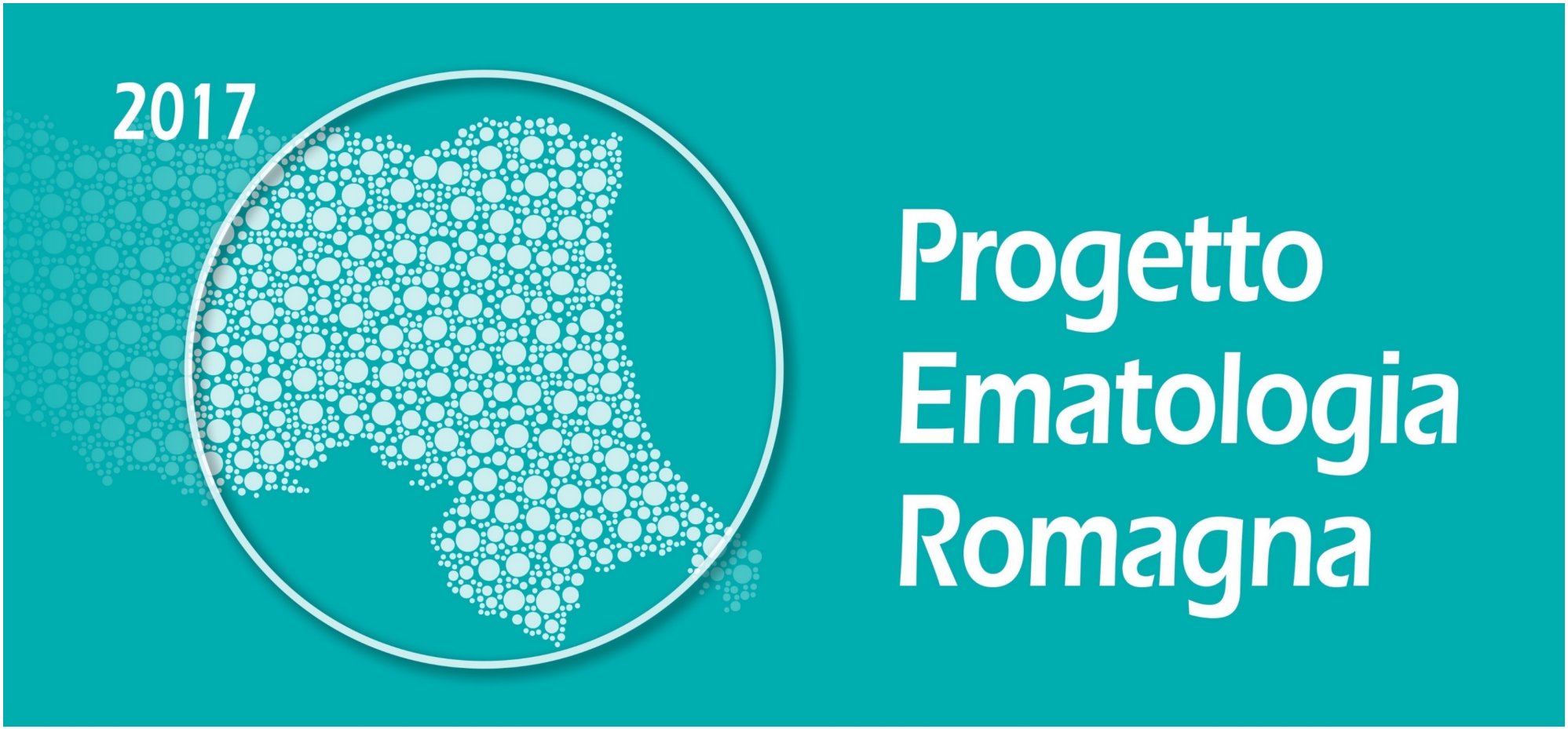
Conflitto di Interessi

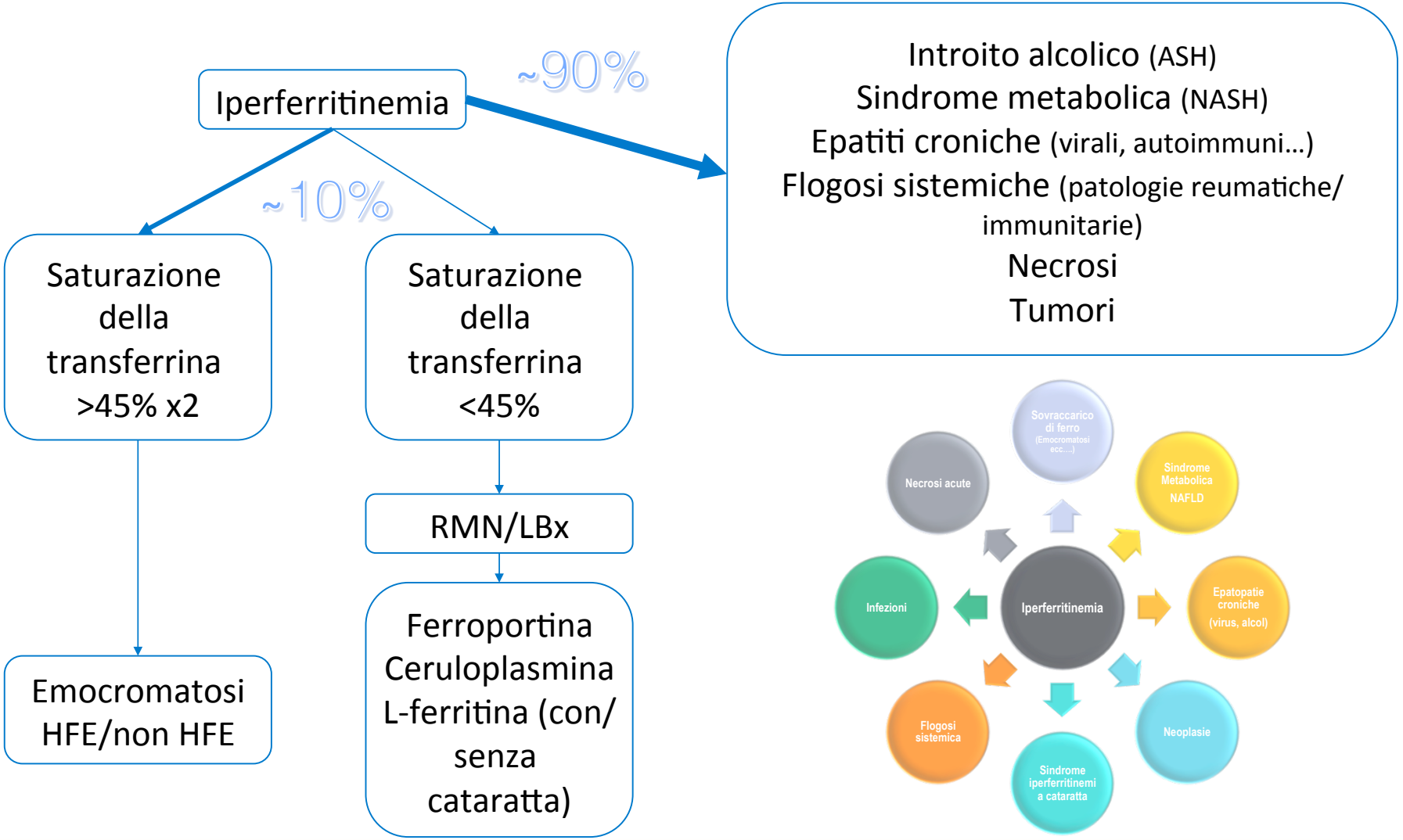
Nessuno



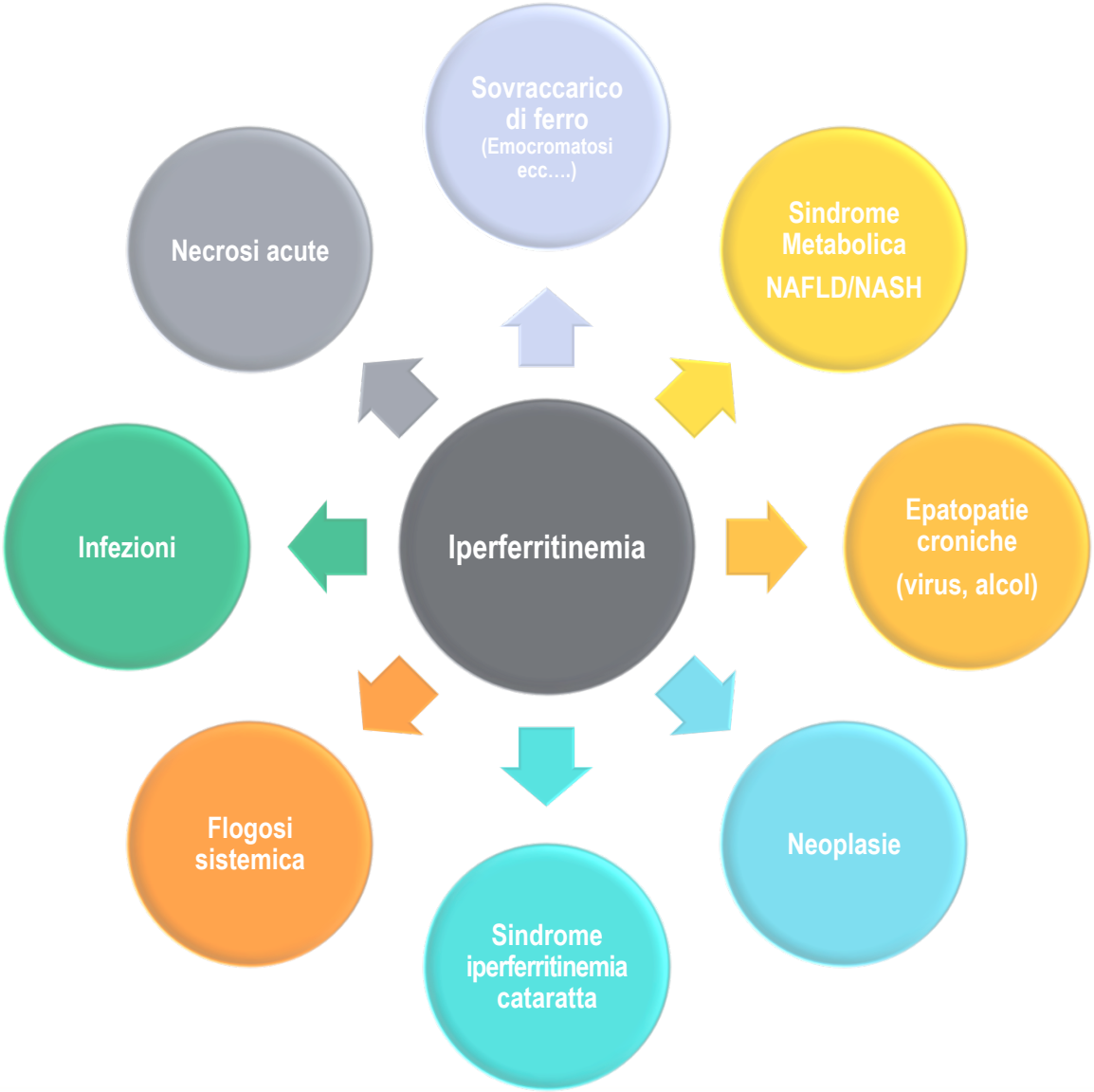
L'approccio Terapeutico

Francesco Azzaroli

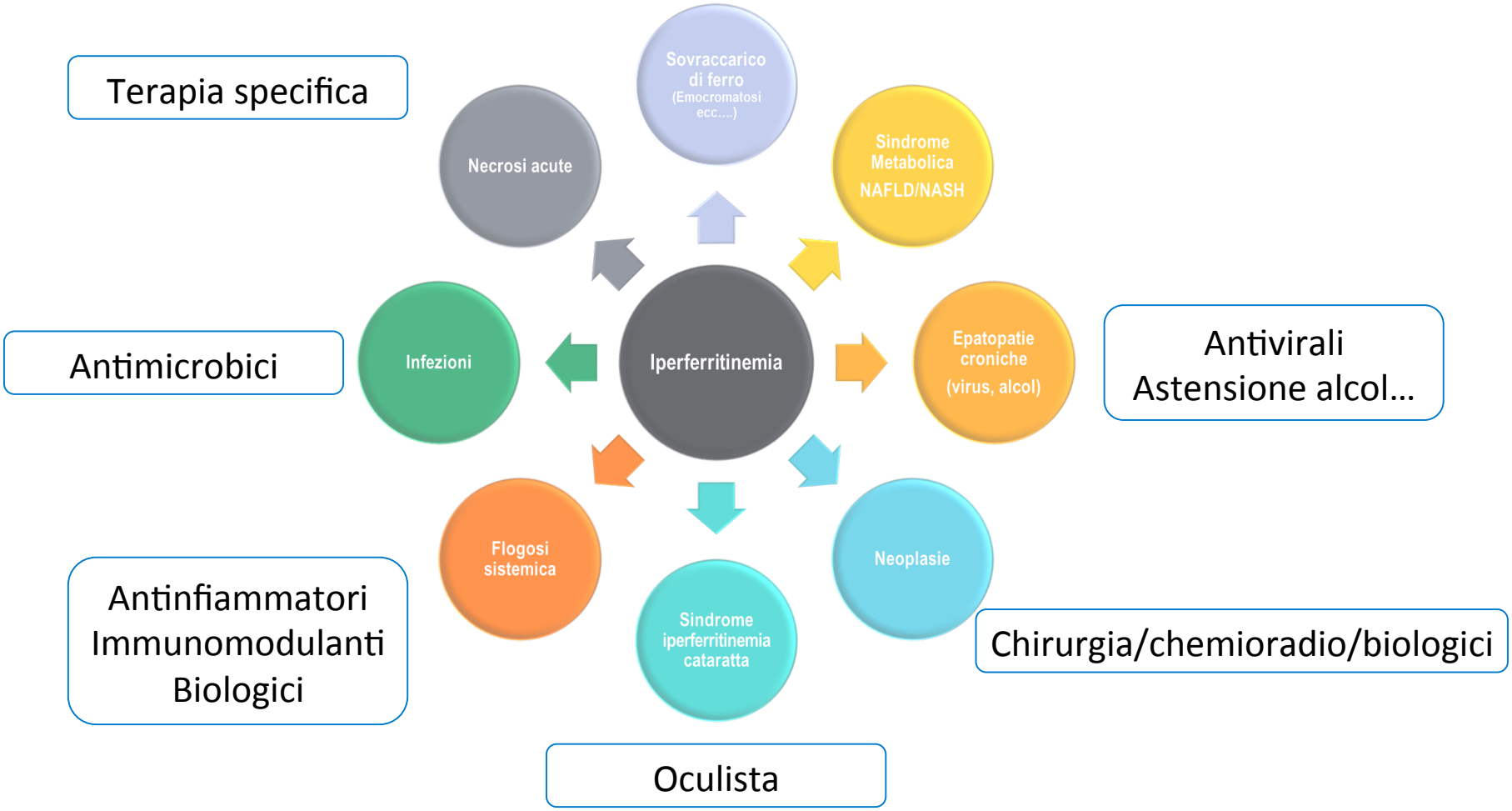
Iperferritinemia



Iperferritinemia



Iperferritinemia



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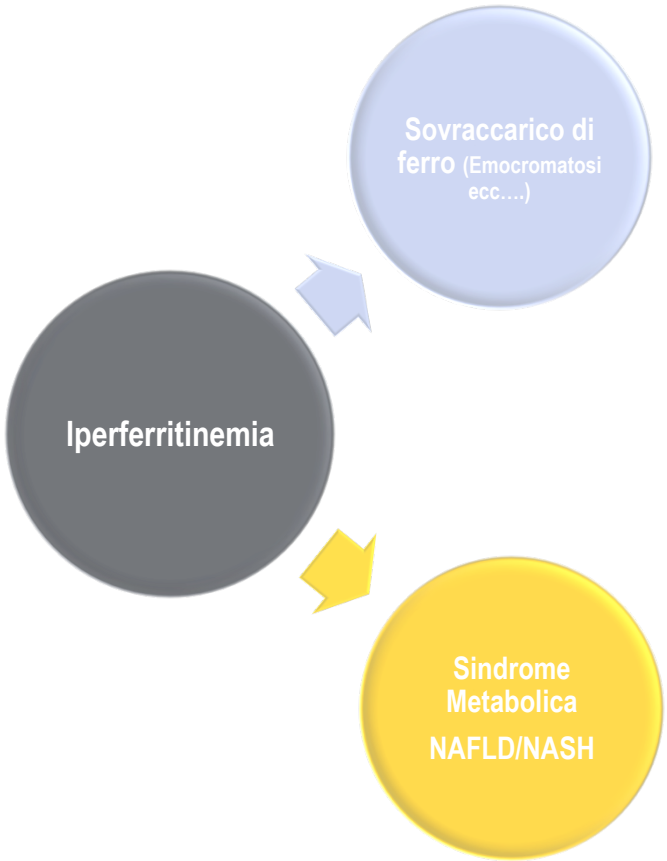
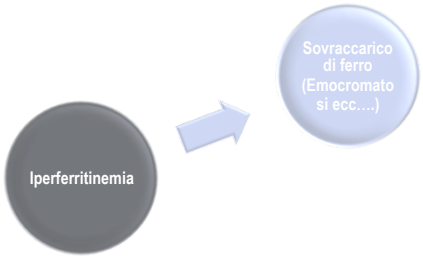


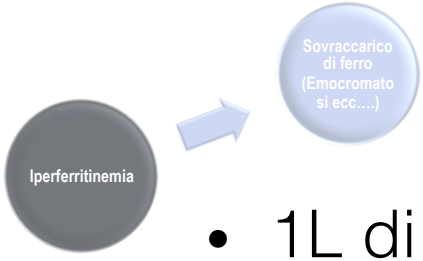
Stile di vita in HH



- Mantenere una dieta equilibrata e varia
- Evitare cibi e integratori supplementati di ferro
- Evitare supplementazioni di Vitamina C superiori a 500 mg/die
- Evitare l'alcol

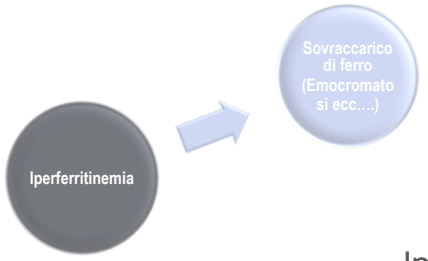
EASL CPG 2010

Flebotomia

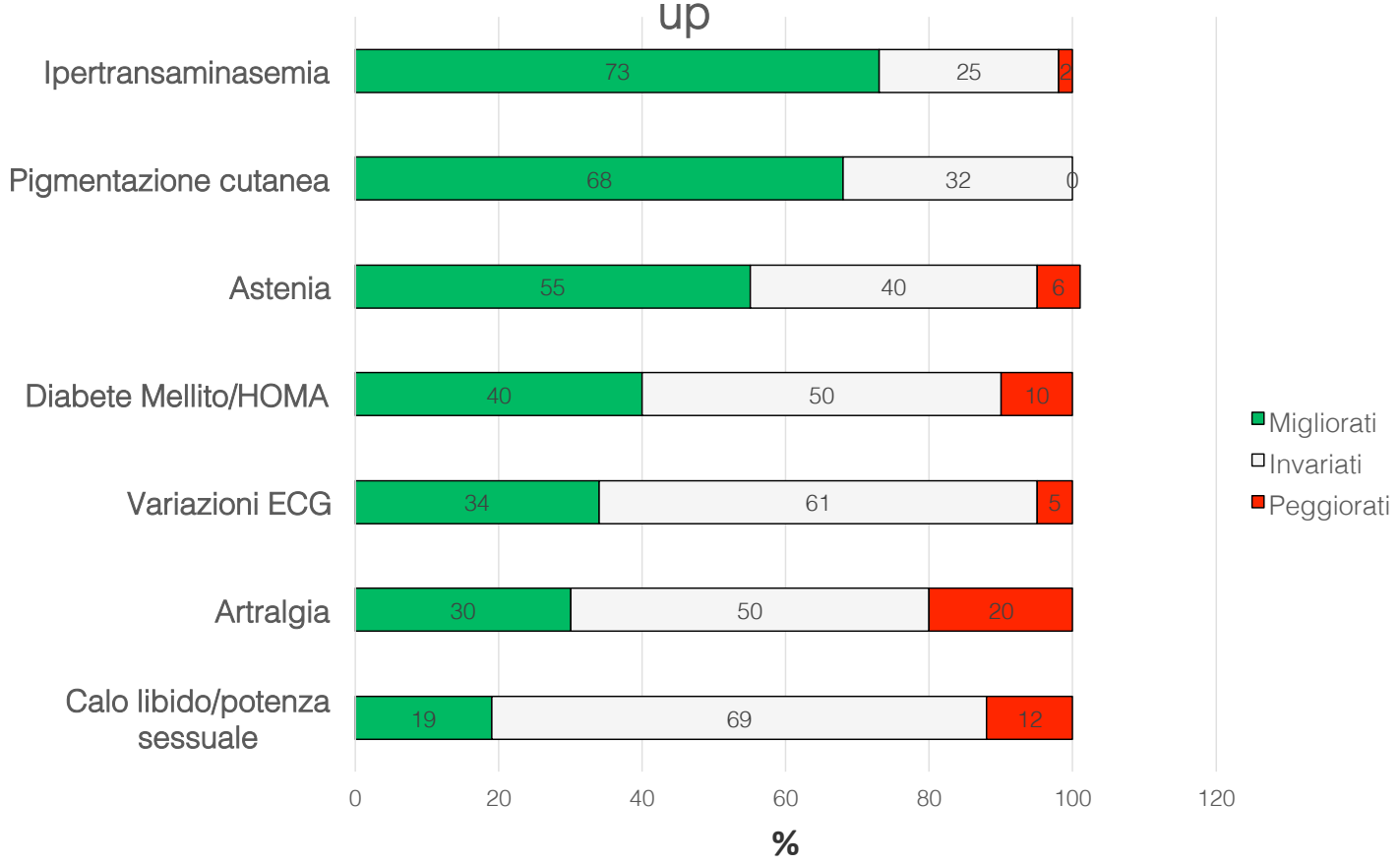


- 1L di sangue = 0,5g di ferro
- 400-500 ml di sangue a settimana fino a raggiungere una ferritinemia ≤50 μg/L con una saturazione del ferro <30%
- Mantenimento
  - 2-4 salassi all'anno
  - Ferritinemia 50-100 μg/L

Flebotomia in HH



Variazioni cliniche rispetto alla diagnosi in 183 pazienti con deplezione marziale epatica alla biopsia di follow-up



Niederau C et al. Gastroenterology 1996

Flebotomia in HH

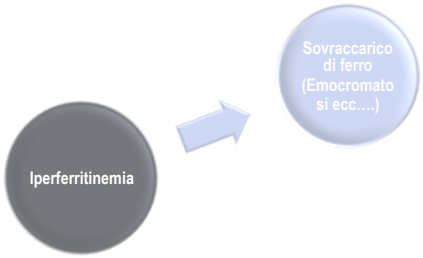


Table 1. Main Characteristics of the 36 Patients, 30 Men and 6 Women, at the Time of the First and Second Biopsies (Mean ± Standard Deviation)

	First Liver Biopsy	Second Liver Biopsy
Age (y)	47.1 ± 8.6	56.7 ± 8.6
BMI (kg/m^2)	24.5 ± 3.2	25.0 ± 3.1
METAVIR fibrosis	3.6 ± 0.5	2.4 ± 1.5
LIC (μmol/g)	388.4 ± 164.8	36.1 ± 85.5
Serum iron (μmol/L)	41.6 ± 29.4	21.1 ± 10.9
Transferrin saturation (%)	83.3 ± 15.8	42.6 ± 26.4
Serum ferritin (μg/L)	3448 ± 1691	179 ± 637
AST (UI/L)	66.3 ± 50.5	27.6 ± 13.6
ALT (UI/L)	88.1 ± 56.7	26.9 ± 12.5
Prothrombin activity (%)	83.8 ± 12.9	87.6 ± 8.9
Platelet count (/mm^3)	190,000 ± 69,600	216,000 ± 102,000
Serum albumin (g/L)	43.5 ± 6.6	44.2 ± 4.3
G-Globulinemia (g/L)	10.3 ± 5.2	9.5 ± 2.8
Fasting serum glucose (mmol/L)	6.1 ± 1.6	6.0 ± 2.0
Uricemia (μmol/L)	327.8 ± 63.4	300 ± 64.8
Iron removed (g)	-	17.0 ± 7.1

BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Follow-up medio: 9.7±5.3 anni

Falize L et al. Hepatology 2006

Flebotomia in HH

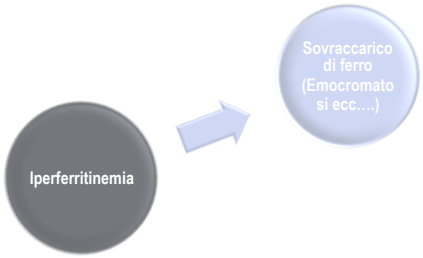


Table 2. Outcome of Fibrosis After Phlebotomy Therapy in Patients With Initial Fibrosis Grade 3 or Cirrhosis

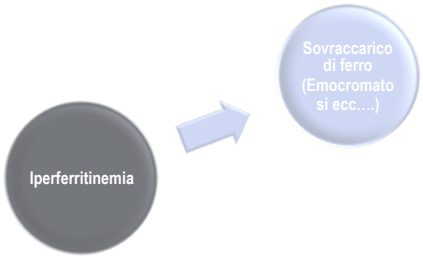
	Second Liver Biopsy					
Fibrosis Assessment	**F 0**	**F 1**	**F 2**	**F 3**	**F 4**	**Total**
First liver biopsy						
F 3	3	6	2	0	2	13
F 4	1	4	3	2	13	23
Total	4	10	5	2	15	36

Table 3. Clinical and Biochemical Comparative Data, at the First Biopsy, According to Regression of Fibrosis or Not (Mean ± Standard Deviation)

	Regression of Fibrosis	No Regression of Fibrosis	*P*
Age (y)	46.0 ± 7.7	48.0 ± 9.3	.32
BMI (kg/m^2)	24.4 ± 4.2	24.7 ± 1.8	.51
ALAT (UI/L)	81.1 ± 52.3	95.1 ± 61.6	.42
ASAT (UI/:)	61.2 ± 58.0	71.4 ± 42.9	.23
Serum cholesterol (mmol/L)	5.4 ± 1.3	5.6 ± 1.0	.65
Serum triglycerides (mmol/L)	1.3 ± 0.5	1.0 ± 0.0	.40
Fasting serum glucose (mmol/L)	5.7 ± 0.9	6.7 ± 2.2	.33
G-Globulinemia (g/L)	7.7 ± 2.1	13.1 ± 6.1	**.01**
Serum ferritin (μg/L)	3231 ± 1351	3695 ± 2038	.39
Transferrin saturation (%)	86.4 ± 6.4	78.7 ± 23.5	.28
Prothrombin activity (%)	91.3 ± 11.6	75.7 ± 8.7	**.002**
Platelet count (/mm^3)	236,200 ± 57,300	136,500 ± 36,100	**<.0001**
Iron removed (g)	17.1 ± 6.5	16.8 ± 8.0	.92
LIC (μmol/g)	440.9 ± 146.8	339.1 ± 169.9	.11
Size of liver biopsy (cm)	2.5 ± 1.1	1.8 ± 1.1	.8
Total iron score (0-60)	35.2 ± 12.6	32.3 ± 14.6	.59

Falize L et al. Hepatology 2006

Flebotomia in HH



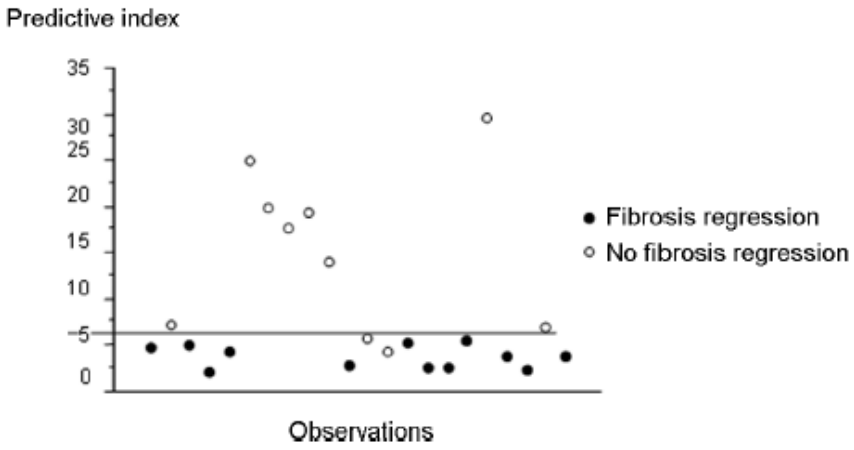


Fig. 1. Regression of fibrosis according to the predictive index defined by the ratio gammaglobulins [g/L] to (platelets [n/mm^3] × prothrombin activity [%]) at the first biopsy.

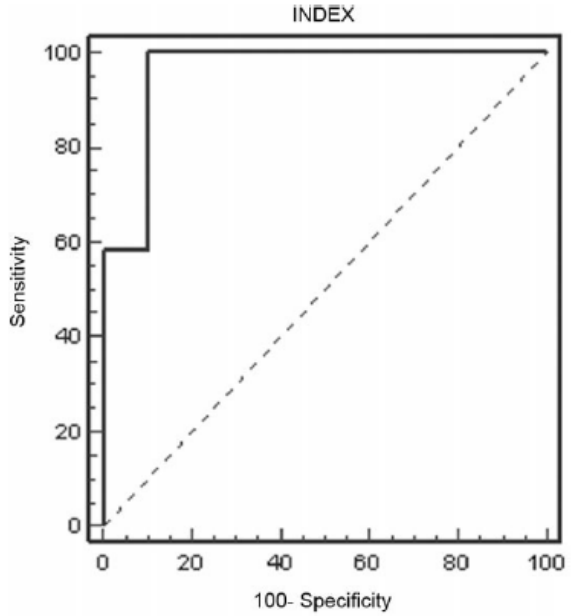
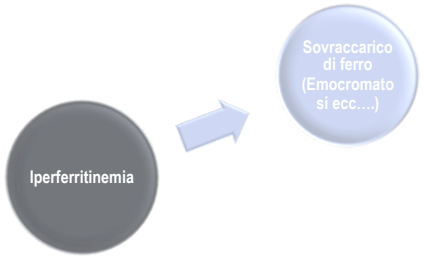


Fig. 2. Receiving operating curve of the regression predictive index in 22 patients. Area under the curve was 0.96 (95% confidence interval: 0.78-0.99; $P < .0001$).

Falize L et al. Hepatology 2006

Chelanti



Agente chelante	Dose (mg/Kg/die) e somministrazione	Metabolismo	Note
Desferoxamina	20-50 s.c./i.v.	Renale/biliare	Poco pratica Tempi di infusione lunghi Reazioni al sito di infusione
Deferiprone	75-100 orale x 3/die	Renale	Neutropenia, agranulocitosi, ipertransaminasemia, artropatia
Deferasirox	20-40 orale x 1/die	Biliare	Ipertransaminasemia, incremento della creatinina, rash cutaneo

Deferasirox in HH

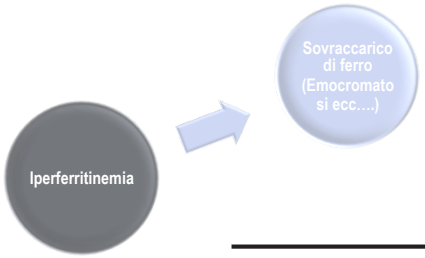
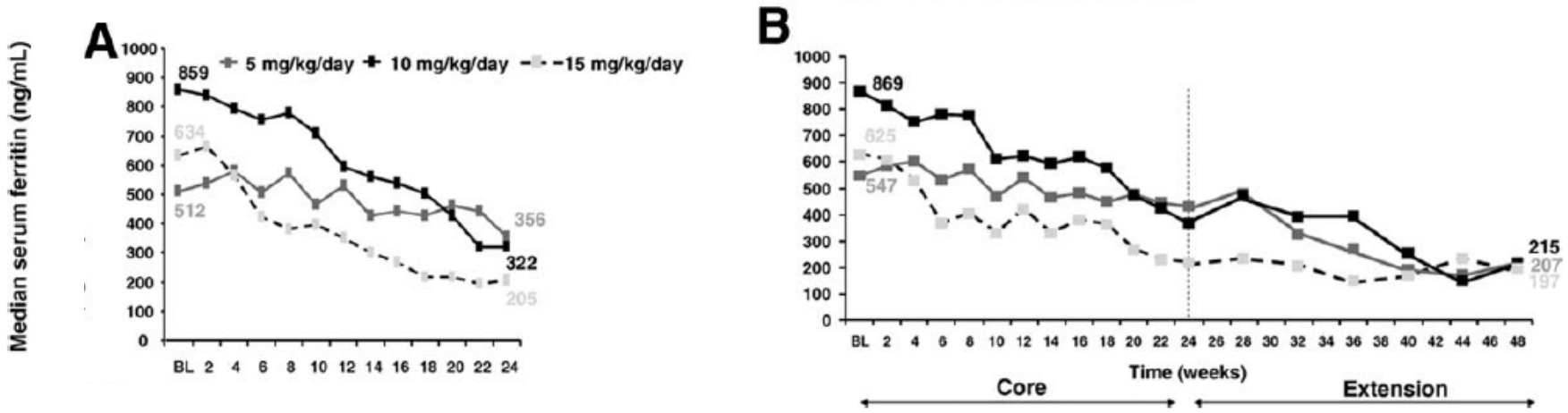


Table 1. Patient Demographics and Characteristics at Baseline

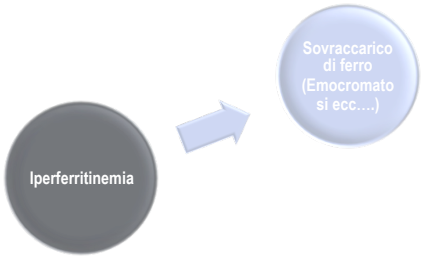
Characteristic	5 mg/kg/day (n = 11)	10 mg/kg/day (n = 15)	15 mg/kg/day (n = 23)	All Patients (n = 49)
Mean age ± SD, years	55.8 ± 12.8	47.8 ± 10.3	49.8 ± 16.4	50.6 ± 14.0
Male:female	9:2	11:4	13:10	33:16
Mean time since diagnosis ± SD, years	6.6 ± 7.0	1.3 ± 2.0	2.6 ± 3.8	3.1 ± 4.7
Median serum ferritin (range), ng/mL*	512 (376–1729)	859 (447–1792)	634 (357–1600)	645 (357–1792)
Mean transferrin saturation ± SD, %*	78.1 ± 17.4	81.0 ± 12.7	74.1 ± 15.4	77.2 ± 15.2

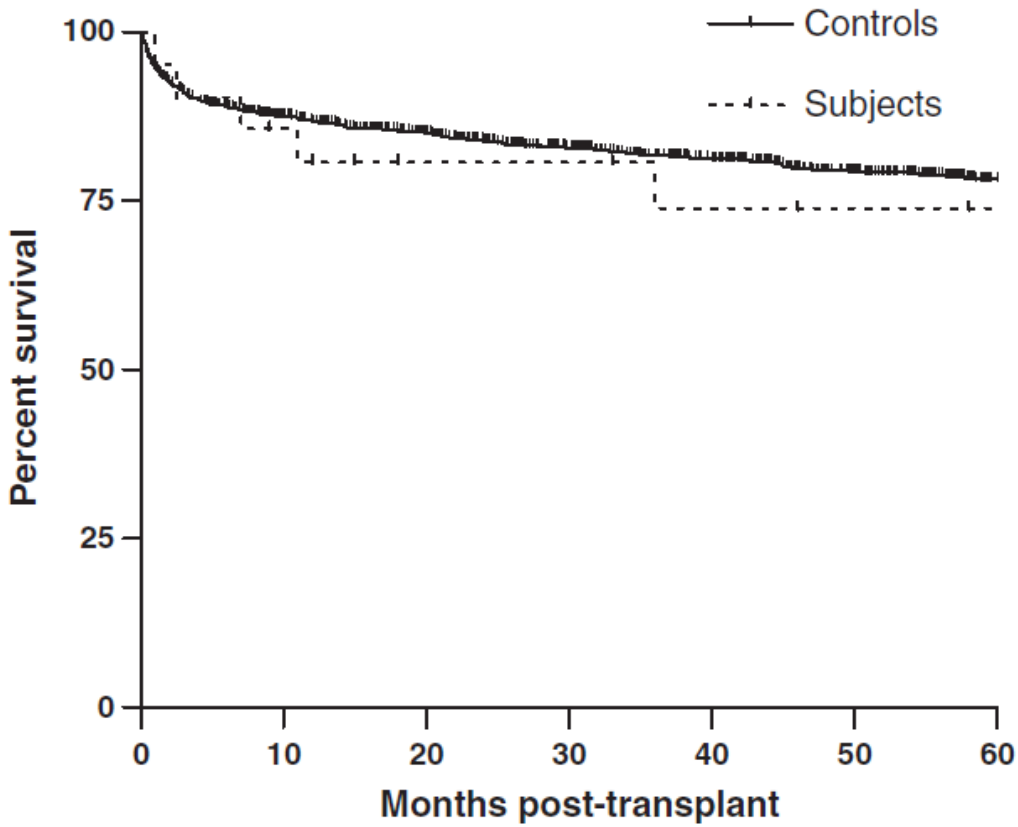
*Based on the per-protocol population.



Phatak P et al. Hepatology 2010

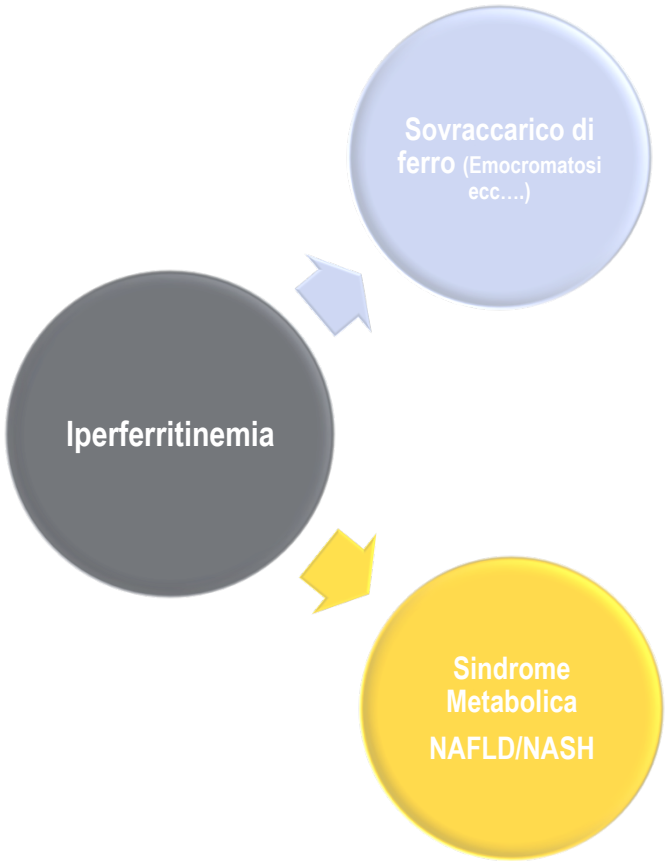
Trapianto epatico in HH



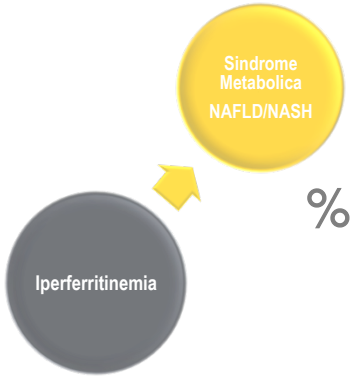


Dar FS et al. Transplant International 2009

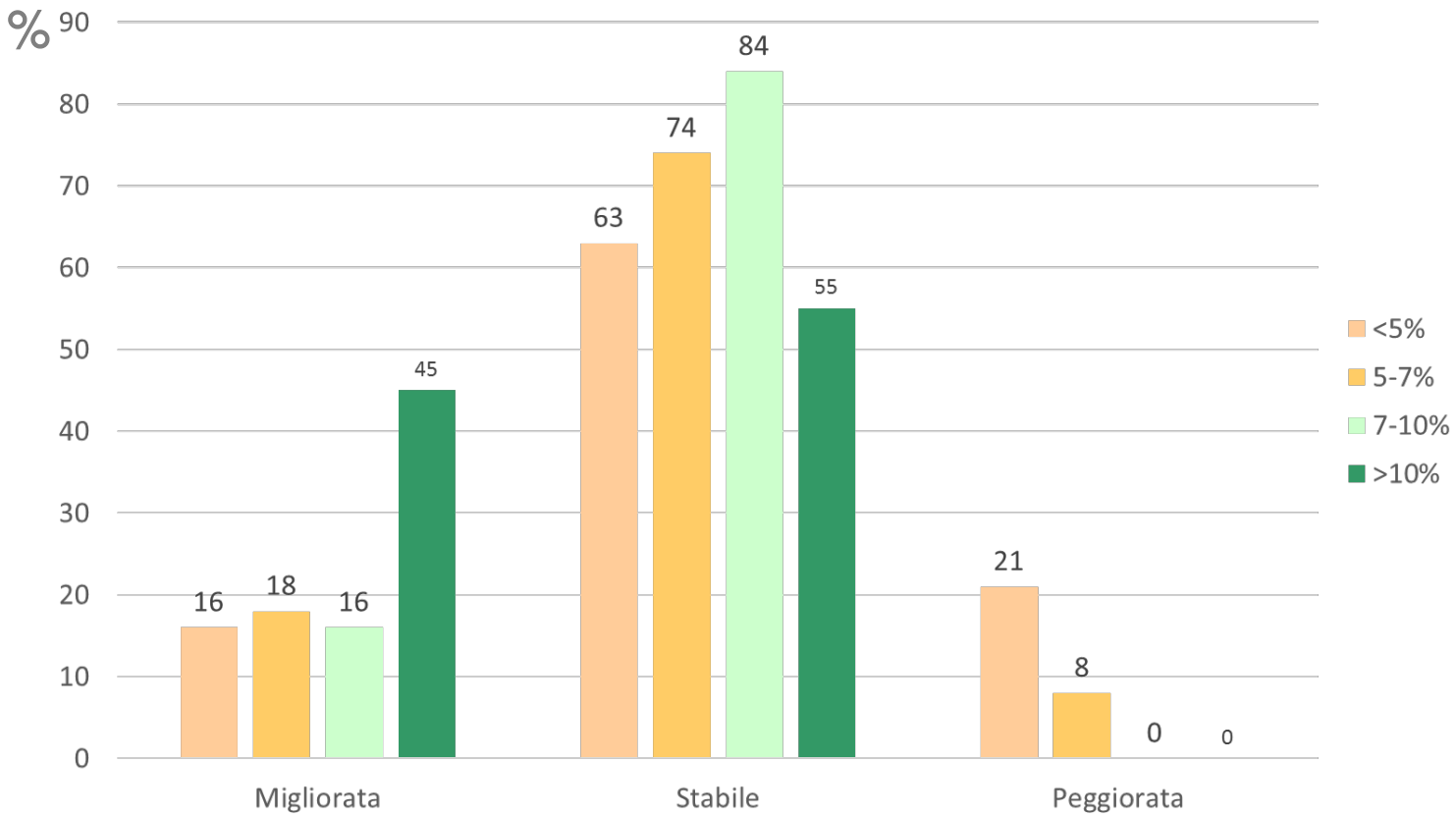
Iperferritinemia



Stile di vita



Impatto del calo ponderale sulla fibrosi nella NASH



N=293

Biopsia pre e dopo 52 settimane

Vilar-Gomez E et al. Gastroenterology 2015

Flebotomia nella NASH

HOMA-R

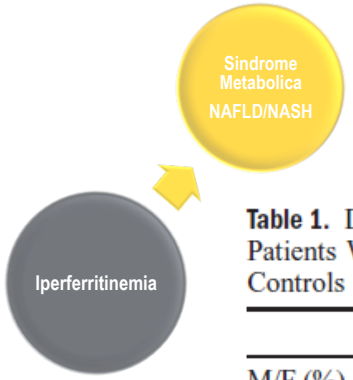
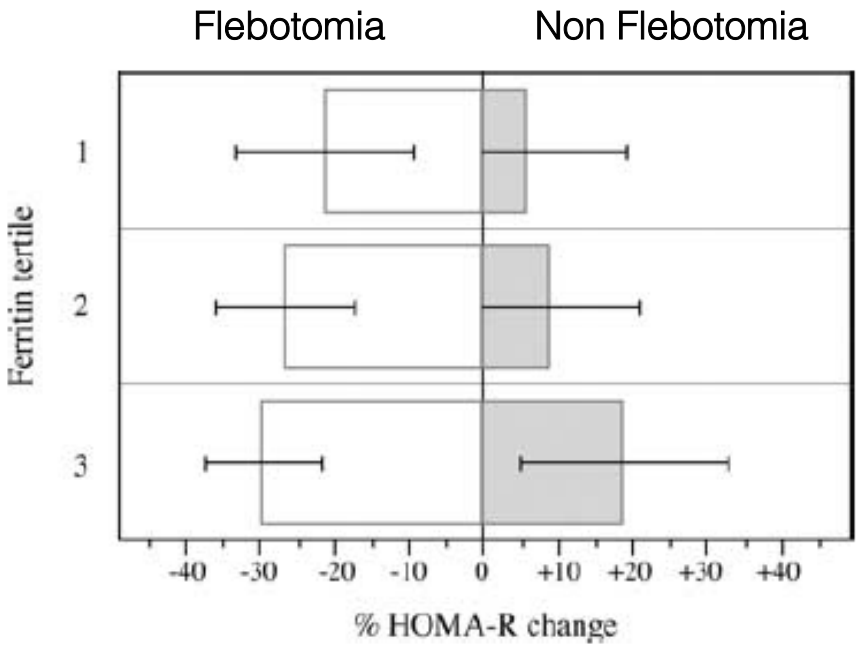


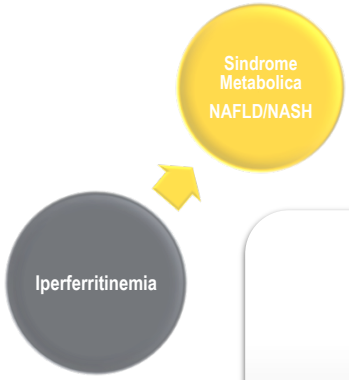
Table 1. Demographic, Anthropometric, and Clinical Features of 64 Patients With NAFLD Submitted to Phlebotomy and 64 Matched Controls

	No Phlebotomy	Phlebotomy
M/F (%)	53/11 (83/17)	53/11 (83/17)
Age (yr)	50.6 ± 12.8	49.3 ± 11.6
BMI (<25 kg/m^2)	27.3 ± 3.7	26.8 ± 2.8
Abdominal circumference M (<102/88 cm M/F)	99.7 ± 10.8	96.8 ± 10.4
Hypertension (%)	23 (36)	27 (42)
LDL (<100 mg/dL)	137.9 ± 42 (85)	139.3 ± 44 (89)
HDL (>55/65 M/F mg/dL)	47.6 ± 14	42.1 ± 12
Triglycerides (<160 mg/dL)	138.2 ± 73	136 ± 71
Uric acid (<6/5.6 mg/dL M/F)	5.7 ± 1.2	5.5 ± 1.2
Glucose (<100 mg/dL)	93.8 ± 17	98.4 ± 16
Fasting insulin (<15 mIU/L)	14.9 ± 8	19.9 ± 11
HOMA-R (<2.7)	3.51 ± 2.3*	4.81 ± 3*
Metabolic syndrome	18 (29)	26 (41)
AST (<40 IU/L)	33.4 ± 17	33.4 ± 18
ALT (<42 IU/L)	52.1 ± 33	57.9 ± 44
GGT (IU/L)	56.2 ± 67	47.9 ± 49
Ferritin† (<320/240 M/F ng/mL)	387 {197–606}	438 {212–628}
Transferrin saturation %	34.9 ± 12	39.2 ± 15.6
HFE mutation status‡		
C282Y +	3/52* (6)	11/54* (20)
H63D +	15/52 (29)	19/54 (39)
Presence of fibrosis§	12 (19)	12 (19)



Valenti L et al. Am J Gastroenterol 2007

Flebotomia nella NASH



38 pazienti randomizzati:

21 Stile vita + flebotomia
17 Stile vita

- 3 persi
- 2 neoplasie
- 14 rifiuto biopsia

19 sottoposti a biopsia epatica prima e dopo 2 anni di follow-up

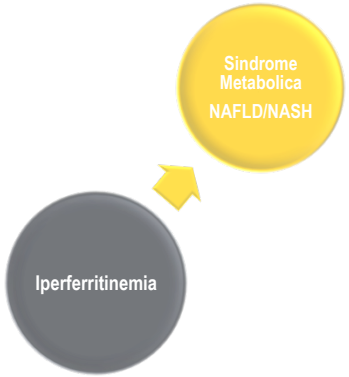
Table 1 Baseline features of 38 randomized subjects with nonalcoholic fatty liver disease and hyperferritinemia/ increased iron stores according to treatment allocation

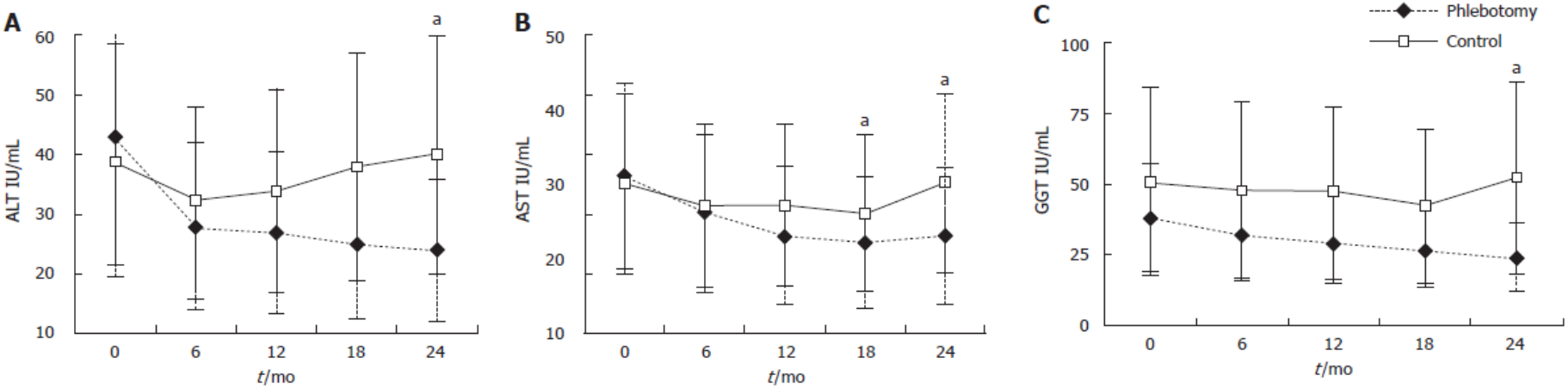
Baseline features	Lifestyle changes alone (n = 17)	Phlebotomy (n = 21)	P value
Age (yr)	53 ± 11	55 ± 8	0.45
Gender (female)	3 (18)	1 (5)	0.31
Waist circumference, cm	103 ± 11	102 ± 10	0.70
BMI (kg/m^2)	28.2 ± 4.7	27.7 ± 3.5	0.71
HOMA-IR	4.1 ± 2.5	4.4 ± 2.3	0.67
HDL chol (mg/dL)	47 ± 18	48 ± 8	0.88
Triglycerides (mg/dL)	141 ± 87	129 ± 53	0.61
Type 2 diabetes	1 (6)	4 (19)	0.23
Ferritin (ng/mL)	642 (505-907)	710 (548-997)	0.40
TS (%)	40 ± 14	42 ± 13	0.67
HIC (μg/100 mg dry tissue)	234 (98-358)	303 (238-570)	0.23
TIS	6 (4-12)	9 (6-11)	0.19
ALT (UI/mL)	39 ± 29	43 ± 25	0.61
AST (UI/mL)	30 ± 14	31 ± 14	0.70
GGT (UI/mL)	40 (24-56)	28 (21-41)	0.36
US Steatosis grade > 1	17 (100)	17 (81)	0.11
NAS ≥ 3	11 (65)	13 (63)	1.00
Fibrosis stage 2-4	3 (18)	7 (33)	0.46
HFE genotype			
C282Y+ or H63D +/+	2 (11)	2 (10)	0.82
Beta-thalassemia trait	4 (23)	4 (19)	1.00

Valenti L et al. WJG 2014

Flebotomia nella NASH

Variazioni biochimiche

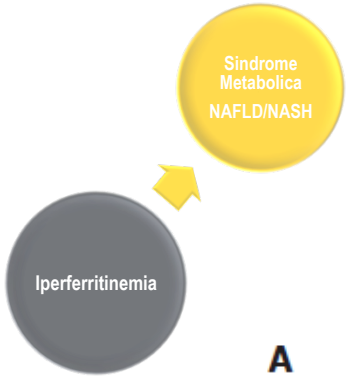


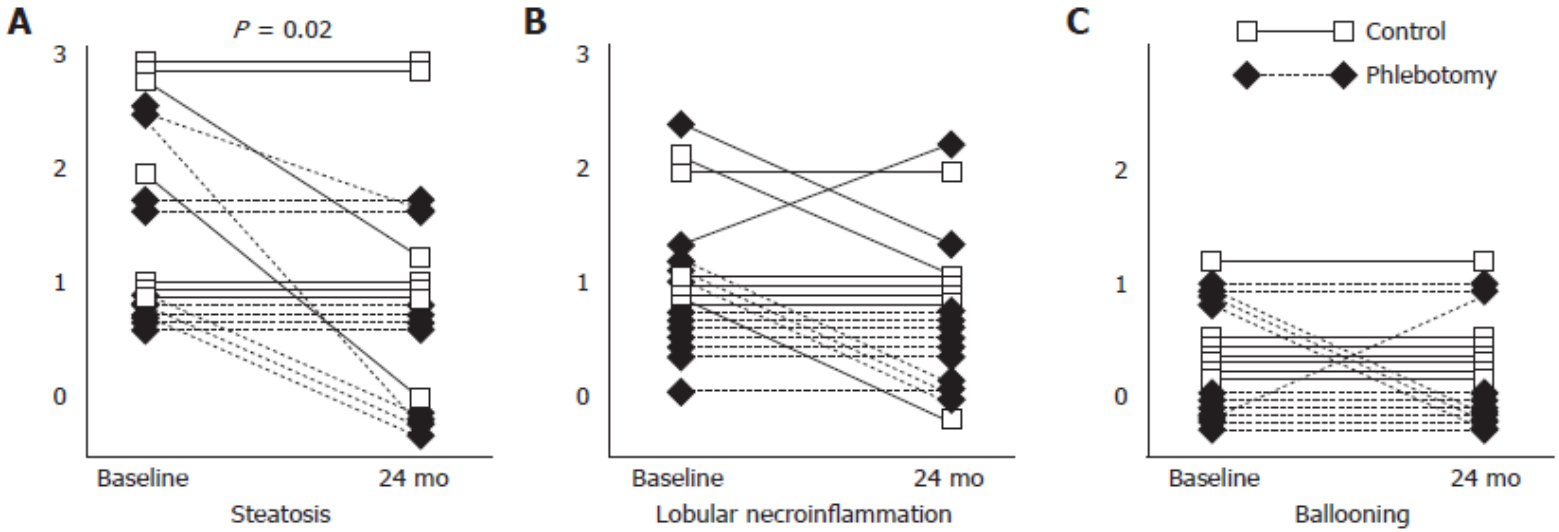


Valenti L et al. WJG 2014

Flebotomia nella NASH

Variazioni istologiche





Valenti L et al. WJG 2014

Flebotomia nella NASH

Sindrome Metabolica
NAFLD/NASH

Iperferritinemia

74 pazienti randomizzati:

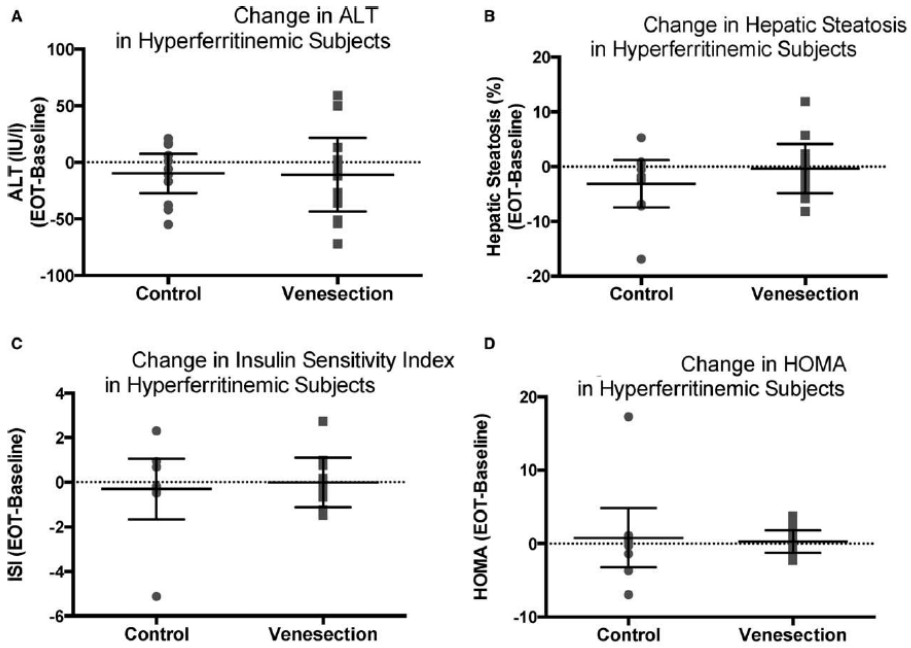
33 (29) Stile vita + flebotomia
41 Stile vita

RMN

9 persi

29 pazienti
32 controlli

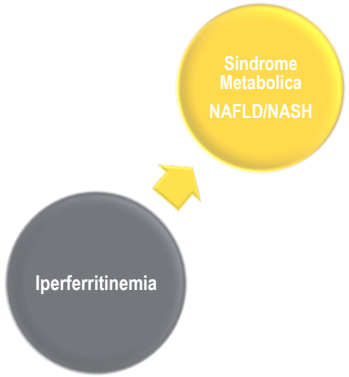
Iperferritinemici
15 pazienti
21 controlli



Adams LA et al. Hepatology 2015

Flebotomia nella NASH

Biochimica e istologia negli iperferritinemici



	Control Group	Venesection Group	p
BMI, Kg/m^2	31.1 (5.3)	31.8 (4.6)	0.6
Waist circumference, cm	104 (16)	108 (12)	0.2

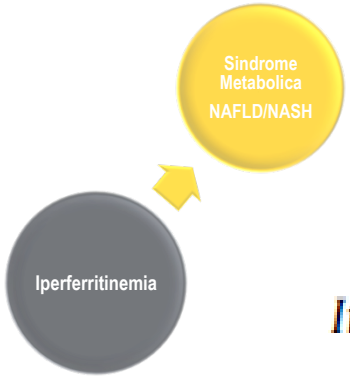
Characteristic		roup (n = 33)	*P* Value
Age, years		53.1 (9.7)	0.3
Male sex (%)	24 (58)	20 (61)	0.9
Caucasian (%)	36 (88)	30 (91)	0.7
BMI, kg/m^2	31.1 (5.3)	31.8 (4.6)	0.6
Waist circumference, cm	104 (16)	108 (12)	0.2
Diabetes (%)	7 (17)	6 (18)	0.9
Hypertension (%)	10 (24)	10 (30)	0.6
Dyslipidemia (%)	6 (15)	5 (15)	0.6
ALT, IU/L	48 (38-85)	48 (37-86)	0.9
AST, IU/L	34 (29-50)	37 (27-48)	0.8
Bilirubin, mg/dL	0.7 (0.3)	0.8 (0.4)	0.3
Alkaline phosphatase, IU/L	85 (23)	87 (25)	0.7
Albumin, mg/dL	4.5 (2.9)	4.4 (2.3)	0.06
CK-18, U/L	208 (154-316)	270 (158-465)	0.4
Hepascore	0.27 (0.21)	0.41 (0.30)	0.03
TG, mg/dL	133 (102-221)	133 (106-173)	0.4
HDL-cholesterol, mg/dL	46 (11)	43 (12)	0.2
Free fatty acids, mmol/L	0.38 (0.18)	0.39 (0.22)	0.9
F2-isoprostanes, pmol/L	1,311 (987-2,140)	1,354 (1,170-1,773)	0.9
Glucose, mg/dL	103 (92-111)	95 (88-126)	0.5
Insulin, mU/L	12 (9-17)	13 (9-20)	0.6
HbA1c, %	5.8 (5.4-6.1)	5.7 (5.4-6.2)	0.5
HOMA	3.0 (2.1-4.4)	3.2 (2.0-5.4)	0.6
ISI	2.6 (1.5-4.3)	2.6 (1.7-3.9)	0.9
Hemoglobin, g/dL	150 (14)	150 (12)	0.9
Platelet, $\times 10^3$/L	237 (53)	233 (91)	0.8
Ferritin, ng/mL	208 (229)	255 (148)	0.3
Transferrin saturation, %	31.3	32.1	0.8
Hepatic IC, mmol/kg		23.0 (17.4)	0.4
HS, %			0.5

Abbreviations: AST

	Control Group	Venesection Group	p
Ferritin, ng/mL	159 (166)	111 (78)	0.6

Adams LA et al. Hepatology 2015

EASL Practice Guidelines 2016



Iron depletion

Hepatic iron accumulation is associated with IR, and iron depletion improves IR [138]. In NAFLD, high ferritin levels are common, in the presence of variable transferrin saturation, independent of gene polymorphisms of familial hemochromatosis. In these patients, a phlebotomy programme to reduce iron stores to near iron deficiency improved the NAS score, without worsening fibrosis [100], but more data are needed.

Approccio farmacologico

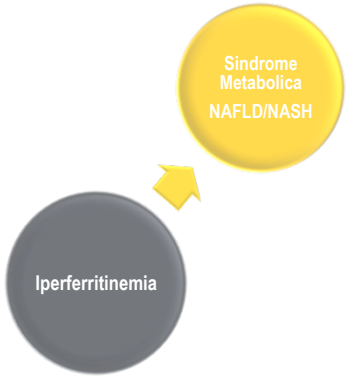


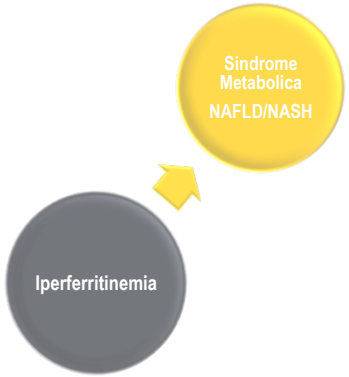
Table 1. Therapeutic approaches in NASH

Metabolically oriented (→ liver)	Liver(-gut) oriented (enterohepatic)
Lifestyle (diet, exercise)	Antioxidative (vitamin E)
Insulin sensitizers, GLP-1	Cytoprotective (UDCA)
Hypolipidemic agents, 3-PUFA	Anti-inflammatory (PFX)
11β-HSD blockers	Antifibrotic (LOXL-2 inhibitors)
Antihypertensive (AT-II)	Anti-/probiotics
Bariatric surgery	Bile acid receptor ligands (FXR agonists)

GLP-1 = Glucagon-like peptide 1; HSD = hydroxysteroid dehydrogenase; PUFA = polyunsaturated fatty acid.

Traussnigg S et al. Dig. Dis. 2015

EASL Practice Guidelines 2016



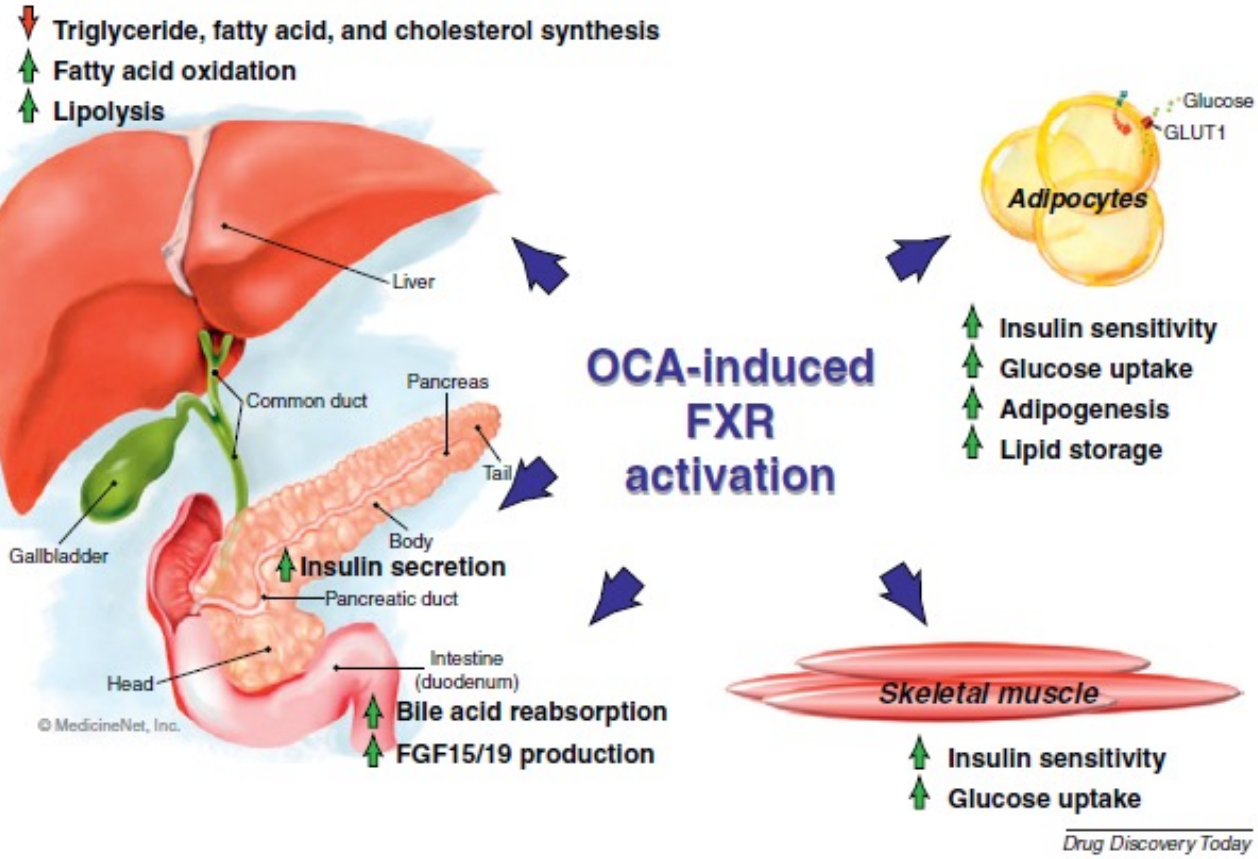
Recommendations

- Pharmacotherapy should be reserved for patients with NASH, particularly for those with significant fibrosis (stage F2 and higher). Patients with less severe disease, but at high risk of disease progression (i.e. with diabetes, MetS, persistently increased ALT, high necroinflammation) could also be candidates to prevent disease progression (**B1**)
- While no firm recommendations can be made, pioglitazone (most efficacy data, but off-label outside T2DM) or vitamin E (better safety and tolerability in the short-term) or their combination could be used for NASH (**B2**)
- The optimal duration of therapy is unknown; in patients with increased ALT at baseline, treatment should be stopped if there is no reduction in aminotransferases after 6 months of therapy; in patients with normal ALT at baseline, no recommendations can be made (**C2**)
- Statins may be confidently used to reduce LDL-cholesterol and prevent cardiovascular risk, with no benefits or harm on liver disease. Similarly *n*-3 polyunsaturated fatty acids reduce both plasma and liver lipids, but there are no data to support their use specifically for NASH (**B1**)

Acido Obeticolico

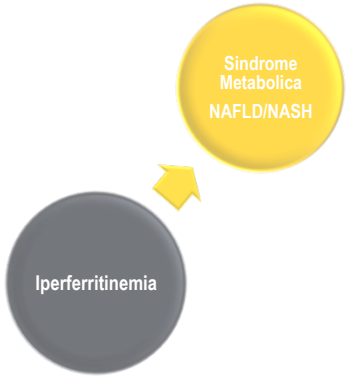
Sindrome Metabolica
NAFLD/NASH

Iperferritinemia

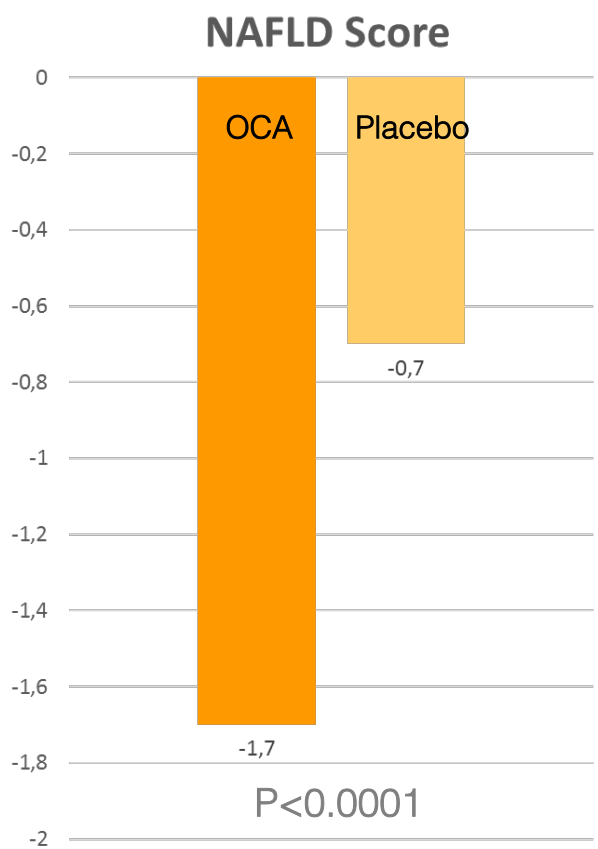


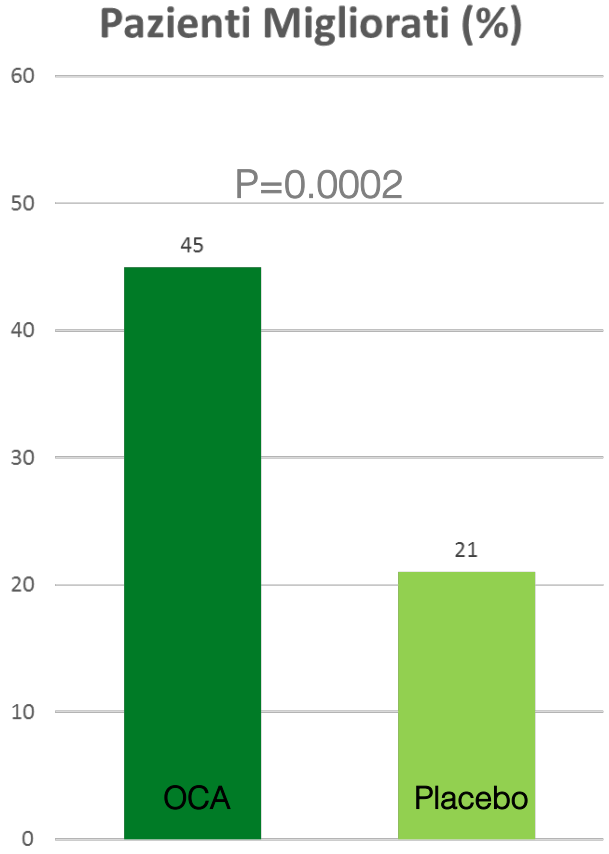
Adorini L et al. Drug Discovery Today 2012

Acido Obeticolico



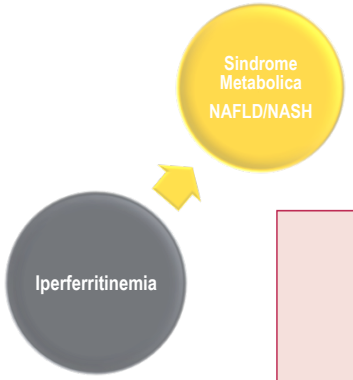
N=219 (110 OCA+109 placebo)
Biopsia dopo 72 settimane





Neuschwander-Tetri BA et al. Lancet 2015

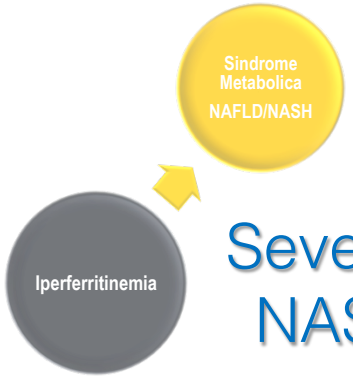
Acido Obeticolico



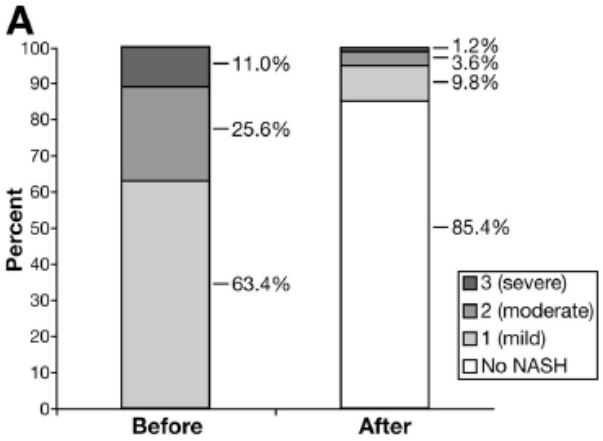
	Change from baseline to 72 weeks (mean [SD])		Mean changes from baseline* (obeticholic acid *vs* placebo) (95% CI)	p value*
	Obeticholic acid (n=126)	Placebo (n=131)		
Liver enzymes				
Alanine aminotransferase (U/L)	−38 (47)	−18 (44)	−20 (−28 to −11)	<0·0001
Asparate aminotransferase (U/L)	−27 (37)	−10 (31)	−12 (−18 to −6)	0·0001
Alkaline phosphatase (U/L)	12 (26)	−6 (20)	18 (13 to 24)	<0·0001
γ-glutamyl transpeptidase (U/L)	−37 (70)	−6 (48)	−24 (−35 to −14)	<0·0001
Total bilirubin (μmol/L)	−1·0 (4·1)	0·6 (3·7)	−1·5 (−2·4 to −0·5)	0·002
Lipids				
Total cholesterol (mmol/L)	0·16 (1·07)	−0·19 (0·96)	0·38 (0·16 to 0·60)	0·0009
HDL cholesterol (mmol/L)	−0·02 (0·20)	0·03 (0·19)	−0·06 (−0·10 to −0·01)	0·01
LDL cholesterol (mmol/L)	0·22 (0·90)	−0·22 (0·80)	0·45 (0·26 to 0·65)	<0·0001
Trigylcerides (mmol/L)	−0·22 (1·27)	−0·08 (1·74)	−0·02 (−0·35 to 0·30)	0·88
Metabolic factors				
Fasting serum glucose (mmol/L)	0·4 (2·1)	0·2 (2·3)	0·3 (−0·2 to 0·8)	0·26
Insulin (pmol/L)	29 (159)	10 (111)	38 (6 to 69)	0·02
HOMA-IR (glucose [mmol/L] × insulin [pmol/L] / 22·5)	15 (50)	4 (29)	13 (3 to 23)	0·01

Modified from Neuschwander-Tetri BA et al. Lancet 2015

Chirurgia bariatrica

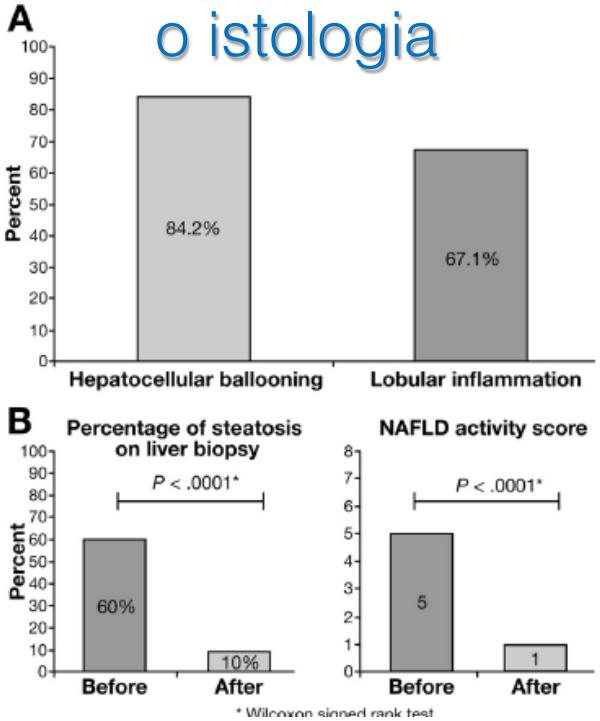


Severità NASH

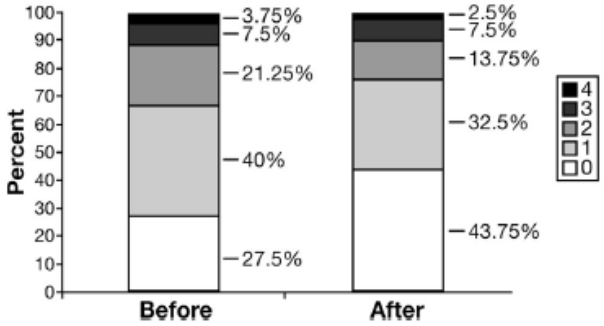


N=109
BMI pre 48.9
Biopsia dopo 1 anno

Miglioramento istologia

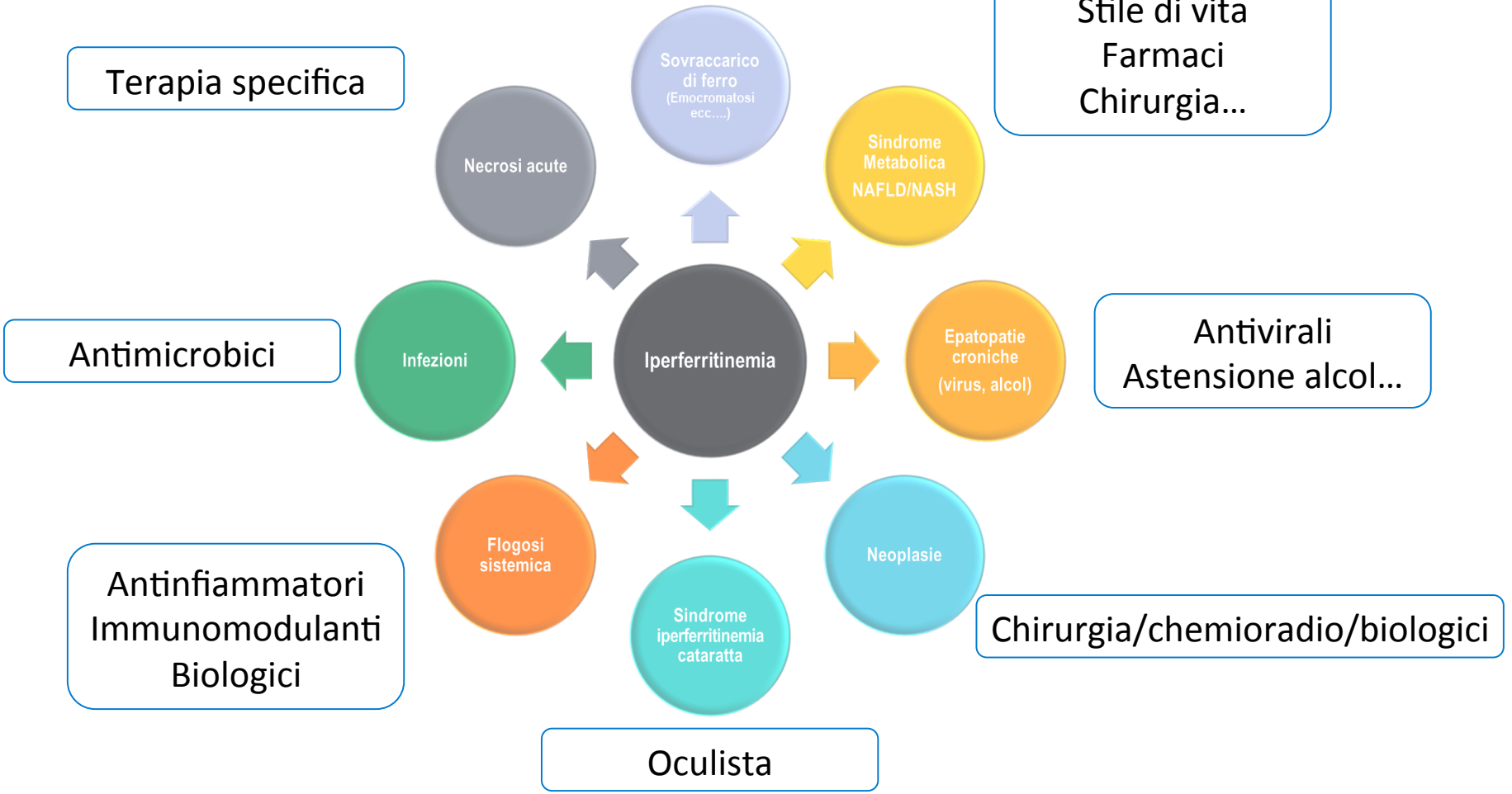


Distribuzione della fibrosi



Lassailly G et al. Gastroenterology 2015

Conclusioni



Grazie per l'attenzione!