>4</sup> Florian Manneville,<sup>5</sup> Mary-Carmen Amigo,<sup>6</sup> Zahir Amoura,<sup>7</sup> Danieli Andrade,<sup>8</sup> Laura Andreoli,<sup>9</sup> <sup>(D)</sup> Bahar Artim-Esen,<sup>10</sup> Tatsuya Atsumi,<sup>11</sup> Tadej Avcin,<sup>12</sup> <sup>(D)</sup> Michael H. Belmont,<sup>13</sup> Maria Laura Bertolaccini,<sup>14</sup> D. Ware Branch,<sup>15</sup> Graziela Carvalheiras,<sup>16</sup> Alessandro Casini,<sup>17</sup> Ricard Cervera,<sup>18</sup> Hannah Cohen,<sup>19</sup> Nathalie Costedoat-Chalumeau,<sup>2</sup> <sup>(P)</sup> Mark Crowther,<sup>21</sup> Guilherme de Jesus,<sup>22</sup> <sup>(D)</sup> Aurelien Delluc,<sup>23</sup> Sheetal Desai,<sup>24</sup> Maria De Sancho,<sup>25</sup> Katrien M. Devreese,<sup>26</sup> Reyhan Diz-Kucukkaya,<sup>27</sup> Ali Duarte-Garcia,<sup>28</sup> <sup>(D)</sup> Camille Frances,<sup>29</sup> David Garcia,<sup>80</sup> Jean-Christophe Gris,<sup>31</sup> Natasha Jordan,<sup>32</sup> Rebecca K. Leaf,<sup>33</sup> Nina Kello,<sup>34</sup> Jason S. Knight,<sup>35</sup> Carl Laskin,<sup>36</sup> Alfred I. Lee,<sup>37</sup> Kimberly Legault,<sup>38</sup> Steve R. Levine,<sup>39</sup> Roger A. Levy,<sup>40</sup> Maarten Limper,<sup>41</sup> Michael D. Lockshin,<sup>1</sup> Karoline Mayer-Pickel,<sup>42</sup> Jack Musial,<sup>43</sup> Pier Luigi Meroni,<sup>44</sup> Giovanni Orsolini,<sup>45</sup> Thomas L. Ortel,<sup>46</sup> Vittorio Pengo,<sup>47</sup> Michelle Petri,<sup>48</sup> <sup>(D)</sup> Guillermo Pons-Estel,<sup>49</sup> <sup>(D)</sup> Jose A. Gomez-Puerta,<sup>50</sup> <sup>(D)</sup> Quentin Raimboug,<sup>51</sup> Robert Roubey,<sup>52</sup> Giovanni Sanna,<sup>53</sup> Surya V. Seshan,<sup>54</sup> Savino Sciascia,<sup>55</sup> <sup>(D)</sup> Maria G. Tektonidou,<sup>56</sup> <sup>(D)</sup> Angela Tincani,<sup>10</sup> Denis Wahl,<sup>2</sup> Rohan Willis,<sup>57</sup> Cecile Yelnik,<sup>58</sup> <sup>(D)</sup> Catherine Zuily,<sup>59</sup> Francis Guillemin,<sup>5</sup> Karen Costenbader,<sup>60</sup> <sup>(D)</sup> and Doruk Erkan,<sup>1</sup> <sup>(D)</sup> on Behalf of the ACR/EULAR APS Classification Criteria Collaborators

To classify:  $\geq$ 3 pts clinical AND  $\geq$ 3 pts lab within 3 years of each other

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oligohydramnios, placenta path showing



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	$\geq$ 1 unexplained fetal death at 16-34 wk Pre-eclampsia <sup>d</sup> OR placental insufficiency <sup>e</sup> with severe features <34 wk Pre-eclampsia <sup>d</sup> AND placental insufficiency <sup>e</sup> with severe features <34 wk	1 3 4	a. Excludes genetic thrombophilia and thoracic outlet Sx. Major, cancer, trauma, fracture, surgery with GA>30', inpatient immobilization	maternal si remodeling vasculopati
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Once Persistent 12 weeks apart	1 5
L or aβ2GP1 ELISA <sup>I</sup> persistent 12 weeks apart	
IgM ≥ 40 units (moderate to high)	1
IgG 40-79 units (moderate)	4
lgG ≥ 80 units (high)	5
lgG ≥ 80 units (high) for both aCL & aβ2GP1	7

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## Validation



"Gold standard" adjudication made by: Robert Roubey (rheumatologist) Zahir Amoura (Internist/immunologist) Hannah Cohen (hematologist)



## New problems?



## New problems?



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## Agenda

### 1. Diagnosis & classification

### 2. Treatment

## Thrombosis: Secondary prevention Warfarin vs DOAC – Meta-analysis





## Thrombosis: Secondary prevention Warfarin vs DOAC in lower risk

Non-randomized studies							
Trial	type	N	Triple+	DOAC <sup>1</sup>	DOAC vs VKA TE risk		
Liu (2022)	Retro	143	<b>0%</b> (100% single+)	R <i>,</i> A	HR 1.08		
Williams (2021)	Retro	96	0%	R, A, D	RR 2.92 (p=0.11)		
Franke (2021)	Retro	200	4%	R, A, D, E	HR 0.78 (p=0.80)		
Malec (2020)	Pro	176	26%	R, A, D	HR 3.98 (p=0.004)		
Sato (2019)	Retro	54	37%	R, A, E	HR 11.9 (p<0.05)		

<sup>1</sup> R, Rivaroxaban; A, Apixaban; D, Dabigatran; E, Edoxaban

Liu 2022 EJH; Williams 2021 JTT; Franke 2021 Blood Coag Fibrin; Malec 2020 Lupus; Sato 2019 Lupus

## Thrombosis: Secondary prevention Recommendations

	EULAR 2019	ISTH 2020	NICE 2023	BSH 2020	CHEST 2021	AHA/ASA 2021
Warfarin	VTE ATE (preferred over ASA)	VTE with +++aPL ATE Microvascular Valvulopathy	VTE with +++ aPL	VTE with +++ aPL ATE	VTE, esp. +++aPL ATE	Stroke/TIA
DOAC	VTE if unable to achieve INR.	VTE with +/++aPL		VTE if already on DOAC.		Avoid Riva.
ASA	ATE (not as preferred as warfarin)					Acceptable while waiting for 2 <sup>nd</sup> aPL test

+++aPL = triple positive (anti-cardiolipin, anti-b2GP1, lupus anticoagulant positive) +/++aPL = single or double positive

Tektonidou 2019 Ann Rheum Dis; Zuily 2020 JTH; NICE guidelines with 2 Aug 2023 update; Keeling 2012 BJH; Arachchillage 2020 BJH; Stevens 2021 Chest; Kleindorfer 2021 Stroke

## Recurrence rates



## Thrombosis: Recurrences





Tektonidou 2019 Ann Rheum Dis; Cohen 2021 Blood (How I Treat); Cohen 2020 Lancet; Manning 2024 JTH

\* INR 2.0-3.0 should reflect Factor 2, 9, 10 down to 15-30%. Strong lupus anticoagulant may prolong PT/INR at baseline and make it look like INR is therapeutic. Strong LAC may also affect 1-step factor assays. Either check a chromogenic F9 or talk to hemepath to check if 1-step F2 and F10 assays with serial dilution show lack of parallelism (inhibitor LAC effect).

## Thrombosis: Recurrences



## Thrombosis: Recurrences





Manning 2024 JTH; Schreiber 2018 Nat Rev Dis Primers; Knight 2023 BMJ

## Future directions for immunomodulation



## Future directions for immunomodulation





## Questions?