

I.MEU

RUOLO.TALENTO.PASSIONE.IDEE

XIII congresso nazionale

simeu

GENOVA 30 MAG - 1 GIU 2024



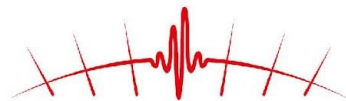
LA CAPILLARY LEAK SYNDROME

Massimo Cazzaniga

Pronto Soccorso

Ospedale A. Manzoni

ASST Lecco



XIII congresso nazionale

simeu

GENOVA 30 MAG - 1 GIU 2024

CHALLENGES IN **CAPILLARY LEAK SYNDROME** MANAGEMENT IN EMERGENCY ROOM

Correct Diagnosis

Quick Diagnosis

Adequate Initial Treatment in Emergency Room

CHALLENGES IN **CAPILLARY LEAK SYNDROME** MANAGEMENT IN EMERGENCY ROOM

Correct Diagnosis

Quick Diagnosis

Adequate Initial Treatment in Emergency Room

DIAGNOSIS

- Da Sydenham (~ 1650) in poi, la diagnosi è una interpretazione di sintomi e segni che serve ad allocare un paziente in una categoria nosologica – una malattia
- Ma fino alla metà (circa) del secolo scorso, la diagnosi era essenzialmente uno strumento di classificazione linneana, con benefici di salute solo per poche malattie
- Oggi, la diagnosi è basata su sintomi, segni e molti altri dati, e la categoria nosologica (=malattia) in cui il paziente è allocato segna l'inizio di terapie molto spesso efficaci
- Alcuni strumenti della diagnosi: illness scripts; heuristics; la storia; Lab; imaging

1. Alcuni strumenti della diagnosi: la storia



La storia: "unica occasione di un vero incontro tra il medico e il malato è delegata dal professore all'aiuto, all'assistente, allo specializzando, allo studente interno, all'ultimo arrivato".



Ciò imprime nello studente e nel medico in formazione "l'idea che questo rapporto con il malato è in fondo un rapporto accessorio, non necessario; questa idea lo studente se la porterà sempre con sé, la porterà anche nell'ospedale, nell'ambulatorio, ovunque"

from a lecture of
Luigi Pagliaro
Profemerito di
Medicina Interna
Università di
Palermo
SIMI 2008

1. Da una lettera di Giulio Maccacaro al Presidente dell'OdM di Milano, 1972

4. L'errore diagnostico: cause cognitive



It never crossed my mind.

I paid too much attention to one finding, especially lab results.

I didn't listen enough to the patient's story.

I was too much in a hurry.

I didn't know enough about the disease.

I let the consultant convince me.

I didn't reassess the situation.

The patient had too many problems at once.

I was influenced by a similar case.

I failed to convince the patient to investigate further.

I was in denial of an upsetting diagnosis.

from a lecture of
Luigi Pagliaro
Profemerito di
Medicina Interna
Università di
Palermo
SIMI 2008

From: Bordage G. Why did I miss the diagnosis? Some cognitive explanations and educational implications. Acad Med 1999; 74: S138-43

IDIOPATHIC CAPILLARY LEAK SINDROME (ICLS) CLARKSON DISEASE

Clarkson et al.

Cyclical edema and shock due to increased capillary permeability
Am J Med 1960;29:193–216

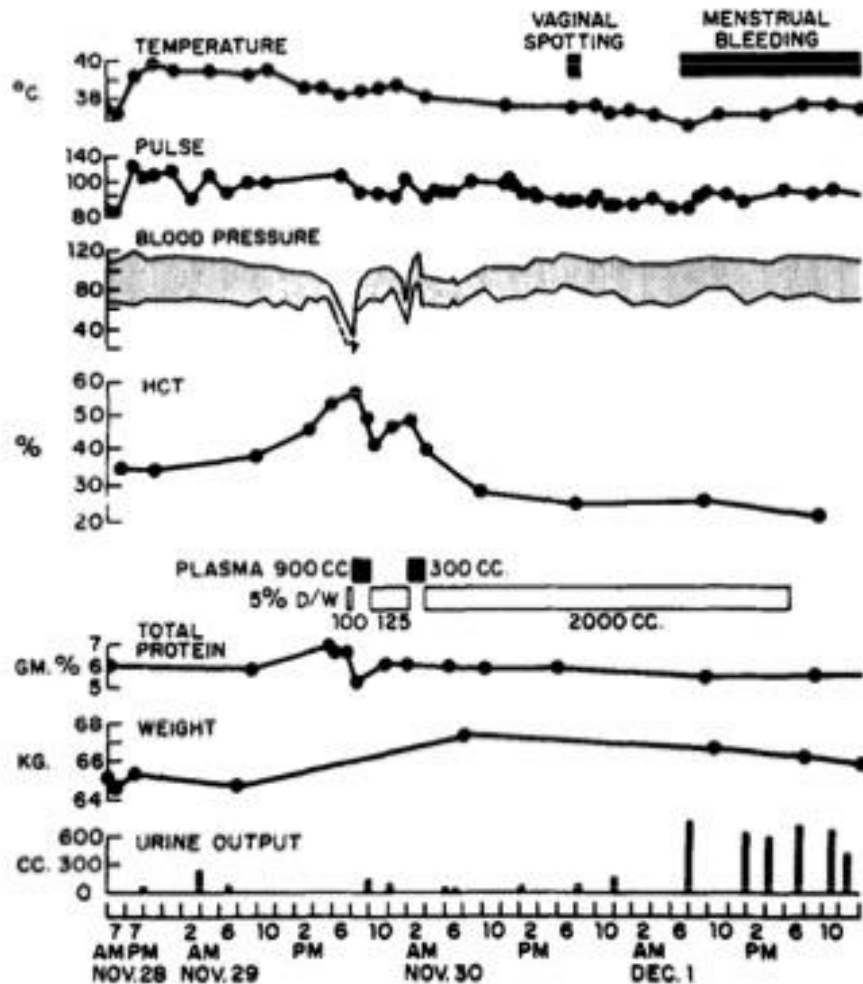
- 34 yrs. white woman of Italian descent
- Benign breast cancer
- In excellent health until 32 yrs
- From February 1956, she experienced episodes of sudden and marked leak of plasma from her vascular bed that she would go into profound hypovolemic shock.



- I. Fatigue, malaise, mild rhinorrhea and hoarse voice some days before her period
- II. Nausea and vomiting, Swelling of face, neck and all extremities, Palpitations and shortness of breath
- III. Resolution of all symptoms

CLARKSON DISEASE

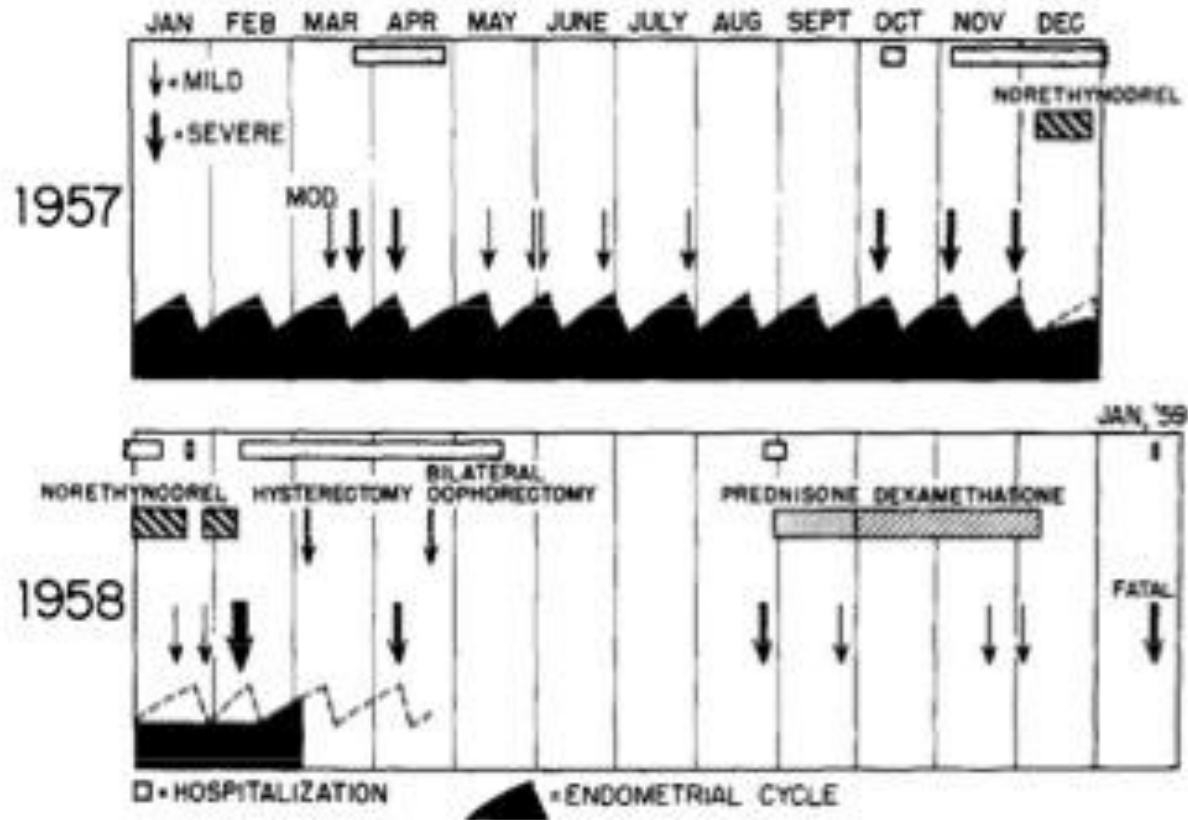
Observations During an Episode of Shock



CLARKSON DISEASE – Characteristics of severe episodes

Date	Edema	Weight gain (Kg)	Max Ht (%)	Min Ht (%)	Highest BUN mg,%)
3/23/57	+	3	74	38	25
4/8/57	++	4	62	29	21
10/7/57	+++	4	58	32	27
11/4/57	++++	6	60	30	31

CLARKSON DISEASE - Time Course

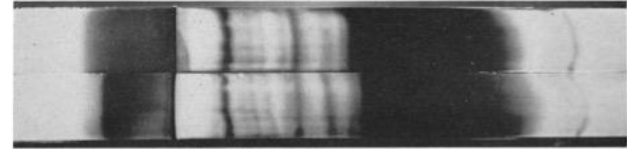
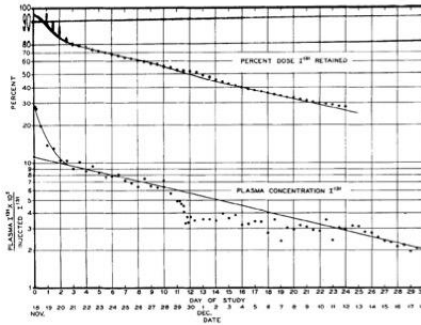


Clarkson et al. Am J Med 1960

CLARKSON DISEASE

Radioactive iodinated serum albumin studies demonstrated increased capillary permeability

Electrophoresis revealed abnormal gamma globulins



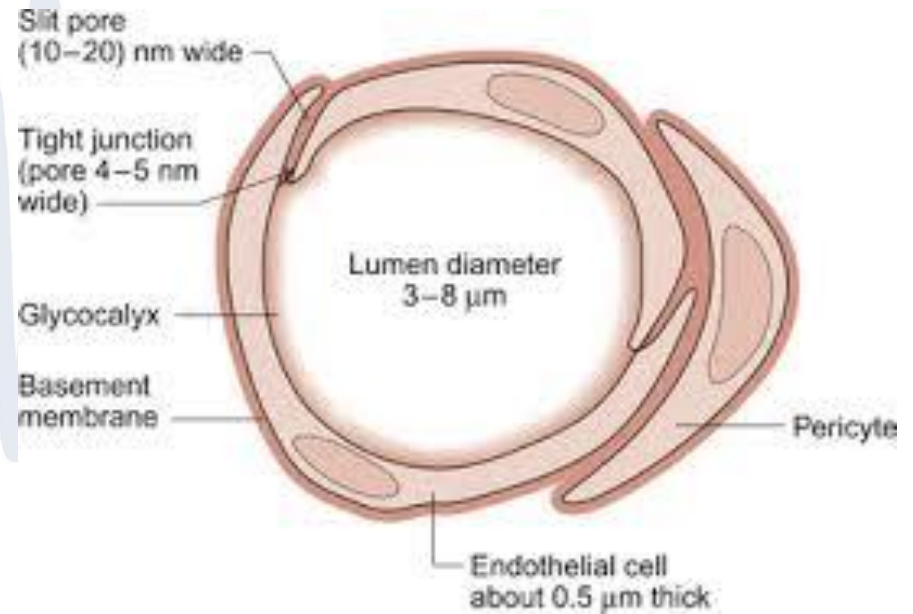
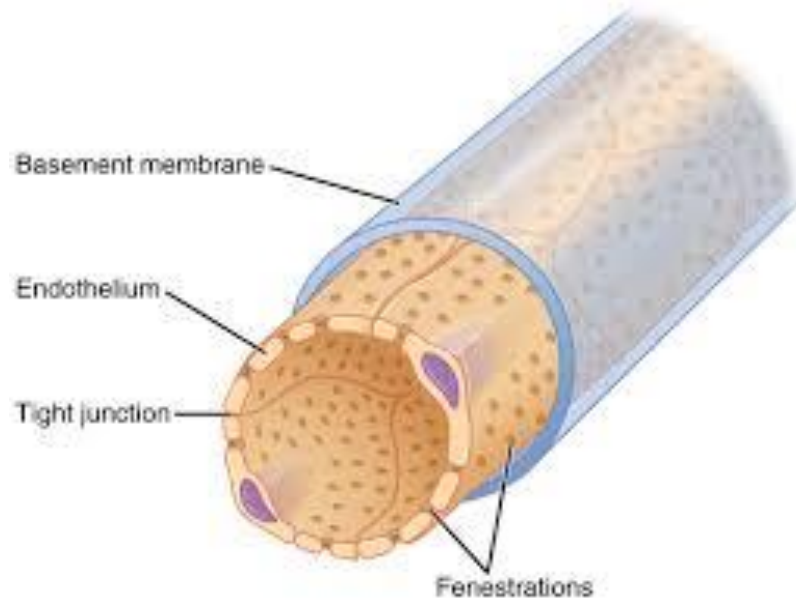
CLARKSON DISEASE

- January 20, 1959
- During an usual episode of shock
 - ...suddenly, with no evidence of congestive failure, she gasped, no heart sounds or pulse could be detected...and the respiratory movements ceased
 - ...the chest was open immediately ..the heart was in asystole
 - ...despite cardiac massage and usual resuscitation procedures
 - ...she was pronounced dead.

Definition of Idiopathic Capillary Leak Syndrome (ICLS) or Clarkson's Disease

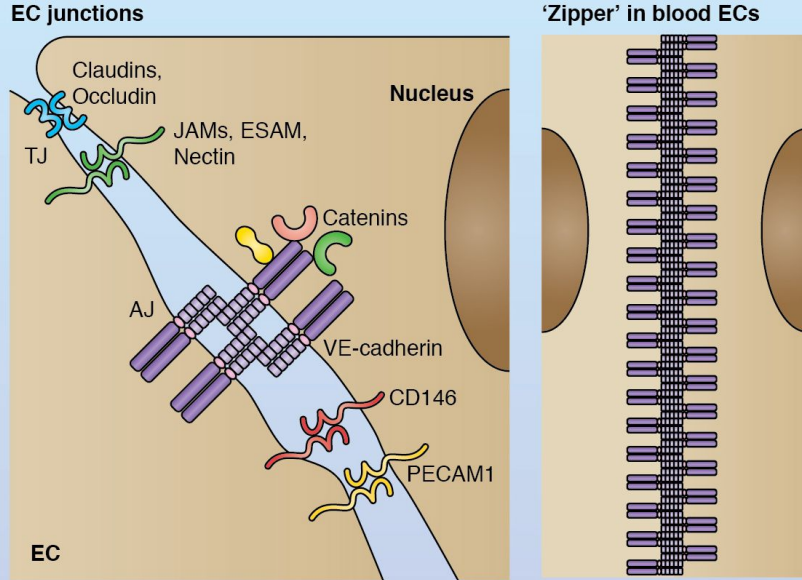
- a rare and potentially fatal condition in otherwise healthy individuals
- characterized by **recurrent episodes of capillary leakage** that occur in three phases:
 - ***Prodromic phase***
 - ***Initial phase*** (fluid extravasation associated with hypovolemia)
 - ***second phase*** (fluid reabsorption associated with polyuria and flash pulmonary edema)

CAPILLARY STRUCTURE

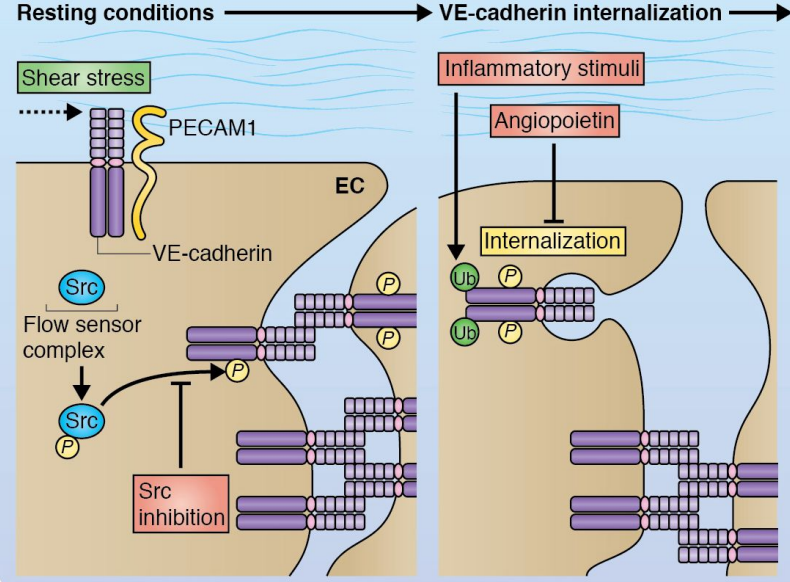


ENDOTHELIAL ADHERENS JUNCTIONS

Overview of different EC junctions



VE-cadherin phosphorylation and internalization



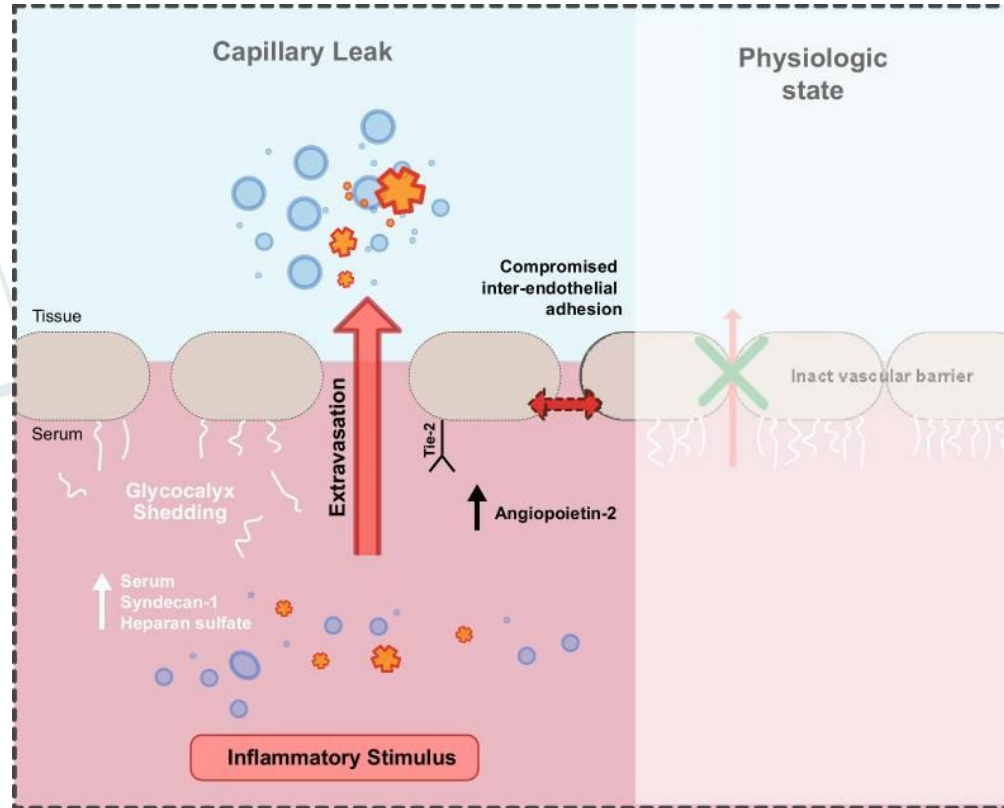
Mechanisms of capillary leakage

$$J_v = K_f([P_c - P_i] - \sigma[\pi_c - \pi_i])$$

PRESSIONE DI FILTRAZIONE = PRESSIONE IDROSTATICA EFFETTIVA - PRESSIONE ONCOTICA EFFETTIVA

- **Increased hydrostatic pressure** -> heart failure, renal failure, cirrhosis
- **Decreased capillary oncotic** -> nephrotic syndrome, protein losing enteropathy, decreased albumin synthesis)
- **Increase capillary permeability** -> it allows fluid and protein to readily pass through the endothelial barrier and into the interstitium

Mechanisms of capillary leakage in ICLS



Hypotheses in ICLS

- Abnormalities in VEGF and angiopoietin 2
- Monoclonal proteins
- Endothelial cell apoptosis
- Involvement of IL-2
- Inflammatory mediators

Different causes of capillary leakage

- *sepsis*
- *anaphylaxis*
- *major burn injuries*
- *ovarian hyperstimulation syndrome*
- *hemophagocytic lymphohistiocytosis*
- *viral hemorrhagic fevers*
- *autoimmune diseases*
- *snakebite envenomation*
- *drugs (interleukins [IL2], monoclonal antibodies, gemcitabine)*

CLINICAL MANIFESTATIONS in ICLS

Prodromic phase

Triggers

- Upper respiratory tract infection
- Flu-like illness
- Physical exertion
- During menses

Prodromal symptoms

- Oliguria
- Fatigue
- Syncope
- Abdominal pain
- Nausea
- Myalgias
- Edema
- Sudden increase in body weight

CLINICAL MANIFESTATIONS in ICLS

Fluid extravasation phase



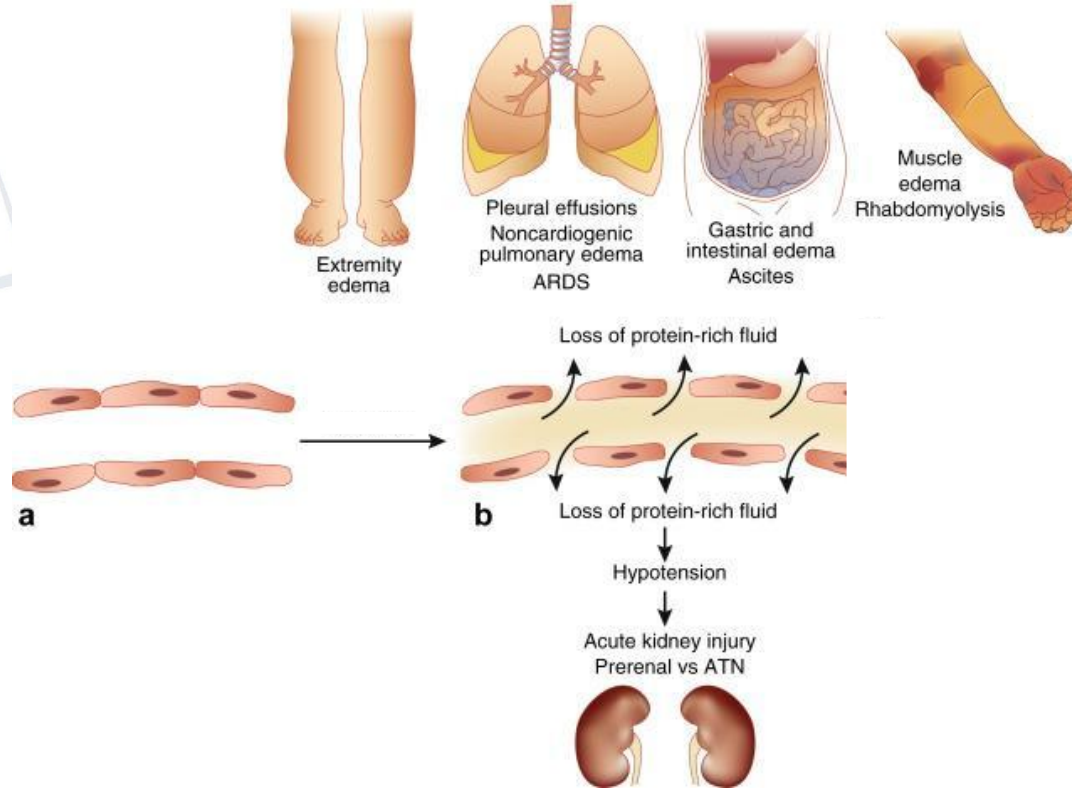
Hypotension

Hemoconcentration

Edema

CLINICAL MANIFESTATIONS in ICLS

Fluid extravasation phase (median duration: 3-4 days)





CLINICAL MANIFESTATIONS in ICLS Recovery (Fluid Reabsorption) phase

Poliuria

Quickly intravascular volume overload

Pulmonary edema

DIAGNOSTIC CLUES OF ICLS

Hypotension

Hemoconcentration

Hypoalbuminemia

Monoclonal Gammopathy

EPIDEMIOLOGY OF ICLS IN FRENCH REGISTRY (EurêClark)

Table 1. Characteristics and Outcomes of 28 New Patients With SCLS

Patient*	Sex	Age, y		Observation Time From Diagnosis, mo	Total Attacks, n		Outcome	Cause of Death
		At Onset	At Diagnosis		All	Severe†		
1	F	46.6	46.6	27.7	1	1	Alive	
2	F	36.4	37.1	161.0	21	6	Alive	
3	M	68.5	70.7	75.0	4	3	Alive	
4	M	59.1	59.8	40.4	6	1	Alive	
5	F	42.9	44.8	66.1	59	5	Alive	
6	M	62.2	64.3	158.9	2	2	Dead	Unknown
7	F	45.1	52.3	159.5	22	5	Alive	
8	F	61.0	63.2	44.5	14	5	Alive	
9	M	64.3	65.0	9.6	4	1	Dead	Myeloma, stroke, and SCLS
10	M	60.9	60.9	40.1	1	1	Alive	
11	F	26.4	26.9	30.9	2	2	Dead	H1N1 influenza and SCLS
12	F	46.9	49.5	140.3	2	2	Alive	
13	F	5.4	5.7	32.5	4	2	Dead	SCLS
14	F	69.1	69.2	0.9	3	2	Dead	SCLS
15	M	59.1	59.1	32.8	1	1	Alive	
16	M	47.8	47.9	86.2	10	0	Alive	
17	M	44.9	45.4	96.9	3	2	Alive	
18	F	47.4	48.5	14.8	8	4	Dead	SCLS
19	F	48.8	58.0	41.0	5	2	Dead	Septic shock
20	F	53.6	53.6	99.2	6	5	Lost to follow-up	
21	F	77.7	78.0	150.5	25	21	Alive	
22	M	49.5	49.5	86.7	7	4	Alive	
23	M	58.4	58.5	80.3	11	3	Alive	
24	F	42.9	43.9	89.5	11	4	Alive	
25	F	43.8	43.8	102.9	10	2	Alive	
26	M	63.7	64.5	10.5	3	2	Dead	SCLS
27	M	43.6	43.6	22.0	3	2	Alive	
28	M	61.0	63.2	15.5	4	2	Alive	

Gousseff et al.
Ann Intern Med 2011

DEMOGRAPHIC, CLINICAL AND LABORATORY FINDINGS OF ICLS IN FRENCH REGISTRY

Characteristics	Pts. n = 28
SEX (m/f)	13 / 15
Age at disease onset (yrs.)	49.1 (5-77)
Age at diagnosis (yrs.)	52.9 (6-78)
Diagnostic delay (mo.)	7 (0-110)
Systolic Blood Pressure [mmHg]	60 (10 – 105)
Weight gain [kg]	7 (3.6 – 12)
Hematocrit [%]	59% (37% - 76%)
Protein [g/dL]	4.3 (2.7 – 6-6)
Albumin [g/dL]	2.1 (1.1 – 3.8)
Creatinine [mg/dL]	1.5 (0.8 – 4.2)
Monoclonal gammopathy	25 (89%)

Gousseff et al.
Ann Intern Med 2011

OUTCOMES OF ICLS IN FRENCH REGISTRY

Outcomes	
Follow-up from diagnosis (mo.)	55.3 (1-161)
Total number of attacks (severe attacks)	252 (92)
Annual frequency per person for attacks	1.23 (0.13 – 21)
Annual frequency per person for severe attacks	0.46 (0.0 – 14)
Deaths	8 (29%)
Deaths directly related to ICLS attack	6 (75%)

Gousseff et al.
Ann Intern Med 2011

COMPLICATIONS OF ICLS IN FRENCH REGISTRY

Table 2. Complications Observed During 252 Attacks Recorded in 28 New Patients With the Systemic Capillary Leak Syndrome

Complication	Patients (n = 28), n (%)	Attacks With Complication, (n = 252), n (%)	Median Attacks With Complication per Patient (Range), n*
Acute renal impairment	25 (89)	77 (31)	2 (1–12)
Rhabdomyolysis	12 (43)	21 (8)	1.5 (1–4)
Arrhythmia†	6 (21)	10 (4)	1.5 (1–3)
Pericardial effusion	4 (14)	5 (2)	1 (1–2)
Compartment syndrome	3 (11)	3 (1)	1 (1–1)
Pancreatitis	2 (7)	3 (1)	1.5 (1–2)
Deep venous thrombosis	1 (4)	1 (0.4)	1 (1–1)
Myocardial edema	1 (4)	1 (0.4)	1 (1–1)

Gousseff et al.
Ann Intern Med 2011

ICLS IN AN ITALIAN SINGLE CENTER EXPERIENCE

Table 1 Baseline and acute-attack vital parameters, together with hematocrit and albumin values recorded at baseline and during attacks

Patient	Base-line BP (mmHg)	Base-line HR (bpm)	Minimum BP during attack (mmHg)	Maximum HR during attack (bpm)	Baseline Hct (%)	Minimum Hct during crisis (%)	Maximum Hct during crisis (%)	Baseline albumin (g/dL)	Minimum albumin during crisis (g/dL)
1	125/70	84	70/50	130	44	56	66	4.2	2.5
2	140/80	72	85/70	100	37	51	72	4.3	3.4
3	140/70	76	80/60	112	35	55	68	n.a.	2.7
4	140/90	76	80/60	100	41	50	67	4.5	2.3
5	120/70	76	80/60	120	30	64	64	n.a.	2.3
6	140/80	70	80/n.a.	160	39	59	74	4	2.7
7	130/80	60	90/50	120	35	29	67	n.a.	1.7
8	140/90	71	80/50	104	44	31	62	3.3	1.9
9	135/80	70	60/35	120	30	45	66	4.1	1.5
10	130/80	70	85/60	125	39	53	60	n.a.	2.7
11	120/75	72	60/n.a.	160	33	55	> 60	4.2	0.9
12	130/70	60	70/n.a.	96	42	51	58	4.2	2.8

Wu et al.
Intern Emerg Med 2019



CHALLENGES IN **CAPILLARY LEAK SYNDROME** MANAGEMENT IN EMERGENCY ROOM

Correct Diagnosis

Quick Diagnosis

Adequate Initial Treatment in Emergency Room

TREATMENT OF ICLS

Internal and Emergency Medicine
<https://doi.org/10.1007/s11739-019-02113-4>

IM-POINT OF VIEW



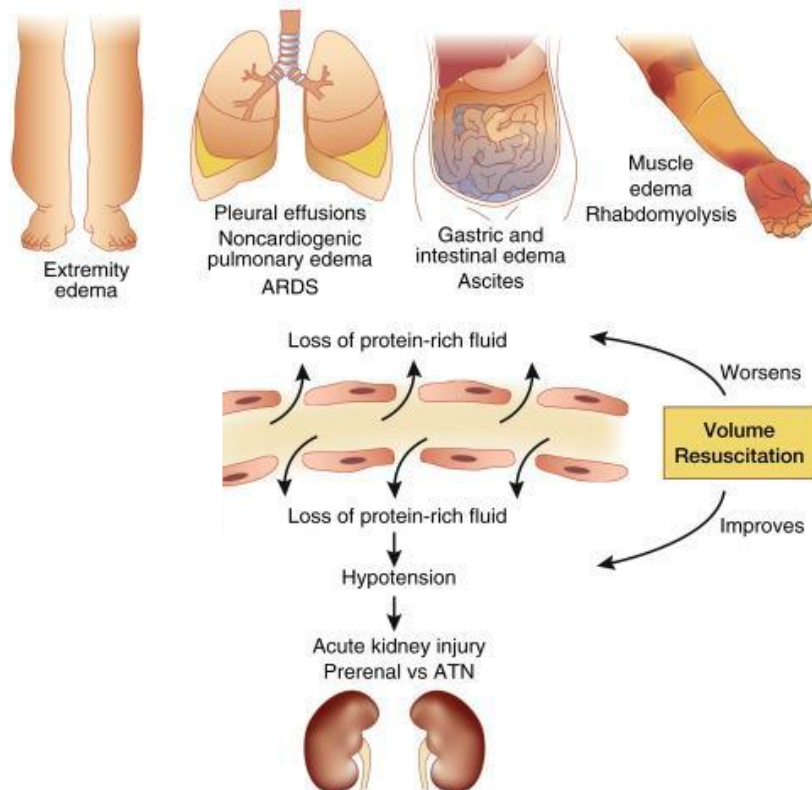
Handling shock in idiopathic systemic capillary leak syndrome (Clarkson's disease): less is more

Maddalena Alessandra Wu¹  · Riccardo Colombo² · Gian Marco Podda³ · Marco Cicardi⁴

Wu et al.
Intern Emerg Med 2019

Received: 16 January 2019 / Accepted: 18 May 2019
© Società Italiana di Medicina Interna (SIMI) 2019

VOLUME RESUSCITATION in ICLS



TREATMENT OF SHOCK (leak) PHASE OF ICLS

- Crystalloids infusion 25 ml/hr
- HMW plasma expanders boluses 200 ml

TREATMENT OF SHOCK (leak) PHASE OF ICLS

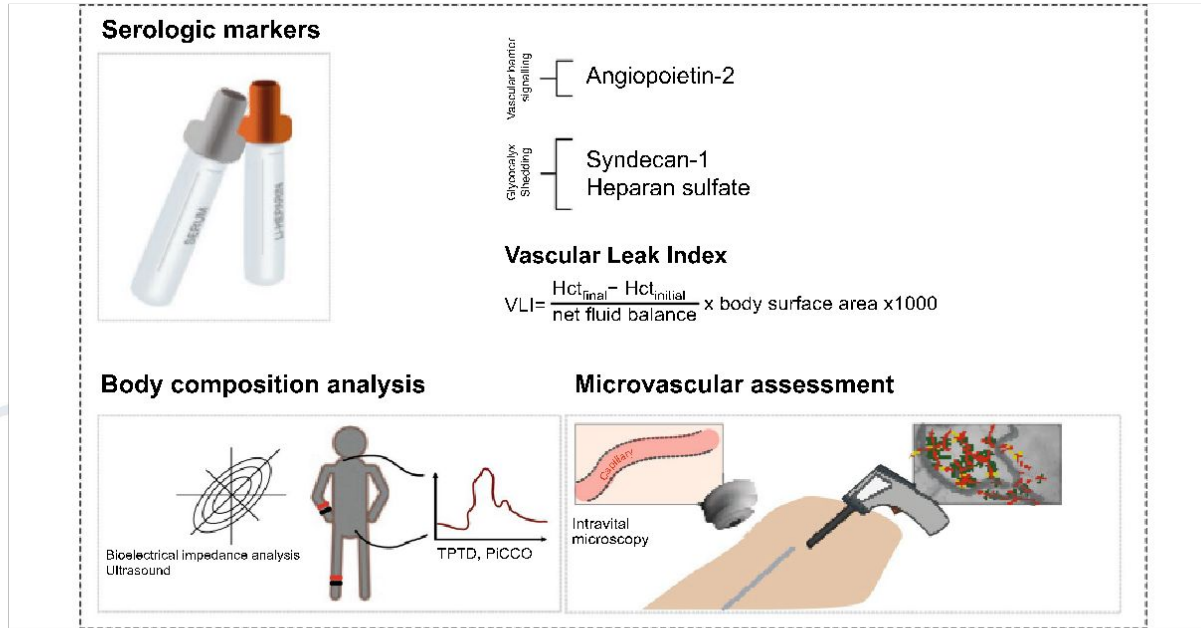


Fig.2 Diagnostic approach to capillary leak syndrome (CLS): both serological markers related to glycocalyx shedding and vascular barrier signaling, as well as the vascular leak index can hint towards a CLS phenotype. More nuanced diagnostic approaches comprise bioelectrical impedance analysis (BIA), transpulmonary thermodilution (TPTD), PiCCOTM (pulse index continuous cardiac output), and intravital microscopy

TREATMENT OF SHOCK (leak) PHASE OF ICLS

- | | |
|----------------------------------|--------|
| • Crystalloids infusion
ml/hr | 25 |
| • HMW plasma expanders boluses | 200 ml |

- Amines
- Vasopressin
- Methylene blue
- Icatibant
- Bevacizumab

TREATMENT OF SHOCK (leak) PHASE OF ICLS

- Crystalloids infusion 25 ml/hr
- HMW plasma expanders boluses 200 ml

- Amines
- Vasopressin
- Methylene blue
- Icatibant
- Bevacizumab

i.v. Immunoglobulin

0.4 -2 g/Kg

TREATMENT OF POST SHOCK (recovery) PHASE OF ICLS

Loop diuretics

CPAP

CVVH

ECMO

PROPHYLAXIS OF ATTACKS

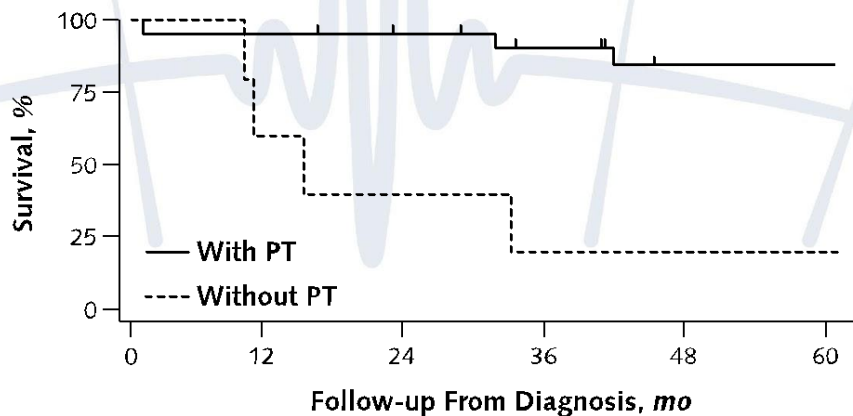
- Theophylline
- Verapamil
- Beta-2- agonists
- Terbutaline
- *Montelukast*
- *Glucocorticoids*
- *Spironolactone*
- *Cyclosporine*
- *Thalidomide*
- *Ginkgo biloba*

i.v. Immunoglobulin

0.4 -2 g/Kg

ACTUARIAL SURVIVAL CURVES ACCORDING TO PROPHYLACTIC TREATMENT OF ICLS IN FRENCH REGISTRY

Figure 2. Comparison of survival in patients with the systemic capillary leak syndrome who were receiving or not receiving prophylactic treatment.



At risk, n						
With PT	23	22	20	17	13	13
Without PT	5	3	2	1	1	1

Tick marks indicate censored patients. PT = prophylactic treatment.

Gousseff et al.
Ann Intern Med 2011

CONCLUSIONS - CAPILLARY LEAK SYNDROME

- Is a **rare and potentially fatal condition** in otherwise healthy midlife individuals
- Is characterized by **recurrent episodes of capillary leakage** with generalized edema associated to a **triad of Hypotension, Hemoconcentration and Hypoalbuminemia**
- **Monoclonal gammopathy** is frequently observed
- Etiology remains unknown

CONCLUSIONS - CAPILLARY LEAK SYNDROME

- Overt clinical features:
 - **Fluid extravasation phase** (compartment syndrome)
 - **Fluid reabsorption (recovery) phase** (volume overload)
- Treatment of attacks is **supportive**
- **Intravenous immunoglobulin** might be useful as prophylaxis of attacks



Quel ramo del lago...

Pescarenico, Lecco