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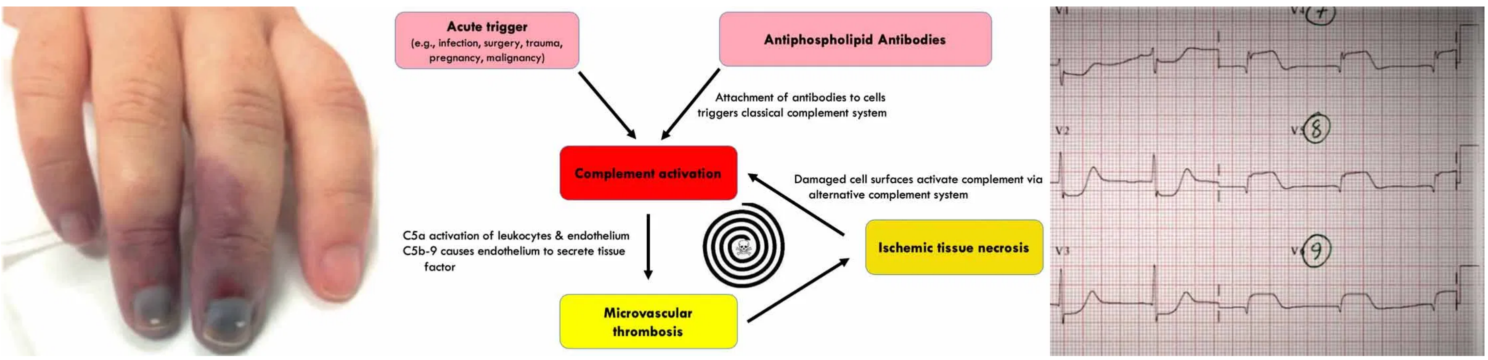
Catastrophic Antiphospholipid Syndrome (CAPS)

July 10, 2020 by **Josh Farkas**



(https://emcrit.org/ibcc/caps/attachment/capsheader/)

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pathophysiology

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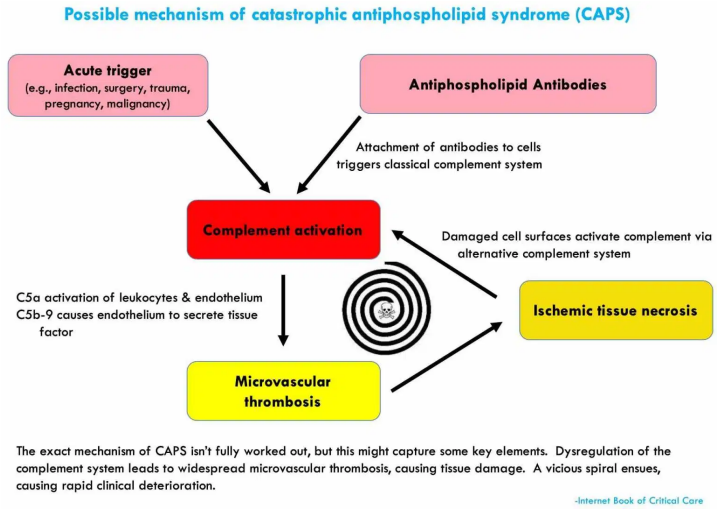
antiphospholipid syndrome

- This is a pro-coagulable condition caused by antibodies which bind to endothelial surfaces and trigger coagulation. Thrombosis may occur in arteries and/or veins.
- Antiphospholipid syndrome is more common in patients with lupus, but it can also occur on its own. It often presents with isolated large vessel vascular occlusions (e.g., DVT or PE).



(https://emcrit.org/ibcc/caps/attachment/capsmech/) **catastrophic antiphospholipid syndrome (CAPS)**

- CAPS is a severe manifestation of antiphospholipid syndrome that involves *accelerated* and *widespread* thrombosis, which may lead to multi-organ failure.
- CAPS appears to involve a vicious spiral of progressive complement activation, leading to microvascular thrombosis and tissue damage. Three general factors seem to be involved in generating this spiral:
  - [1] Antiphospholipid antibody.
  - [2] Genetic mutations which predispose the patient towards dysregulated complement activation. (31812994 (https://pubmed.ncbi.nlm.nih.gov/31812994/))
  - [3] Triggers which stimulate complement activation (e.g. acute infection).

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epidemiology & precipitating factors

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overall epidemiology

- CAPS is extremely rare.
- CAPS is the *initial* manifestation of antiphospholipid syndrome in about half of diagnosed CAPS patients. Remaining patients will carry a history of pre-existing antiphospholipid syndrome.
- Most patients with CAPS have *isolated* antiphospholipid syndrome, but some patients may have associated disorders (most often lupus, rheumatoid arthritis, or other rheumatologic disorders).

precipitating factor is present in about half of cases (29779928 (https://pubmed.ncbi.nlm.nih.gov/29779928/))

- Infection (49%)
  - Respiratory
  - Urinary tract
  - Skin
  - Gastrointestinal tract
- Surgery or trauma (17%)
- Malignancy (16%)
  - Especially hematologic: Hodgkin's and non-Hodgkin's lymphoma, acute lymphocytic leukemia, angiocentric lymphoma, chronic myelocytic lymphoma
  - Solid tumors: Most often lung or colon adenocarcinoma
- Anti-coagulation withdrawal or sub-therapeutic anti-coagulation (8%)
- Pregnancy complications or initiation of oral contraception (8%)
  - HELLP syndrome
  - Placental infarction
  - Pelvic thrombosis

- **Medications** (5%)
- **Flare of underlying autoimmune disease** (e.g., lupus)(3%)

clinical presentation

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renal failure (75% of patients)

- Acute kidney injury may occur.
- Hypertension may result from renovascular occlusion.
- Proteinuria may be seen (>500 mg/24 hours).

respiratory involvement (60% of patients)

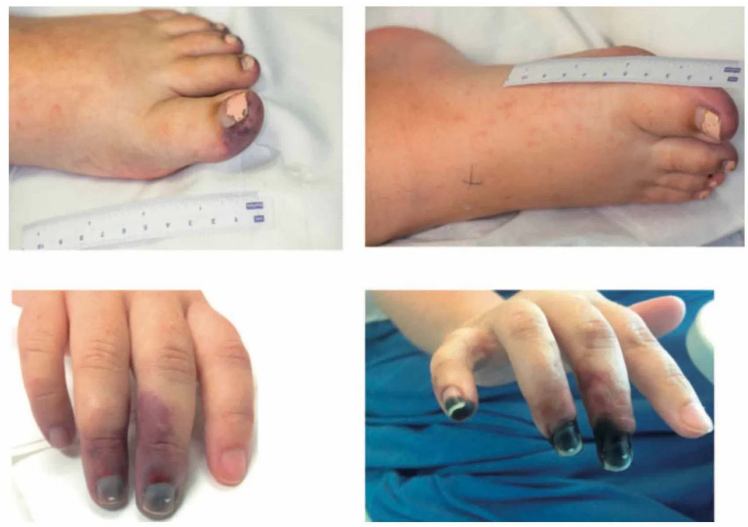
- Pulmonary Embolism is common.
- ARDS can occur, sometimes with pulmonary hemorrhage.

neurologic involvement (50% of patients)

- Encephalopathy, sometimes to the point of coma
- Seizure
- Large vessel infarction in ~10%
- Cerebral venous occlusion

cardiac involvement (45% of patients)

- Heart failure and myocardial infarction can occur. *Microvascular occlusions* can cause heart failure despite a normal-appearing cardiac catheterization.
- Noninfectious, Libman-Sacks endocarditis
- Adrenal insufficiency occurs in 15%, which may contribute to shock.



Necrosis of several digits was a sign of CAPS in this postpartum patient.
Sadick V, Lane S, Fisher E et al. 2018 J Intensive Care Soc

(https://emcrit.org/ibcc/caps/attachment/capsskin/)

skin manifestations (~40%)

- Livedo reticularis (40%)
- Cutaneous necrosis with digital gangrene (~15%)
- Purpura or splinter hemorrhages (31677977 (https://pubmed.ncbi.nlm.nih.gov/31677977/))

other less common manifestations

- Infarction of testes, ovaries, or prostate
- Gastric or colonic ulceration
- Thrombotic pancreatitis
- Adrenal infarction

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lab tests

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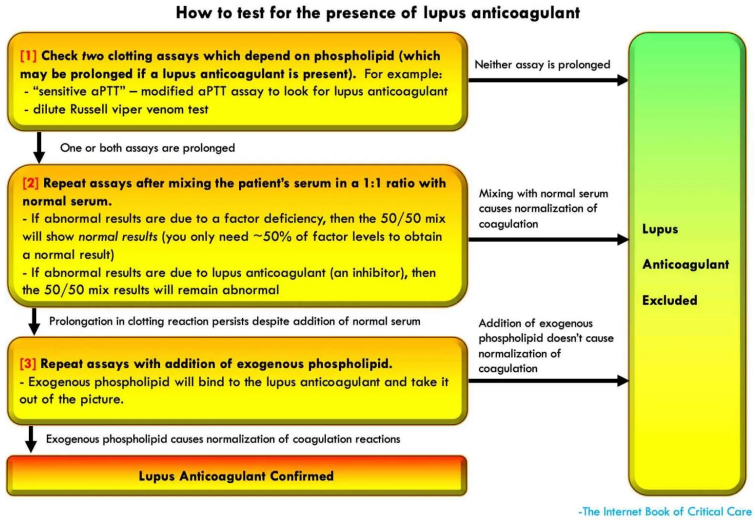
tests for antiphospholipid syndrome (if not already known)

- These include:
  - Anti-cardiolipin antibody (IgG & IgM) – Less specific (e.g. found in 1/3 of patients with heparin-induced thrombocytopenia).
  - Anti-beta-2-glycoprotein type I (IgG & IgM)
  - Lupus anticoagulant may be evaluated for as well (figure below and explored further here (https://emcrit.org/pulmcrit/lupus-anticoagulant/)).
- Antiphospholipid antibodies may be present in low levels, as an epiphenomenon due to other conditions which cause endothelial damage (e.g., sepsis). Thus, the mere presence of antiphospholipid antibodies doesn't establish the diagnosis.
  - Antibodies will usually be present in high titers among CAPS patients. (29779928 (https://www.ncbi.nlm.nih.gov/pubmed/29779928)) However, it is also possible that antibodies can be consumed by thrombosis, leading to low levels.



(https://emcrit.org/ibcc/caps/attachment/lupusanticoag/)

acute derangement of coagulation

- Thrombocytopenia (60%)
- Microangiopathic hemolytic anemia (20%)
  - Lab features of microangiopathic hemolytic anemia include markedly elevated lactate dehydrogenase (LDH), low haptoglobin, and schistocytes.
  - Schistocytes, if present, are usually scanty (unlike the abundant numbers seen in thrombotic thrombocytopenic purpura).(29779928 (https://www.ncbi.nlm.nih.gov/pubmed/29779928))
- Disseminated intravascular coagulation (~25%)
- PTT prolongation due to lupus anticoagulant may be seen.

systemic inflammation

- Elevated ferritin levels (>1,000 ng/ml)

labs panel for investigation of possible CAPS:

- Anti-phospholipid antibodies (anti-cardiolipin IgG & IgM, anti-beta-2-glycoprotein type I IgG & IgM)
- Laboratory evaluation for lupus anticoagulant (e.g. beginning with measurement of PTT and dilute Russel Viper Vemon test; see figure above).
- Anti-Nuclear Antibody (ANA)

- Electrolytes, BUN/Cr
- Complete Blood Count with blood smear examination
- Lactate dehydrogenase (LDH), haptoglobin
- D-dimer, coagulation studies

tissue diagnosis

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- Definitive diagnosis of CAPS requires biopsy evidence of small vessel thrombosis, but this is often not possible (due to the patient's instability and coagulation abnormalities).
- If skin lesions are present, these may be biopsied to demonstrate thrombosis.
- The risk/benefit ratio of pursuing biopsy of other organs is unknown. (29978552 (https://pubmed.ncbi.nlm.nih.gov/29978552/))

differential diagnosis

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closest mimics of CAPS (30504326 (https://pubmed.ncbi.nlm.nih.gov/30504326/))

- Microangiopathic hemolytic anemia
  - Thrombotic thrombocytopenic purpura (TTP)
  - Hemolytic uremic syndrome (HUS) & atypical HUS
  - Heparin induced thrombocytopenia (HIT)
  - Disseminated intravascular coagulation (DIC) with purpura fulminans
  - Medication-related microangiopathic syndromes
  - Malignant hypertension
  - Disseminated malignancy
- Sepsis
- Adrenal insufficiency (note: CAPS may *cause* adrenal insufficiency)
- Endocarditis
- Vasculitis
- Cholesterol emboli

comparison among some micro-angiopathic hemolytic disorders

	TTP	HUS	Atypical HUS	CAPS	HIT	DIC	Scleroderma renal crisis
Past medical history				- Antiphospholipid syndrome - SLE - Thrombotic events (e.g. pregnancy loss)			Scleroderma
Preceding symptoms/ trigger		Diarrhea due to Shigella or E. coli 0157:H7 infection	Pregnancy Malignant HTN Stem cell transplant (Disease itself may cause diarrhea due to GI involvement)	Pregnancy Sepsis Trauma/surgery D/c anticoagulation SLE flare Malignancy	Heparin exposure UFH > LMWH Surgery > Medical pt	Sepsis Malignancy Trauma	
Distinguishing laboratory abnormalities	- Low ADAMTS13 - Thrombocytopenia more severe (<30) - Schistocytes - PT/PTT often normal	- Schistocytes - PT/PTT often normal	- Schistocytes - PT/PTT often normal	- Antiphospholipid antibodies - +/- schistocytes - May see PTT prolongation due to lupus anticoagulant	- +/- schistocytes - Anti-PF4 antibodies	- +/- schistocytes - PT/PTT abnormal - D-dimer markedly elevated - Fibrinogen can be low	- +/- schistocytes
Size of vessel involvement	Small vessels	Small vessels	Small vessels	Large/small vessels	Large/small vessels	Large/small vessels	Small vessels
Organ system involvement	- Kidneys (typically mild, Cr <2.5) - CNS - Heart - Alimentary tract (n/v, diarrhea)	- Kidney only	- Kidney - Alimentary tract (n/v, diarrhea)	- Renal failure - CNS - Heart - Lungs - Prominent skin necrosis may occur		- Prominent skin necrosis may occur	
Response to plasmapheresis	Generally clinical response within 3-5 days	No significant improvement.	At best partial response in laboratory values, but organ failure continues.				

-The Internet Book of Critical Care

(https://emcrit.org/ibcc/caps/attachment/capstable/)

diagnostic criteria

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diagnostic criteria

1. Involvement of three or more organs, systems, or tissues.

2. Development of manifestations simultaneously or in less than a week.
3. Confirmation by histopathology of small vessel occlusion in at least one organ or tissue.
4. Laboratory confirmation of the presence of anti-phospholipid antibodies (i.e., lupus anticoagulant and/or anti-cardiolipin antibodies).

definition of CAPS:

- **Definite CAPS** = all four criteria. Sources disagree about whether it is necessary to demonstrate that antiphospholipid antibodies *persist* for six weeks after the initial episode (if anti-phospholipid syndrome wasn't previously diagnosed).
- **Probable CAPS** may be reached in a variety of different ways:
  - All four criteria, except that only two organs/systems involved.
  - All four criteria, except for absence of laboratory confirmation due to early death of a patient never tested for antiphospholipid antibodies.
  - Criteria #1, #2, and #4 (everything except pathological confirmation).
  - Criteria #1, #3, and #4 are met, with the development of a third event within 1-4 weeks after presentation (despite anticoagulation).

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treatment

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Treatment for CAPS is poorly defined, due to the rarity of this condition (no RCT-level evidence exists). To make matters more confusing, *treatment often needs to be started before the diagnosis is entirely certain*. Initial treatments are shown below, but hematology consultation should be obtained regarding additional therapies (e.g., rituximab, eculizumab, plasmapheresis).

general measures

- Identify and treat any underlying cause (e.g., sepsis, debridement/amputation of necrotic tissue).
- Aggressive anti-hypertensive therapy (uncontrolled hypertension may worsen intravascular hemolysis).
- Avoid intravascular catheters (especially arterial lines), as these tend to clot off.

heparin anti-coagulation

- Heparin is probably the most important treatment (correlating most strongly with good outcomes in retrospective series).
- Heparin infusion is used initially, although low molecular weight heparin also seems to work.
  - Ideally, heparin infusions should be titrated against anti-Xa level (because many patients will have lupus anticoagulant, which artificially increases the PTT).
- Eventually, heparin should be transitioned to oral anticoagulation with warfarin. Case reports suggest oral anti-Xa inhibitors may not work well. (32223511 (https://pubmed.ncbi.nlm.nih.gov/32223511/))

steroid

- Rationales for steroid use:
  - CAPS typically involves a pro-inflammatory state.
  - Steroid could treat some underlying rheumatological disorders (e.g., lupus), potentially decreasing the production of anti-phospholipid antibodies.
- The CAPS registry shows that steroid was used in 99% of cases. Unfortunately, there is no high-quality data to support steroid use.
- The optimal steroid dose is unknown. Traditionally a pulse of methylprednisolone is used (e.g., 1,000 mg/day for 3-5 days), but it's dubious whether such a high dose is actually needed. For example, 250-750 mg methylprednisolone daily for three days could be sufficient. (29779928 (https://www.ncbi.nlm.nih.gov/pubmed/29779928)) The McMaster guidelines recommended against steroid *monotherapy*, but *did* recommend steroid in combination with heparin and IVIG or plasmapheresis – illustrating the level of equipoise regarding steroid. (29978552) (https://pubmed.ncbi.nlm.nih.gov/29978552/)

plasmapheresis and/or intravenous immunoglobulin

- These are both nonspecific therapies aimed at reducing the activity of anti-phospholipid antibodies. Plasmapheresis removes antibodies directly, whereas intravenous immunoglobulin may increase antibody turnover.

- Where these therapies should fit within an overall treatment strategy remains unclear. To date, retrospective case series suggest the best outcomes occur when treatment includes steroid, heparin, and either plasmapheresis or IVIG. (29779928 (https://www.ncbi.nlm.nih.gov/pubmed/29779928) , 29978552 (https://pubmed.ncbi.nlm.nih.gov/29978552/))
- Plasmapheresis
  - Plasmapheresis might be preferred over IVIG in patients with microangiopathic hemolytic anemia or renal dysfunction (given the risk of kidney injury with IVIG). (29978552 (https://pubmed.ncbi.nlm.nih.gov/29978552/))
- IVIG
  - IVIG might be preferred over plasmapheresis in CAPS patients with immune thrombocytopenia, given evidence of benefit in that condition. (29978552 (https://pubmed.ncbi.nlm.nih.gov/29978552/))
  - Typical regimens include 0.4 g/kg/day for five days or 1 g/kg/day for two days.

eculizumab

- This is a monoclonal antibody that binds and inhibits complement protein C5.
- Traditionally eculizumab has been reserved for more refractory cases. However, increasing insight into the pathophysiology suggests that complement activation is a primary driver of the illness, suggesting that eculizumab may be beneficial if initiated earlier. (31812994 (https://pubmed.ncbi.nlm.nih.gov/31812994/))
- Several case reports describe efficacy at initial doses of ~900 mg weekly (analogous to the regimen of eculizumab for atypical hemolytic uremic syndrome).(32252584 (https://pubmed.ncbi.nlm.nih.gov/32252584/))
- Eculizumab increases the risk of meningococcal meningitis by ~1,000-fold, so meningococcal vaccines and antibiotic prophylaxis should be considered.

rituximab

- B-cell suppression may be a rational strategy with a goal of reducing anti-phospholipid antibody production.
- This may be considered for refractory cases. (29978552 (https://pubmed.ncbi.nlm.nih.gov/29978552/))

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summary

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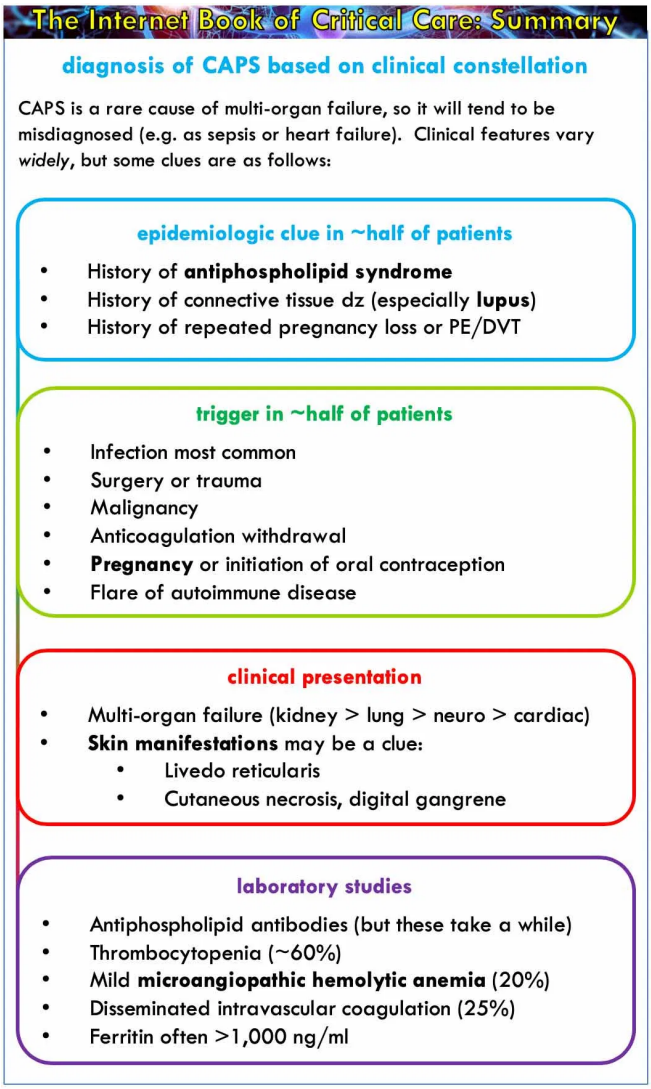

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podcast

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questions & discussion

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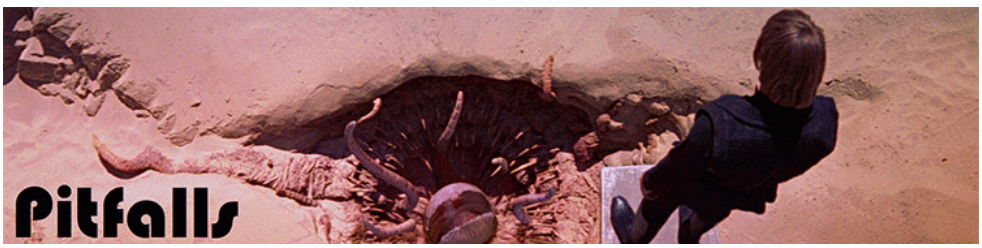
To keep this page small and fast, questions & discussion about this post can be found on another page ***here*** (https://emcrit.org/pulmcrit/caps/) .



(https://i0.wp.com/emcrit.org/wp-content/uploads/2016/11/pitfalls2.gif)

- Failure to consider CAPS as a competing diagnosis, in a patient with multi-organ failure who has been labeled as having septic shock.
- Delaying therapy for CAPS pending arrival at a definitive diagnosis.

Going further:

- CAPS (http://www.emdocs.net/catastrophic-antiphospholipid-syndrome-caps/) (emDocs, Tim Montrief)
- CAPS case (http://maryland.ccproject.com/2014/05/07/catastrophic-antiphospholipid-syndrome-e-clotting-gone-wild/) (Maryland CC project, Katelyn Donohue and Christina Tupe)

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The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.

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