Sindrome da anticorpi anti-fosfolipidi: che cosa abbiamo imparato dalla pandemia da COVID 19

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Torino

April 23, 2020

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

COVID-19 CASES

To rapidly communicate information on the global clinical effort against Covid-19, the Journal has initiated a series of case reports that offer important teaching points or novel findings. The case reports should be viewed as observations rather than as recommendations for evaluation or treatment. In the interest of timeliness, these reports are evaluated by in-house editors, with peer review reserved for key points as needed.

Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19

Yan Zhang et al. Wuhan - China

testing was performed while the patients were acutely ill.

Antiphospholipid antibodies abnormally target phospholipid proteins, and the presence of these antibodies is central to the diagnosis of the antiphospholipid syndrome. However, these antibodies can also arise transiently in patients with critical illness and various infections.[1] The presence of these antibodies may rarely lead to thrombotic events that are difficult to differentiate from other causes of multifocal thrombosis in critically patients, such as disseminated intravascular coagulation, heparin-induced thrombocytopenia, and thrombotic microangiopathy.

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Disclosure forms provided by the authors are available with the full text of this case at NEJM.org.

This case was published on April 8, 2020, at NEJM.org.

1. Uthman IW, Gharavi AE. Viral infections and antiphospholipid antibodies. Semin Arthritis Rheum 2002;31(4):256-63.

DOI: 10.1056/NEJMc2007575

Table 1. Demographic and Clinical Characteristics and Laboratory Findings.*

Characteristic	Patient 1	Patient 2	Patient 3
Demographic characteristics			
Age — yr	69	65	70
Sex	Male	Female	Male
Initial findings			
Medical history	Hypertension, diabetes, stroke	Hypertension, diabetes, coronary artery disease, no history of thrombosis	Hypertension, emphysema, nasopharyngeal carcinoma, stroke
Symptoms at disease onset	Fever, cough, dyspnea, diarrhea, headache	Fever, cough, dyspnea	Fever, fatigue, dyspnea, headache
Imaging features	Ground-glass opacity, bilateral pulmonary infiltrates	Ground-glass opacity, bilateral pulmonary infiltrates	Bilateral pulmonary infiltrates
Treatment before admission to ICU	Oseltamivir, intravenous immune globulin	Antibiotics	Antibiotics, ribavirin, rosuvastatin
Days from disease onset to thrombotic event	18	33	10
Findings on admission to ICU			
Days since disease onset	24	21	24
Disease severity	Critical	Critical	Critical

Prothrombin time (sec)	17.0	17.2	15.1
Activated partial-thromboplastin time (sec)	43.7	45.3	47.6
Fibrinogen (g/liter)	4.15	4.42	6.42
Fibrin degradation products (mg/liter)	85.5	8.1	7.3
D-dimer (mg/liter)	>21.00	2.84	3.23
Serum ferritin (μg/liter)	ND	2207.8	ND
Procalcitonin (ng/ml)	0.11	0.18	0.40
High-sensitivity C-reactive protein (mg/liter)	112.0	56.0	125.4
Antiphospholipid antibodies	Anticardiolipin IgA, anti–β_2-glycoprotein I IgA and IgG	Anticardiolipin IgA, anti–β_2-glycoprotein I IgA and IgG	Anticardiolipin IgA, anti–β_2-glycoprotein I IgA and IgG
Imaging features	Multiple cerebral infarctions in bilateral frontal parietal occipital lobe and bilateral basal ganglia, brain stem, and bilateral cerebellar hemispheres	Multiple cerebral infarctions in right frontal and bilateral parietal lobe	Multiple cerebral infarctions in frontal lobe, right frontal parietal temporal occipital lobe, and bilateral cerebellar hemispheres

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Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19

Antiphospholipid antibodies abnormally target phospholipid proteins, and the presence of these antibodies is central to the diagnosis of the antiphospholipid syndrome. However, these antibodies can also arise transiently in patients with critical illness and various infections.[1] The pres-

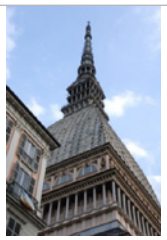
Caratteristiche di laboratorio

Covid- induced coagulopathy (CIC) *(Zang et al. NEJM 23/4/2020)*

- D-dimero elevato
- PT/PTT non disponibili ratios (ma di poco allungati…)
- ACA/IgA ed antibeta 2 GP1/IgG ed IgA pos, ma
- LA test non eseguito, ACA/IgG non disponibile
- "Titolo" dei tests I.E. non disponibile
- Test di conferma mancante

Commenti e quesiti

- Questi pazienti hanno una APS ?
- Che correlazione vi è fra COVID-19 ed APS ?
- L' APS può avere un rapporto causale nelle trombosi da Covid-19 ?
- Differenziare la CIC (Covid induced coagulopathy) da una DIC, HIT (heparin induced thrombosis), MOF, TMA (thrombotic microangiopathy) non è banale…



Covid 19 ed APS : Una associazione significativa ?

Dall'aprile -maggio 2020:

- Numerosi articoli (*PubMed: n. 93 nel 2020, 88 nel 2021*), nessuno definitivo
- Consorzio APS Regione Piemonte e Valle d'Aosta (Rete Malattie rare)
- GET UP (Gruppo Emostasi e trombosi Regione Piemonte e valle d'Aosta)

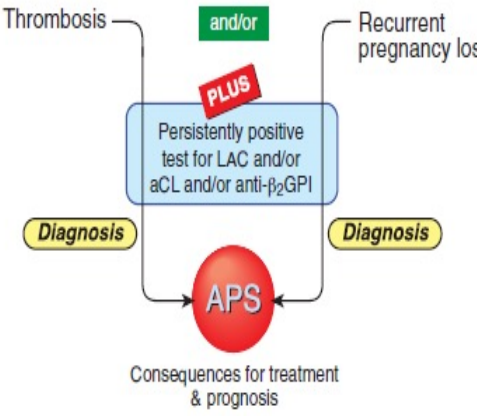
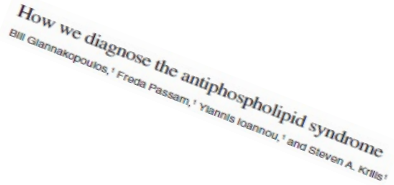


Figure 1. The updated classification criteria for APS.

SINDROME DA ANTICORPI ANTI-FOSFOLIPIDI (APS):

DEFINIZIONE


How we diagnose the antiphospholipid syndrome
Elli Giannakopoulos,[1] Freda Passam,[1] Yiannis Ioannou,[1] and Steven A. Krilis[1]

Sindrome acquisita, ***immuno-mediata, caratterizzata da manifestazioni cliniche (trombosi arteriose o venose, poliabortività o complicanze gravidiche tardive) associate alla evidenza di laboratorio di persistente presenza auto-anticorpi diretti contro i complessi anionici proteina-fosfolipidi***

M. Bazzan

Criteri classificativi SYDNEY 2006

Journal of Thrombosis and Haemostasis, **4**: 295–306

SPECIAL ARTICLE

International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS)

S. MIYAKIS,* M. D. LOCKSHIN,† T. ATSUMI,‡ D. W. BRANCH,§ R. L. BREY,¶ R. CERVERA,** R. H. W. M. DERKSEN,†† P. G. DE GROOT,†† T. KOIKE,‡ P. L. MERONI,‡‡ G. REBER,§§ Y. SHOENFELD,¶¶ A. TINCANI,*** P. G. VLACHOYIANNOPOULOS††† and S. A. KRILIS*

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Table 2 Revized classification criteria for the antiphospholipid syndrome

Antiphospholipid antibody syndrome (APS) is present if at least one of the clinical criteria and one of the laboratory criteria that follow are met*

Clinical criteria

1. Vascular thrombosis†

One or more clinical episodes‡ of arterial, venous, or small vessel thrombosis§, in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (i.e. unequivocal findings of appropriate imaging studies or histopathology). For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

2. Pregnancy morbidity

(a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or

(b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe pre-eclampsia defined according to standard definitions [11], or (ii) recognized features of placental insufficiency¶, or

(c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

In studies of populations of patients who have more than one type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b, or c above.

Laboratory criteria**

1. Lupus anticoagulant (LA) present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on LAs/phospholipid-dependent antibodies) [82,83].
2. Anticardiolipin (aCL) antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (i.e. >40 GPL or MPL, or >the 99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA [100,129,130].
3. Anti-β_2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titer >the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures [112].

*Classification of APS should be avoided if less than 12 weeks or more than 5 years separate the positive aPL test and the clinical manifestation. †Coexisting inherited or acquired factors for thrombosis are not reasons for excluding patients from APS trials. However, two subgroups of APS patients should be recognized, according to: (a) the presence, and (b) the absence of additional risk factors for thrombosis. Indicative (but not exhaustive) such cases include: age (>55 in men, and >65 in women), and the presence of any of the established risk factors for cardiovascular disease (hypertension, diabetes mellitus, elevated LDL or low HDL cholesterol, cigarette smoking, family history of premature cardiovascular disease, body mass index ≥30 kg m^{-2}, microalbuminuria, estimated GFR <60 mL min^{-1}), inherited thrombophilias, oral contraceptives, nephrotic syndrome, malignancy, immobilization, and surgery. Thus, patients who fulfil criteria should be stratified according to contributing causes of thrombosis. ‡A thrombotic episode in the past could be considered as a clinical criterion, provided that thrombosis is proved by appropriate diagnostic means and that no alternative diagnosis or cause of thrombosis is found. §Superficial venous thrombosis is not included in the clinical criteria. ¶Generally accepted features of placental insufficiency include: (i) abnormal or non-reassuring fetal surveillance test(s), e.g. a non-reactive non-stress test, suggestive of fetal hypoxemia, (ii) abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia, e.g. absent end-diastolic flow in the umbilical artery, (iii) oligohydramnios, e.g. an amniotic fluid index of 5 cm or less, or (iv) a postnatal birth weight less than the 10th percentile for the gestational age. **Investigators are strongly advised to classify APS patients in studies into one of the following categories: I, more than one laboratory criteria present (any combination); IIa, LA present alone; IIb, aCL antibody present alone; IIc, anti-β_2 glycoprotein-I antibody present alone.

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APS vascolare

Uno o piu' episodi clinici di trombosi venosa o arteriosa, in qualsiasi organo o tessuto, validato con criteri clinici (imaging) o istopatologici

DIAGNOSI

APS ostetrica

1) Una o piu' morti fetali > 10° settimana di gestazione
2) Una o piu' nascite di feti morfologicamente normali < 34° settimana per eclampsia, pre-eclampsia o insufficienza placentare
3) Tre o piu' aborti spontanei consecutivi < 10° settimana

Valutare LA, ACA ed antibeta 2 GP1 (IgG ed M)

↓

Se positività al primo controllo di almeno 1 dei tests :
RIPETIZIONE ESAMI (*TUTTI* : LAC, ACA, anti beta 2 GP1)
DOPO ALMENO 12 SETTIMANE

↓

SE NUOVAMENTE POSITIVO, SI CONFERMA LA DIAGNOSI DI SINDROME

Antiphospholipid syndrome in northwest Italy (APS Piedmont Cohort): demographic features, risk factors, clinical and laboratory profile

MT Bertero[1], M Bazzan[2], R Carignola[3], B Montaruli[4], E Silvestro[1], S Sciascia[5], A Vaccarino[2], S Baldovino[5], D Roccatello[5] and on behalf of the Antiphospholipid Piedmont Consortium*

[1]Immunologia Clinica, AO Ordine Mauriziano; [2]Ematologia e Malattie Trombotiche PO Torino Nord Emergenza S. Giovanni Bosco; [3]Day Hospital Internistico Controllizzato, AOU San Luigi Gonzaga di Orbassano; [4]Patologia Clinica, AO Ordine Mauriziano; and [5]Centro di Ricerche di Immunopatologia e Documentazione sulle Malattie Rare, PO Torino Nord Emergenza S. Giovanni Bosco, Italy

Table 1 General characteristics and index events in the APS Piedmont Cohort compared to the Euro-Phospholipid Cohort.[2]

Manifestation	*Piedmont Cohort* N *(%)*	*Euro-Phospholipid Cohort* N *(%)*
Number of patients	217	1000
Classification criteria	Myakis 2006[1]	Wilson 1999[5]
Mean age at study entry	43 ± 15	42 ± 14
PAPS	115 (52.9)	531 (53.1)
Male	55 (25.3)	180 (18.0)
CAPS	3 (1.3)	8 (0.8)
Deep venous thrombosis*	81 (31.3)	317 (31.7)
Pulmonary thromboembolism	26 (12.0)	90 (9.0)
Stroke	53 (24.4)	131 (13.1)
Acute myocardial infarction	10 (4.6)	28 (2.8)
Fetal loss	38 (17.5)	83 (8.3)

APS: antiphospholipid syndrome; PAPS: primary APS; CAPS: catastrophic APS. *Some patients presented with both deep venous thrombosis and pulmonary thromboembolism.

Lupus

STRATIFICAZIONE DEL RISCHIO ("aPL profile")

- Il tipo di positività ed il titolo della positività e l'isotipo delle Ig correlano un differente comportamento clinico

Triplice positività : rischio più elevato (LAC+ACA+antiB)(Pengo et al.)

Miyakis tipo 1 : associazioni di due test positivi

tipo 2a : LAC positivo isolato

tipo 2 b : ACA pos isolato

tipo 2 c : anti beta2GP1 pos isolato

- La **coesistenza** di fattori di rischio vascolare (fumo, ipertensione, ecc) e/o di condizioni pro-trombotiche congenite è da ricercare e valutare per la stratificazione del rischio
- **IgG >>>IgM**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19

Maximilian Ackermann, M.D., Stijn E. Verleden, Ph.D., Mark Kuehnel, Ph.D., Axel Haverich, M.D., Tobias Welte, M.D., Florian Laenger, M.D., Arno Vanstapel, Ph.D., Christopher Werlein, M.D., Helge Stark, Ph.D., Alexandar Tzankov, M.D., William W. Li, M.D., Vincent W. Li, M.D., Steven J. Mentzer, M.D., and Danny Jonigk, M.D.

Marzo 2020

METHODS

We examined 7 lungs obtained during autopsy from patients who died from Covid-19 and compared them with 7 lungs obtained during autopsy from patients who died from acute respiratory distress syndrome (ARDS) secondary to influenza A(H1N1) infection and 10 age-matched, uninfected control lungs. The lungs were studied with

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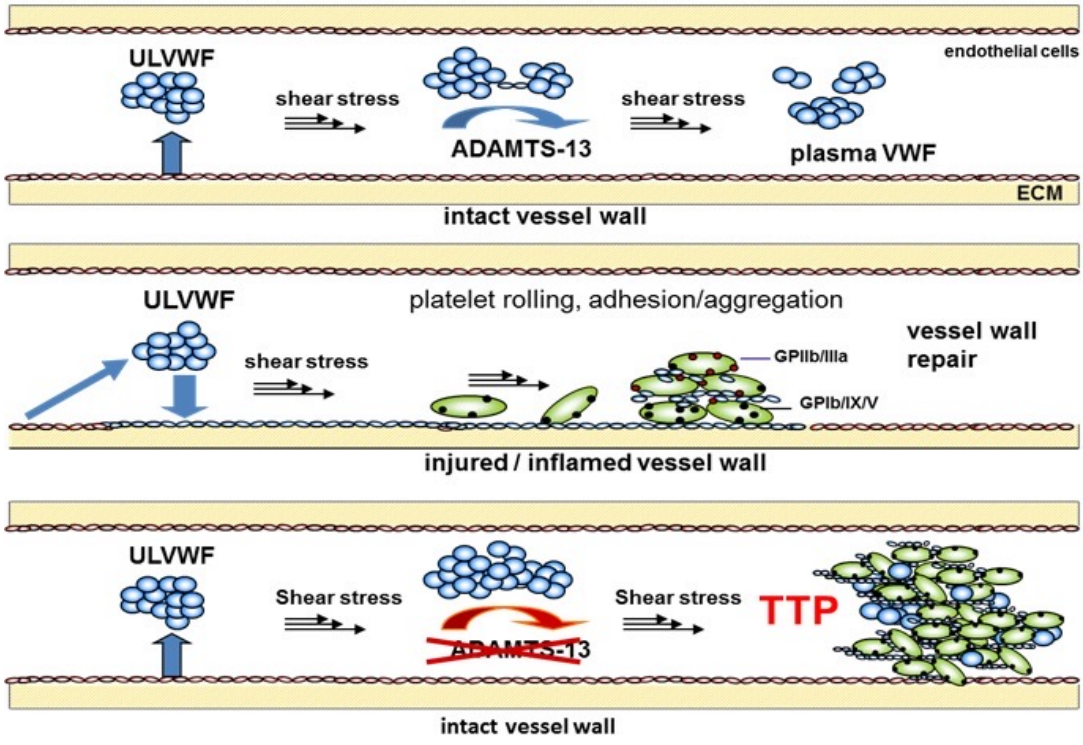
with perivascular T-cell infiltration. The lungs from patients with Covid-19 also showed distinctive vascular features, consisting of severe endothelial injury associated with the presence of intracellular virus and disrupted cell membranes. Histologic analysis of pulmonary vessels in patients with Covid-19 showed widespread

Coagulopatia da Covid -19 : profilo di laboratorio

- PT ed aPTT modicamente allungati, fibrinogeno normale o elevato (non è una CID)
- APL incostantemente presenti, raramente isotipo IgG, quasi mai triplice positività (non pare vera APS)
- D-dimero correla con mortalità, LDH elevato
- Moderata piastrinopenia (ma non come nella TTP)
- Istologia polmonare con grave danno endoteliale

….e se fosse una microangiopatia trombotica ?
Quali sono i livelli di ADAMTS-13 circolanti ?

ADAMTS 13 function



Internal and Emergency Medicine (2020) 15:861–863
https://doi.org/10.1007/s11739-020-02394-0

CE-RESEARCH LETTER TO THE EDITOR

Low ADAMTS 13 plasma levels are predictors of mortality in COVID-19 patients

30 Maggio 2020

Mario Bazzan[1] · Barbara Montaruli[2] · Savino Sciascia[3] · Domenico Cosseddu[2] · Claudio Norbiato[4] · Dario Roccatello[3]

Received: 26 May 2020 / Accepted: 30 May 2020 / Published online: 18 June 2020

Table 1 Laboratory profile at hospital admission dividing patients according to the outcome

	Not survivors = 9		Survivors = 79		*p*
Male (*N*, %)	6	66.7%	54	68.4%	0.91
Age (years: mean; SD)	71.89	7.1	59.37	12.7	0.037
PLTs (N/μL; mean ± SD)	139.65	81.4	267.9	163.09	0.022
vWF (IU/dL, mean; SD)	395.52	113.21	295.5	132.76	0.033
ADAMTS-13 (%, mean; SD)	32.17	15.56	50.6	18.17	0.035
PT/INR (mean; SD)	1.22	0.30	1.1	0.11	0.055
D-Dimer (ng/ml; mean ± SD)	4198.33	4947.33	1494.6	2024.17	0.106
D-Dimer > 3000 ng/ml (*N*, %)	5	55.6%	7	(8.8%)	0.0001
F/U days (mean; SD)	11.6	7.7	10.7	6.95	0.077

vWF von Willebrand factor, *PLTs* platelets, *F/U* follow-up

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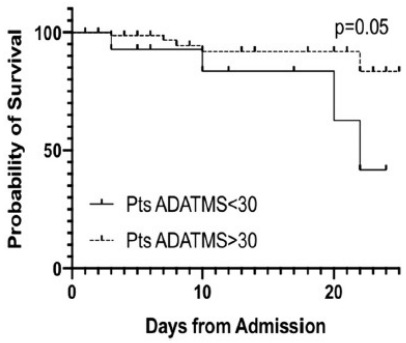

Fig. 1 Kaplan–Meier survival curves in COVID-19 patients according to ADATMS-13 plasma activity

with a fatal outcome [4, 5]. Taken the above together, CAC features seems more in line with a thrombotic, TTP-like microangiopathy (almost normal hemostasis, elevated vWF high and low ADAMTS-13, platelet count slightly reduced) rather than with a DIC (PT and antithrombin levels reduced, reduced fibrinogen, PLTS variably reduced, ADAMTs-13

Coagulation abnormalities and thrombosis in patients with COVID-19

www.thelancet.com/haematology Vol 7 June 2020

The combination of thrombocytopenia, prolonged prothrombin time, and increased D-dimer is suggestive of DIC, although the pattern is distinctively different to DIC seen in sepsis.[2] In sepsis, thrombocytopenia is usually more profound, and D-dimer concentrations do not reach the high values seen in patients with COVID-19. In fact, most patients with COVID-19 would not be classified as having DIC according to the DIC score of the International Society on Thrombosis and Haemostasis.[2,3]

Coagulation abnormalities and thrombosis in patients with COVID-19

Currently, there are no data on ADAMTS13 concentrations in patients with severe COVID-19 infection.

Coagulopatia da Covid -19

- La coagulopatia Covid-indotta non è una CID né una APS, ma una TMA atipica, Covid 19 indotta
- I livelli di ADAMTS-13 e la ratio VWF/ADAMTS-13 correlano con il rischio di mortalità.* *dati confermati da Peyvandi et al, Thromb and Hemost, dic 2020.*

…ma allora che ruolo hanno gli APL spesso riscontrati nei pazienti con COVID-19 grave ?

frontiers in Immunology

PERSPECTIVE
published: 16 June 2021
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Giugno 2021

Antiphospholipid Antibodies and Infection: *Non Nova Sed Nove*

Savino Sciascia[1,2], Massimo Radin[1], Mario Bazzan[3], Barbara Montaruli[4], Domenico Cosseddu[4], Claudio Norbiato[4], Maria Tiziana Bertero[4], Renato Carignola[5], Beatrice Bacco[4], Silvia Gallo Cassarino[4] and Dario Roccatello[1,2]*

METHODS

We included 261 patients (divided in three age and sex-matched controls groups of 87 patients):

1) Consecutive PCR-confirmed COVID-19–infected patients admitted at the AO Ordine Mauriziano Hospital, Torino, Italy
2) Age- and sex-matched controls with viral and bacterial infections* and no previous history of thrombotic events attending the S. Giovanni Bosco Hospital, Torino, Italy
3) Age and sex-matched patients with APS fulfilling Sidney's criteria (1) admitted at the S. Giovanni Bosco Hospital, Torino, Italy

frontiers in Immunology

PERSPECTIVE

Antiphospholipid Antibodies and Infection: *Non Nova Sed Nove*

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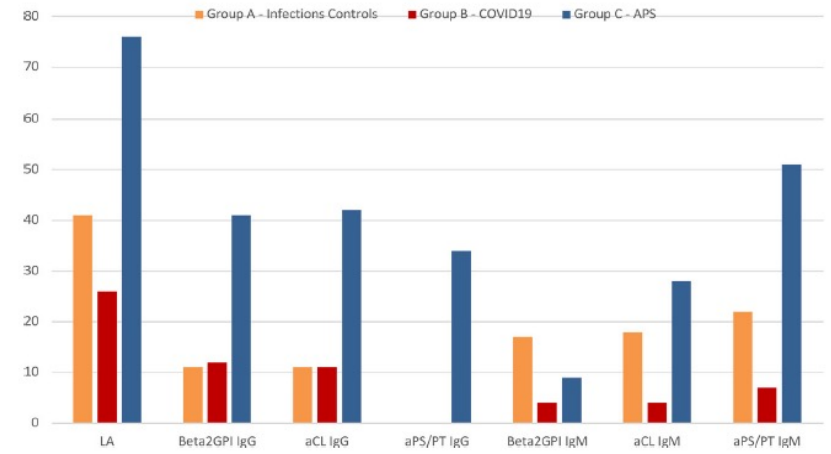
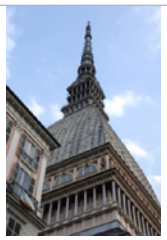


FIGURE 1 | Graphical representation of the rate of antiphospholipid antibodies positive patients between groups. APS, antiphospholipid syndrome; LA, lupus anticoagulant; aPS/PT, anti-phosphatidylserine/prothrombin antibodies; aβ2GPI, anti-β2-glycoprotein-I antibodies; aCL, anticardiolipin antibodies; Ig, immunoglobulin.

COVID 19 e coagulopatia : cosa abbiamo imparato

- Il Covid 19 “severo” si associa a presenza di aPL, come (o meno) di molte altre infezioni
- La presenza di aPL è con basso aPL profile, quasi sempre non patogenetica
- La coagulopatia Covid-indotta non è una CID né una APS, ma una TMA “atipica” virus-indotta
- I livelli di ADAMTS-13 e la ratio VWF/ADAMTS-13 correlano con la mortalità in questi pazienti.



….MA C’È ANCORA MOLTO DA IMPARARE

GRAZIE PER L’ATTENZIONE !

RINGRAZIAMENTI A :
CONSORZIO APS REGIONE PIEMONTE E VALLE D’AOSTA
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