



# **INFANTILE HEPATIC HEMANGIOMAS CURRENT TREATMENT OPTIONS**

**Dept. of Cardiology Department, Children 2 Hospital**



# INTRODUCTION

## **BACKGROUND**

- Infantile hemangiomas affect 4-5% of white infants, mostly cutaneous
- Hepatic hemangiomas is the most common benign liver neoplasm in infants

## **PRESENTATION**

- Wide range – most are asymptomatic
- High output heart failure due to arteriovenous shunting
- Hypothyroidism: overproduction of iodothyronine deiodinase
- Kasabach-Merritt Syndrome: thrombocytopenia and coagulopathy

## **DIAGNOSTIC IMAGING**

- Ultrasonographic, CT or MRI

## **TYPE**

- Focal, multi-focal and diffuse



PEDIATRICS  
INTERNATIONAL

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the Japan  
Pediatric Society



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## Review Article

# Critical hepatic hemangioma in infants: Recent nationwide survey in Japan

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### Abstract

The International Society for the Study of Vascular Anomalies (ISSVA) classification divides vascular lesions into two major entities: neoplasms originating from the vascular endothelium and vascular malformations. Although this concept has been widely accepted, little has been established regarding vascular lesions in deep organs, such as infantile hepatic hemangioma (IHH). The current nationwide survey identified 19 critical infantile hemangiomas during the most recent 5 years. On histopathology all the lesions examined were neoplastic, but portovenous shunt was found histologically or clinically in some cases. **High-output cardiac failure, consumption coagulopathy, and respiratory distress were the major symptoms, and treatment-resistant coagulopathy seemed to be the most reliable predictor of fatal outcome. Although steroid has been the gold standard treatment for these lesions,** 25% of the patients were totally insensitive to steroids, whereas propranolol had a prompt effect in one case. For critical IHH with steroid-insensitive thrombocytopenia and prothrombin time prolongation, novel therapeutic options including beta-blocker therapy, surgery, and liver transplantation should be urgently considered as alternative treatment. The present review summarizes the results of the survey.

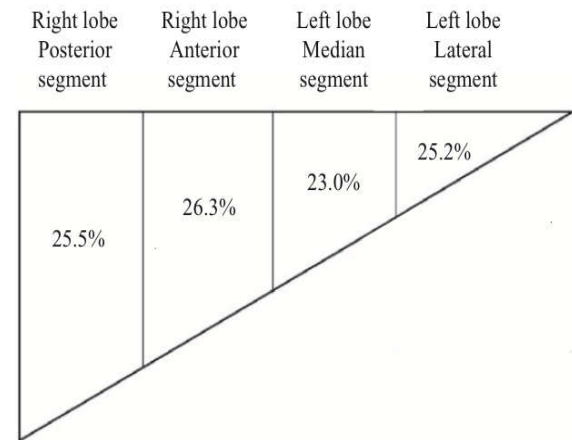


# CLINICAL SYMPTOMS

**Table 2** Clinical symptoms identified in the survey

Symptom	%
Abdominal distension	47.4
High-output cardiac failure	47.4
Coagulopathy	42.1
Respiratory distress	31.6
Liver dysfunction	15.9
Renal failure	10.6
Hypertrophic cardiomyopathy	5.3
Hepatosplenomegaly	5.3
Hypothyroidism	5.3
Failure to thrive	5.3
Hypergalactosemia/hyperammonemia	10.6
CCAM of the lung	5.3
Beckwith–Wiedemann syndrome	5.3

CCAM, congenital cystic adenomatoid malformation.



**Fig. 1** Tumor locations. Solitary lesion, 18 patients; multiple lesions, eight patients (no. lesions, 2–10); extrahepatic lesions, three patients (all skin lesions).



# DIAGNOSTIC IMAGING

**Table 1.** Sensitivity and specificity of the diagnostic methods.

Diagnostic method	Sensitivity (%)	Specificity (%)
Ultrasonography	96.9	60.3
Computed tomography	98.3	55.0
Magnetic resonance imaging	100	85.7
Tc-99m RBC blood pool scintigraphy	75	100
Angiography	na	na
PET/TC	na	na

na: not available.

***Adriana Toro. Concise review in indications and treatment of hepatic hamangiomas. Annal of Hepatology, 2014 .***



# DIAGNOSTIC IMAGING

Ara Kassarian, MD  
Josée Dubois, MD  
Patricia E. Burrows, MD

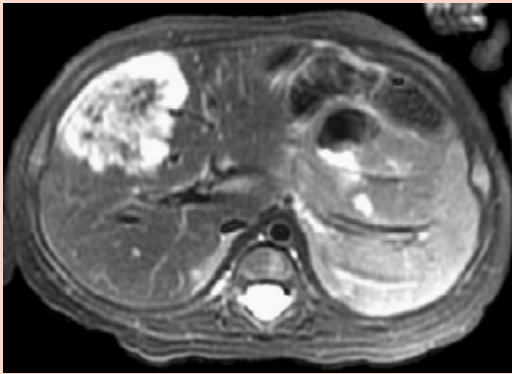
## Angiographic Classification of Hepatic Hemangiomas in Infants<sup>1</sup>

**TABLE 1**  
**Classification of Hepatic Hemangiomas in Infants with Angiographic Findings**

Type of Hemangioma	Angiographic Findings
1	Early filling of abnormal channels, stagnation and pooling of contrast material, without early opacification of hepatic veins, no shunt
2	High-flow nodules, early filling of veins, no visible direct shunts
3	Direct arteriovenous (including arterioportal) shunt
4	Direct portovenous shunt
5	Direct portovenous and arteriovenous shunts

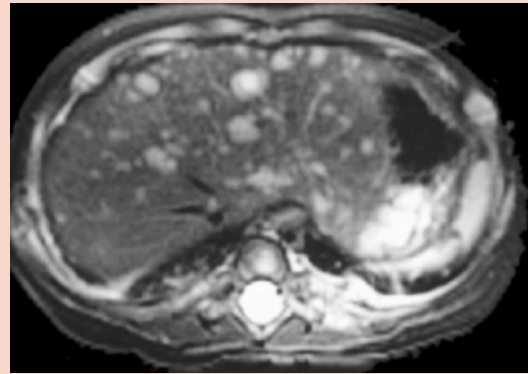
# TYPES OF HEPATIC HEMANGIOMA

## FOCAL



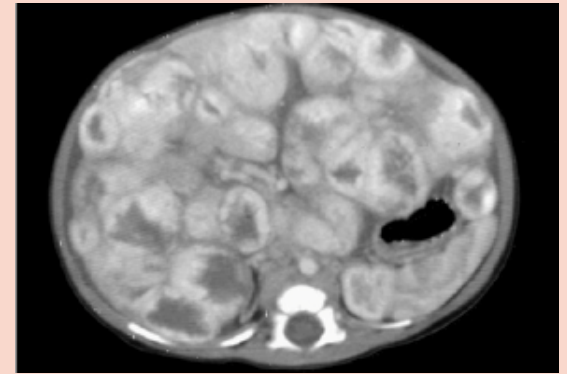
- Rarely associated with cutaneous hemangiomas
- GLUT1 negative

## MULTIFOCAL



- Often detected on screening due to multiple cutaneous hemangiomas
- GLUT1 positive

## DIFFUSE



- Association with high output cardiac failure
- More serious course
- GLUT1 positive

*Belinda D, Roshni D. Journal of Pediatric Surgery, 2009*





# THERAPEUTIC OPTIONS

## MEDICAL THERAPY

### High dose corticosteroids

- Until recently was the main stay of therapy
- Exact mechanism unknown (possible mechanism includes inhibition of VEGF –A)
- Causes slowing and stabilization of progression but not involution
- Only 30-60% respond clinically to steroids
- Adverse effects: growth retardation, adrenal suppression, hypertension, insomnia, immunosuppression





# THERAPEUTIC OPTIONS

## MEDICAL THERAPY

### Interferon -alpha

- Second line option (usually reserved for steroid – nonresponsive)
- Unknown mechanism
- May cause up to 50% regression
- Adverse effects: risk of spastic diplegia, may have rebound growth with discontinuation of therapy



# THERAPEUTIC OPTIONS PROPRANOLOL



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## Propranolol for Severe Hemangiomas of Infancy

N Engl J Med 2008; 358:2649-2651 | [June 12, 2008](#) | DOI: 10.1056/NEJMc0708819



# THERAPEUTIC OPTIONS PROPRANOLOL

- Found to treat cutaneous hemangioma incidentally in 2008 and no RCT assessing use in cutaneous or hepatic hemangioma
- Mechanism: decreased renin production causing decreased VEGF and vasoconstriction
- Can cause involution of hemangioma, mean response 98% (all locations)
- Adverse effects: hypotension, hypoglycemia, wheezing or bronchoconstriction, insomnia, nightmares

# PROPRANOLOL FOR HEPATIC HEMANGIOMA

Authors	Date	Number/ Type of cases	Age at diagnosis	Presentation	Dose/ Duration	Outcomes
Mazereeuw-Hautier et al (J of Pediatrics)	2010	4 multifocal 4 diffuse	0.5 – 10 months	Heart failure (3) Hypothyroidism (3)	2-3.5 mg/kg/d	Undetectable (3) > 50% reduction (5)
					0.5 - 10 mo	
Sarialioglu et al (Ped Blood Cancer)	2010	1 diffuse (hemangioido-thelioma)	4 months	Respiratory distress Cutaneous hemangiomas	2.5 mg/kg/d	Decrease in size and number of hepatic lesions, partial resolution of cutaneous lesions
					2.5 mo	
Morais et al (Cutan Ocul Toxicol)	2010	1 Focal	2 months	Cutaneous hemangiomas Parotid hemangiomas	2mg/kg/d	Complete resolution of all hemangiomas
					16 mo	
Mhanna et al (Ped Dermatology)	2011	1 diffuse 2 multifocal	3 - 8 wks	Cutaneous hemangiomas (3) Hypothyroidism (2) Heart Failure (2)	1.5-2 mg/kg/d	Partial response hepatic lesions (2) Resolution of hepatic lesions (1) Heart failure resolved (2) Hypothyroidism resolved (2)
					4 - 17 mo (ongoing)	
Sciveres et al (JPGN)	2011	1 multifocal	3 months	Cutaneous hemangiomas Heart Failure	1-2 mg/kg/d	Dramatic reduction at 3 months Complete resolution at 14 months Heart failure resolved after 4 weeks
					14 m (ongoing)	
Tan et al (Pediatrics)	2010	1 diffuse	3 wks	Cutaneous hemangiomas	1.5 mg/kg/d	Near complete resolution of hepatic lesions at 4 months
					12 mo	
Bosemani et al (Eur J Pediatr)	2012	1 multifocal	15 wks	Heart Failure Cutaneous hemangiomas	0.5 – 2 mg/kg/d	Near complete resolution of hepatic lesions Resolution of heart failure
					30 wks	
Avagyan et al (JPGN)	2013	1 diffuse (hemangioido-thelioma)	2 wks	Cutaneous hemangiomas Hypothyroidism	0.25-2 mg/kg/d	Significant regression of all lesions at 3months Resolution of all but 1 hepatic lesions by 14 mo Hypothyroidism resolved
					12 mo	



# PROPRANOLOL FOR HEPATIC HEMANGIOMAS

8 reports from 2010-2014

## ***PATIENTS***

- 17 pts age 2wks-10months
- 8 diffuse hemangioma, 8 multifocal hemangioma, 1 focal hemangioma
- 8 with heart failure, 6 with hypothyroidism, All had cutaneous hemangiomas

## ***TREATMENT***

- Dose: 0.25 – 2 mg/kg/d
- Duration: 2.5- 17 months (some still ongoing)

## ***OUTCOMES***

- All showed decrease in hemangioma size
- 6 showed complete resolution
- All cases of HF and hypothyroidism resolved

## ***ADVERSE EVENTS***

- 2 pts developed symptomatic bradycardia requiring decreased doses
- No other adverse effects reported



# HEPATIC ARTERY EMBOLIZATION/ SURGICAL RESECTION

- Invasive treatment options should be limited to cases with significant symptoms that are refractory to medical management as most hemangiomas will regress
- Hepatic artery embolization can lead to significant improvement in heart failure in patients with shunting
- Significant risks are present even with embolization: including thrombosis, repeat procedures and even death
- Surgical resection can be technically challenging, especially in infants
- Multifocal/Diffuse lesions may not be amenable to resection and may require transplantation

## What is changing in indications and treatment of hepatic hemangiomas. A review

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### ABSTRACT

Hepatic cavernous hemangioma accounts for 73% of all benign liver tumors with a frequency of 0.4-7.3% at autopsy and is the second most common tumor seen in the liver after metastases. Patients affected by hemangioma usually have their tumor diagnosed by ultrasound abdominal examination for a not well defined pain, but pain persist after treatment of the hemangioma. The causes of pain can be various gastrointestinal pathologies including cholelithiasis and peptic ulcer disease. The malignant transformation is practically inexistent. Different imaging modalities are used to diagnosis liver hemangioma including ultrasonography, computed tomography (CT), magnetic resonance (MR) imaging, and less frequently scintigraphy, positron-emission tomography combined with CT (PET/CT) and angiography. Imaging-guided biopsy of hemangioma is usually not resorted to except in extremely atypical cases. The right indications for surgery remain rupture, intratumoral bleeding, Kasabach-Merritt syndrome and organ or vessels compression (gastric outlet obstruction, Budd-Chiari syndrome, etc.) represents the valid indication for surgery and at the same time they are all complications of the tumor itself. The size of the tumor do not represent a valid indication for treatment. Liver hemangiomas, when indication exist, have to be treated firstly by surgery (hepatic resection or enucleation, open, laproscopic or robotic), but in the recent years other therapies like liver transplantation, radiofrequency ablation, radiotherapy, trans-arterial embolization, and chemotherapy have been applied.



# RESULTS OF THE TREATMENTS

Table 2. Results of the treatments.

Treatment	Mortality	Morbidity	Recurrence
Surgical Procedure	0-3%	10-27%	0%
Radiofrequency ablation	0%	33%	7,3%
Monoclonal antibody	na	na	na
Radiotherapy	na	na	na
TAE	0%	54%	0%
Chemotherapy	na	na	na
Liver transplantation	na	na	na

na: not available.



# Management of Hemangioma of the Liver: Surgical Therapy or Observation?

Süleyman Yedibela · Sedat Alibek · Volker Müller · Ünal Aydin · Melanie Langheinrich · Clemens Lohmüller · Werner Hohenberger · Aristotelis Perrakis

**Table 2** Demographic data of all patients with giant hemangioma

	Surgery ( <i>n</i> = 103)	Observation ( <i>n</i> = 143)	<i>p</i> value
Clinical presentation (%) <sup>a</sup>			
Abdominal discomfort/pain	62 (60)	73 (51)	0.765
Tumor enlargement	9 (9)	2 (1)	
Uncertainty of diagnosis	11 (11)	3 (2)	
Anxiety	21 (20)	13 (9)	
Incidental finding	38 (37)	70 (49)	
Age mean, years (range)	52 (24–81)	47 (19–73)	0.687
Gender (%)	0.734		
Men	32 (31)	31 (22)	
Women	71 (69)	112 (78)	
Tumor diameter (cm)			
Mean (range)	9.1 (4–23)	7.6 (1–21)	0.076
Number of lesions (%)			0.869
Solitary	67 (65)	104 (73)	
Multiple	36 (35)	39 (27)	
Location (%)			
Right lobe	66 (64)	89 (62)	0.967
Left lobe	21 (20)	37 (26)	0.921
Bilateral	16 (16)	17 (12)	0.923
Intrahepatic site (%)			
Subcapsular	61 (59)	52 (36)	0.048
Intaparenchymal	42 (41)	91 (64)	
Other gastrointestinal disease (%)			0.875
No	90 (87)	119 (83)	
Yes	13 (13)	34 (24)	
History of cancer			0.745
No	87 (84)	131 (92)	
Yes	16 (16)	12 (8)	
Previous hormonal therapy			0.002
No	47 (66)	26 (23)	
Yes	24 (34)	86 (77)	
GOT (U/L)	32.6 ± 7.9	28.3 ± 6.1	0.765
GPT (U/L)	41.8 ± 13.6	32.7 ± 5.3	0.781
GGT (U/L)	92.3 ± 243.4	63.5 ± 22.3	0.255
Alkaline phosphatase (U/L)	132.1 ± 55.7	110.8 ± 40.7	0.578
Bilirubin, mg/dL	1.94 ± 2.6	1.10 ± 0.8	0.125

GGT  $\gamma$ -glutamyl transferase;  
GPT glutamic pyruvic  
transaminase; GOT glutamic-  
oxaloacetic transaminase

<sup>a</sup> Multiple answers permitted



## Management of Hemangioma of the Liver: Surgical Therapy or Observation?

Süleyman Yedibela · Sedat Alibek · Volker Müller · Ünal Aydin · Melanie Langheinrich · Clemens Lohmüller · Werner Hohenberger · Aristotelis Perrakis

**Table 4** Outcome after liver resection or observation for symptomatic or asymptomatic patients

	Surgery			Observation			<i>p</i> value <sup>a</sup>
	Symptomatic ( <i>n</i> = 62)	Asymptomatic ( <i>n</i> = 41)	All patients <sup>a</sup> ( <i>n</i> = 103)	Symptomatic ( <i>n</i> = 73)	Asymptomatic ( <i>n</i> = 70)	All patients <sup>a</sup> ( <i>n</i> = 143)	
No abdominal complaints (%)	51 (82)	40 (98)	91 (88)	6 (8)	57 (81)	63 (44)	<0.001
Continuous or new onset of abdominal complaints (%)	11 (18)	1 (2)	12 (12)	67 (92)	13 (19)	80 (56)	<0.001
Complications (%)	15 (24)	3 (7)	18 (17)	6 (8)	3 (4)	9 (6)	0.06
Hepatic	7 (11)	1 (2)	8 (8)	6 (8)	3 (4)	9 (6)	0.85
Biliary/jaundice (%)	3 (5)	–	3 (3)	4 (5)	2 (3)	6 (4)	
Hepatic insufficiency	2 (3)	–	2 (2)	–	–	–	
Rupture/bleeding	2 (3)	1(2)	3 (3)	1 (2)	1 (1)	2 (1)	
Venous obstruction	–	–	–	1 (1)	–	1 (1)	
Extrahepatic complications (%)	8 (10)	2 (5)	10 (10)	3 (4) <sup>c</sup>	–	3 (2)	0.35
Other therapy (%)							
TAE	–	–	–	8 (11)	–	8 (6)	
Radiation	–	–	–	5 (7)	–	5 (3)	
Death <sup>b</sup>	–	–	–	1 (1)	1 (1)	2 (1)	<0.001

TAE transarterial embolization

<sup>a</sup> All patients for each parameter in surgery and observation group

<sup>b</sup> Related to liver hemangiomas

<sup>c</sup> Recurrent pleural effusion (%)



# CASE REPORT

- Male infant
  - ❖ Diagnosed with hepatic mass on prenatal US at 32 weeks
  - ❖ Delivered at 39 3/7 weeks in Tu Du hospital
- Admission
  - ❖ well w/o respiratory support
  - ❖ Total enteral feeding
  - ❖ No cutaneous hemangiomas
  - ❖ Mild thrombocytopenia, normal coagulation
  - ❖ Thyroid function: no screening

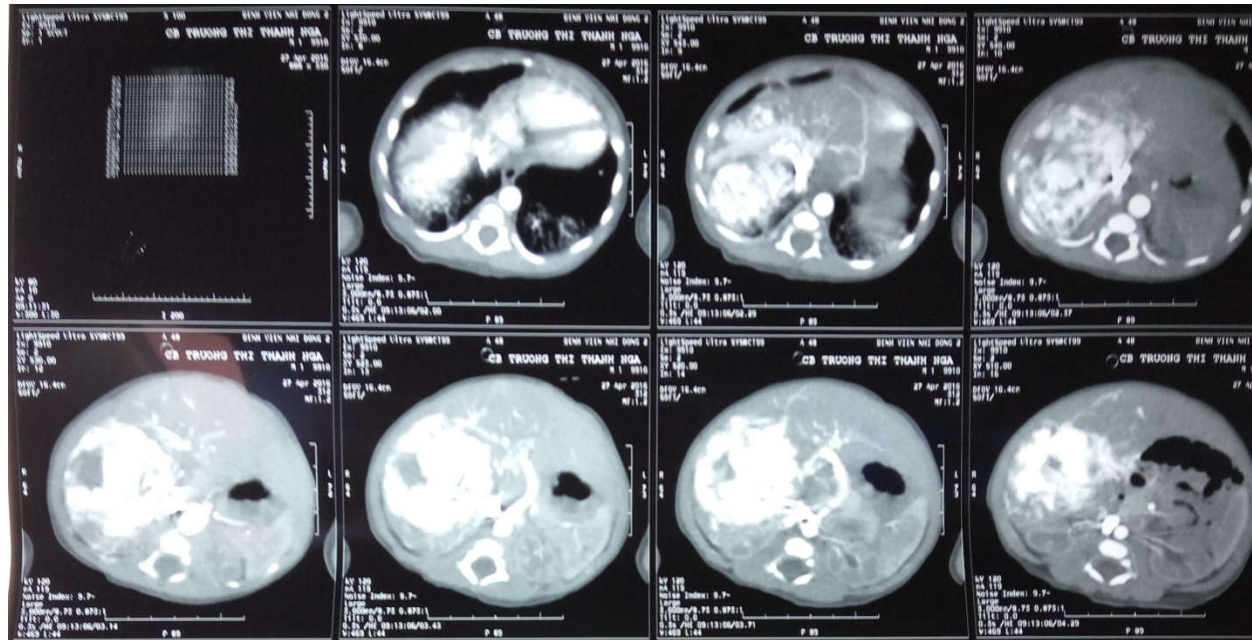


# CASE REPORT

- **Initial abdomen US:** complex cystic/solid mass in the right hepatic lobe measuring 41 x 36 mm
- **Initial Echocardiography:** PFO 5mm, PDA 2mm L-R shunt, cardiomegaly with predominant right cardiac, Moderate TR with PAPS 40 mmHg, normal LV size and function



# CASE REPORT



- ❖ Focal hepatic hemangiomas in the right hepatic lobe (53 x 54 x 50 mm)
- ❖ Supply arteries arise from right hepatic artery and small branch from abdominal aorta, then return via right superior hepatic vein



# CASE REPORT

## Day 13

- Sign of heart failure & severe pneumonia
- Management: TAE (transarterial embolization)

## After TAE

***Blood flow ↓ significantly, ↓ size of the hepatic hemangiomas and the right heart ventricles.***



CB TRUONG THI THANH NGA

ID: 16033488

F: 20/04/2016

Study 1

12/05/2016

12:09:31

1 IMA 41 FRM 3

H

Bệnh Viện Nhi Đông 2

AXIOM-Artis

HFS

X2 Distance: 45.54 mm

R

X2

X1 X1 Distance: 59.25 mm

Card <20kg

Card <20kg

BIPLANE A

CAU 1

LAO 0

W: 187

C: 115



CB TRUONG THI THANH NGA

ID: 16033488

F: 20/04/2016

Study 1

12/05/2016

12:49:05

1 IMA 67 FRM 10

H

Bệnh Viện Nhi Dong 2

AXIOM-Artis

HFS

R



Card <20kg

Card <20kg

BIPLANE A

CAU 1

LAO 0

W: 187

C: 123



**THANK YOU FOR YOUR ATTENTION**

