

Calciophylaxis/ Calcific uremic arteriolopathy (CUA)

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Background:

Incidence:

Calciophylaxis or calcific uremic arteriolopathy (CUA), is a rare and serious syndrome of systemic arterioles calcification, thrombosis and subcutaneous skin necrosis (1,2). It is most commonly seen in end-stage renal disease (but it can occur in the absence of renal failure) (3). In the dialysis population the prevalence is estimated to 4.1% (4). It is more commonly seen in women and in those with diabetes and obesity, but some studies have also suggested other risks factors such as increased phosphorus concentration, medications (including warfarin, calcium-based binders and vitamin D analogues, and systemic glucocorticoids), hypercoagulable states (protein C and S deficiency and antiphospholipid syndrome) and Hypoalbuminemia (5,6,7).

Clinical manifestations:

CUA manifestations are described as areas of extreme pain and ischemic necrosis, usually on abdomen, buttock, and thigh. The lesions include violaceous, painful, nodules or indurated plaques that can rapidly evolve in necrotic ulcers, with eschars that often become superinfected (8). Usually a skin biopsy is made to help confirm the diagnosis. Laboratory abnormalities may be observed such as elevated levels of parathyroid hormone (PTH), phosphorous, calcium, and the calcium-phosphorous (Ca x P) product (9).

Treatment:

The optimal treatment of CUA is not known. A multi-interventional strategy is probably more effective than any single therapy (10).

A good wound care and pain control is recommended. Surgical debridement is controversial, because it can increase the risk of sepsis by removing the protective layer of necrosis, exposing vital tissue to bacteria (11). The control of

Calcium and Phosphate Balance, by diet, noncalcium-containing phosphate binders, such as sevelamer carbonate or lanthanum carbonate, and dialysis are also suggested. Other therapies include normobaric oxygen therapy (10-15L/min by face mask, 2/24h) (10), administration of intravenous sodium thiosulfate three times per week (off label and mechanism not known) (12), treatment of elevated PTH with Cinacalcet other definitive parathyroidectomy.

Rationale for HBO use

CUA is a syndrome of small vessel calcification of unknown aetiology, that progress in skin non-healing ulcers and gangrene. The mortality is 60-80% due to sepsis from secondary infection of the calciphylaxis wounds (13).

As seen in chronic non-healing wounds from other causes, there is a severe hypoxia with reduced transcutaneous oxygen pressure ($P_{tc}O_2$) of 5-20mmHg. With O_2 tension below 20mmHg healing is impaired. As shown in previous studies, HBO restores $P_{tc}O_2$ to physiological normal or supra-normal levels promoting fibroblast proliferation, collagen formation and angiogenesis and could also enhances mobilisation of vasculogenic stem cells.

HBO also helps treating sur-infection of calciphylaxis wounds by improving neutrophil function and polymorphonuclear leukocyte-mediated bacterial killing of organisms (14).

In this two ways HBO can help improving/treating CUA lesions.

Evidence – Based review of HBO use

There is no published randomized controlled clinical trial which include HBO and CUA. Evidence is therefore of low level.

The MEDLINE and RUBICON repository were searched with the query: “Hyperbaric oxygen therapy”, “calciphylaxis” and “Calcific uremic arteriolopathy”. 28 records were identified. We obtained 14 records after excluding those with no reporting data, commentary or those with abstracts only.

All the studies identified are small case series or uncontrolled retrospective reports and case reports with therefore risk of selection bias.

The first retrospective case series that we found is from Podymow & al. They reviewed five patients with CUA. Photos were taken prior to HBOT and after. Each patient received 25-35 treatment of HBO at 2.5 ATA for 90min. Two

completely healed their necrotic skin ulcers and the other three did not healed, but show some reduction of their lesions.

A more recent study of An & al identified 46 patients with CUA in their institution and from them 34 received HBOT. 58% showed improvement of their wounds, with more than half having complete resolution. It is interesting to note, that those who received HBOT survive on average for more than 3 years.

We found the same results in a study from Melbourne in 2008 by Edsell & al, who reviewed all patients with CUA from 1997 to 2006 in their hospital. 20 patients received HBOT with 55% showing a benefit and 30% experiencing complete resolution of their ulcers. Their HBOT consist of 90min at 2-2.4 ATA for a minimum of 10 to a maximum of 79 sessions.

The other case reports like the retrospective case series showed some benefit of HBOT in the treatment of patients with necrotic ulcers due to CUA, in a multi-interventional approach. Indeed, all patients received dialysis, good wound care and other treatments like those mentioned in the "Introduction".

Patients selection for HBO

Any patient with the diagnosis of CUA.

Current protocol

2-2.5ATA for 90min
20-60 HBO sessions

Cost impact

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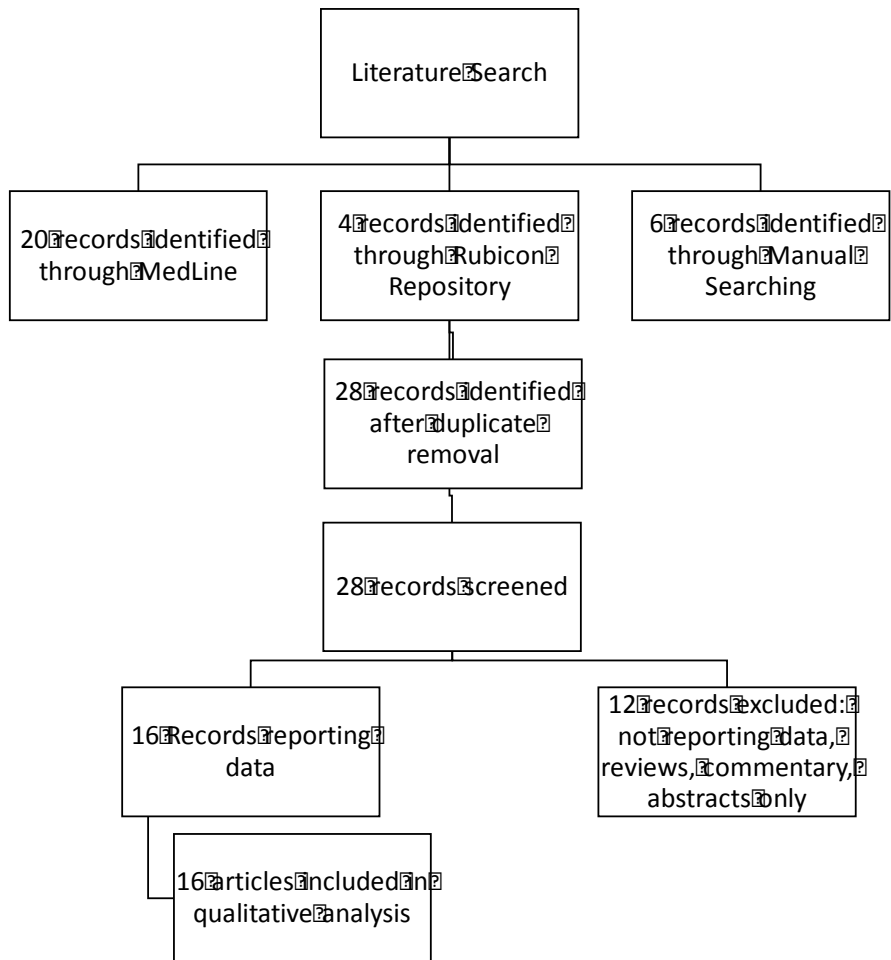
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Conclusion: Recommendation

We suggest the use of HBOT as part of a multi-interventional approach in the treatment of CUA. (Recommendation level 2, low level of evidence grade C)
We recommend to perform randomized studies.



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Study (authors, year)	Type	Nb patients	Aim(s) / Evaluation criteria	Inclusion / Exclusion criteria	HBO protocol (pressure, time, nb of session)	Results	Conclusion / comment
2015 – An et al.	Retrospective Case Series	46, HBOT in 34 patients	Wound healing under HBO and factors that predict wound healing or survival	Patient with calciphylaxis	Mean of 44 HBO sessions 2-2.4ATA 90min	58% improved and more than half of them 100% healed	Possible role for HBOT in the treatment of Calciphylaxis/ Diabetes only factor associated with improved wound healing and mortality
2014 – Borges et al.	Case report	1	Wound healing	Patient with calciphylaxis	54 HBO sessions 2.4ATA 90min	100% healed	Support of HBOT as part of a multi-interventional approach
2014 – Wangen et al.	Case report	1	Wound healing	Patient with calciphylaxis	90 HBO sessions 2ATA 90min	100% healed	Support of HBOT as part of a multi-interventional approach
2014 – Deng et al.	Case report	1	Wound healing	Patient with calciphylaxis	21 HBO sessions 2.5ATA 90min	100% healed	Favourable adjunctive treatment
2013 – Savoia et al.	Retrospective Case Series	4, HBOT in 3 patients	Wound healing	Patient with calciphylaxis	Not reported	75% improved	Support of HBOT as part of a multi-interventional approach
2012 – Malabu et al.	Retrospective Case Series	6, HBOT in 4	Wound healing	Patient with calciphylaxis/	2.4ATA 90min	50% healed	Support of HBOT as an

		patients		excluded nonuremic calciphylaxis			adjunctive treatment
2011 – New et al.	Retrospective Case Series	5, HBOT in 2 patients	Wound healing	Patient with calciphylaxis	5-30 HBO sessions	80% healed	Support of HBOT as part of a multi-interventional approach
2011 – Baldwin et al.	Retrospective Case Series	7, HBOT in 6 patients	Wound healing	Biopsy proven calciphylaxis	10-65 HBO sessions	86% healed	Support of HBOT as part of a multi-interventional approach
2010 – Jean et al.	Retrospective Case Series	6, HBOT in 4 patients	Wound healing	Patient with calciphylaxis	20-40 HBO sessions	5/6 healed 1 died (also treated with HBO)	Support of HBOT as an adjunctive treatment
2009 – Alikadic et al.	Case report	1	Wound healing	Patient with calciphylaxis	19 HBO sessions 2.5ATA 90min	100% healed	Support of HBOT as an adjunctive treatment
2008 – Arenas et al.	Case reports	2	Wound healing	Patient with calciphylaxis	20-30 HBO sessions	100% improved	Possible role for HBOT in the treatment of Calciphylaxis
2008 – Rogers et al.	Retrospective Case Series	12	Wound healing	Patient with calciphylaxis	7-41 HBO sessions 2ATA 90min	92% healed	Support of HBOT as an adjunctive treatment
2008 – Edsell et al.	Retrospective Case Series	20	Wound healing	Chronic skin ulcers due to calciphylaxis	17-83 HBO sessions 2-2.4ATA 90min	55% improved 30% healed	Possible role for HBOT in the treatment of Calciphylaxis
2002 – Dwyer et al.	Case Report	1	Wound healing	Patient with calciphylaxis	23 HBO sessions 2.4ATA 90min	100% healed	Favourable adjunctive treatment

2002 – Basile	Retrospective Case Series	11	Wound healing	Patients with calciphylaxis	20-108 HBO sessions	89% improved 73% healed	Possible role for HBOT in the treatment of Calciphylaxis
2001 – Podymow et al.	Retrospective Case Series	5	Wound healing	Patients with calciphylaxis	25-35 HBO sessions 2.5ATA 90min	60% improved 40%healed	Possible role for HBOT in the treatment of Calciphylaxis