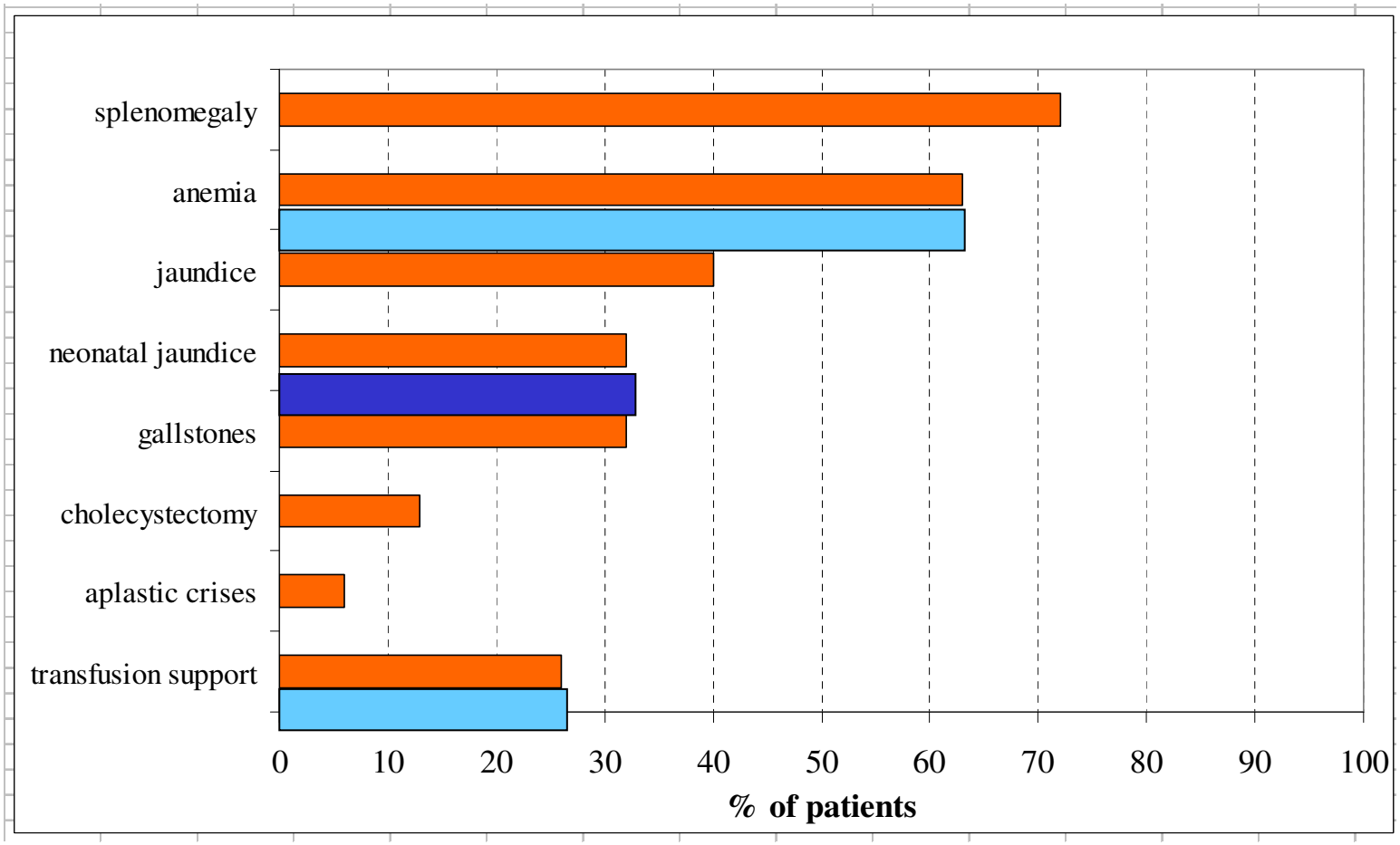
# Dati clinici di 259 pazienti con SE non splenectomizzati




**ANEMIA: grave 6%, moderata 16%, lieve 40%, compensata 38%**

**EXSANGUINOTRASFUSIONE**: 14/82 casi

# Complicanze

• **Litiasi biliare**: è la più frequente complicanza. La concomitante presenza di una sindrome di Gilbert determina un'insorgenza più precoce e più frequente di tale complicanza.

• **Crisi emolitiche**: in genere scatenate da infezioni, per lo più virali, sono caratterizzate da un'accentuazione, in genere lieve, dell'emolisi e conseguente peggioramento dell'anemia.

• **Crisi aplastiche**: comuni ad altre anemie emolitiche croniche, sono dovute all'infezioni da Parvovirus B19, agente eziologico dell'eritema infettivo o V malattia.

• **Crisi megaloblastiche**: l'accentuazione dell'anemia è conseguenza della carenza di acido folico.

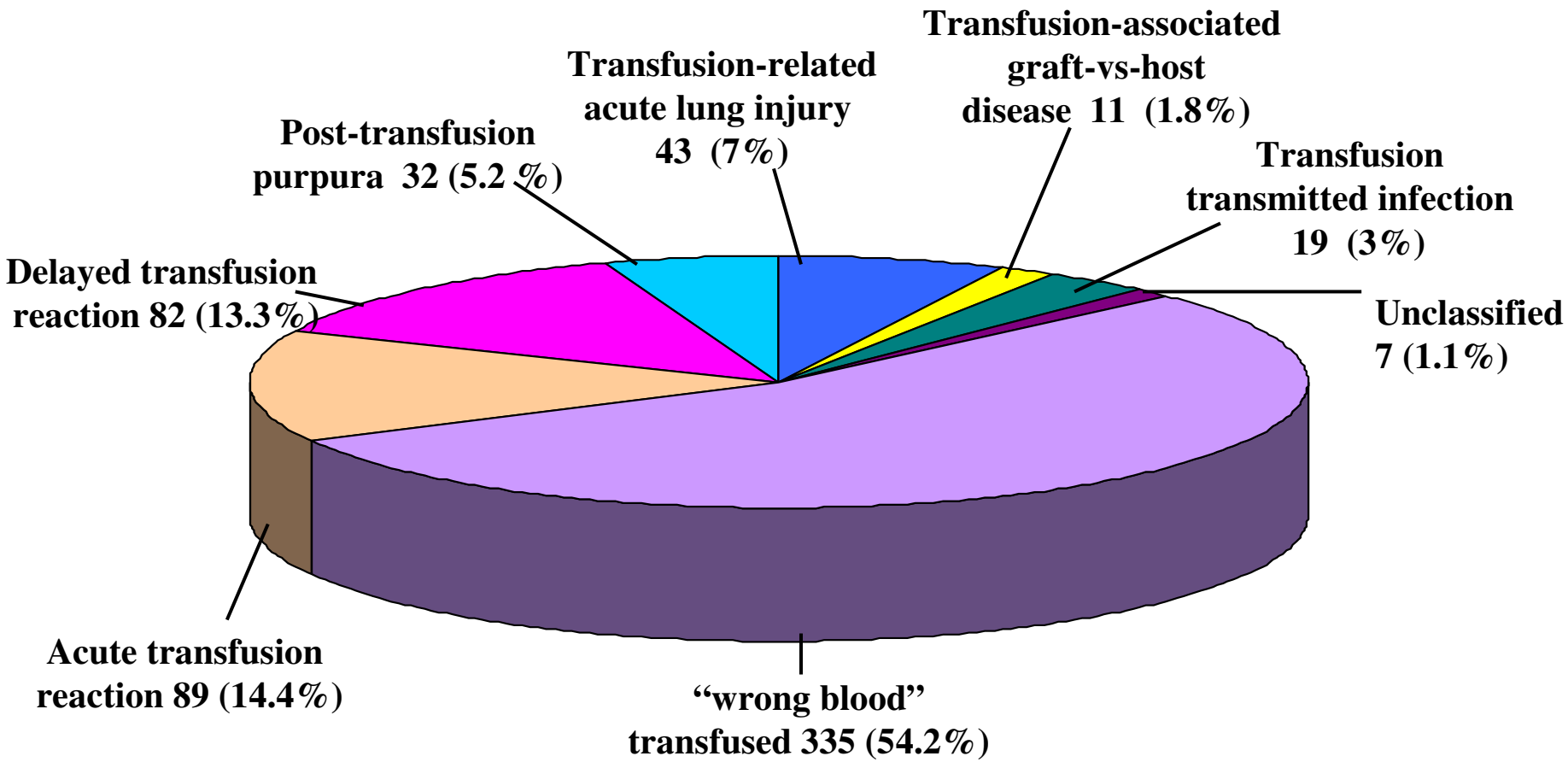
• **Sovraccarico di ferro**: importante nelle anemie diseritropoietiche. Nelle altre forme favorito dalla presenza di mutazioni del gene HFE, associate a emocromatosi idiopatica

# Terapia

- **Somministrazione di acido folico**
- **Emotrasfusioni**
  - **nei casi più gravi, in particolare nei primi anni**
  - **in caso di infezioni intercorrenti, in gravidanza**
  - **nelle crisi aplastiche**

  **N.B. basarsi sulle condizioni cliniche, non su Hb**
- **Splenectomia**
- **Ferrochelazione**

# Overview of 618 cases for which initial reports forms were received **(SHOT, 1996-1999)**



# Terapia

- **Somministrazione di acido folico**
- **Emotrasfusioni**
- **Splenectomia**
  - **non arresta l'emolisi in tutte le malattie**
  - **spesso riduce o elimina il fabbisogno trasfusionale**
  - **riservata a casi gravi, giovani, che richiedono trasfusioni o in pazienti che non tollerano l'anemia**
  - **non esclude l'insorgenza di crisi aplastiche**
- **Ferrochelazione**

Original Article

# Clinical and hematologic features of 300 patients affected by hereditary spherocytosis grouped according to the type of the membrane protein defect

Mariagabriella Mariani,[1] Wilma Barcellini,[1] Cristina Vercellati,[1] Anna Paola Marcello,[1] Elisa Fermo,[1] Paola Pedotti,[1] Carla Boschetti,[1] and Alberto Zanella[1]

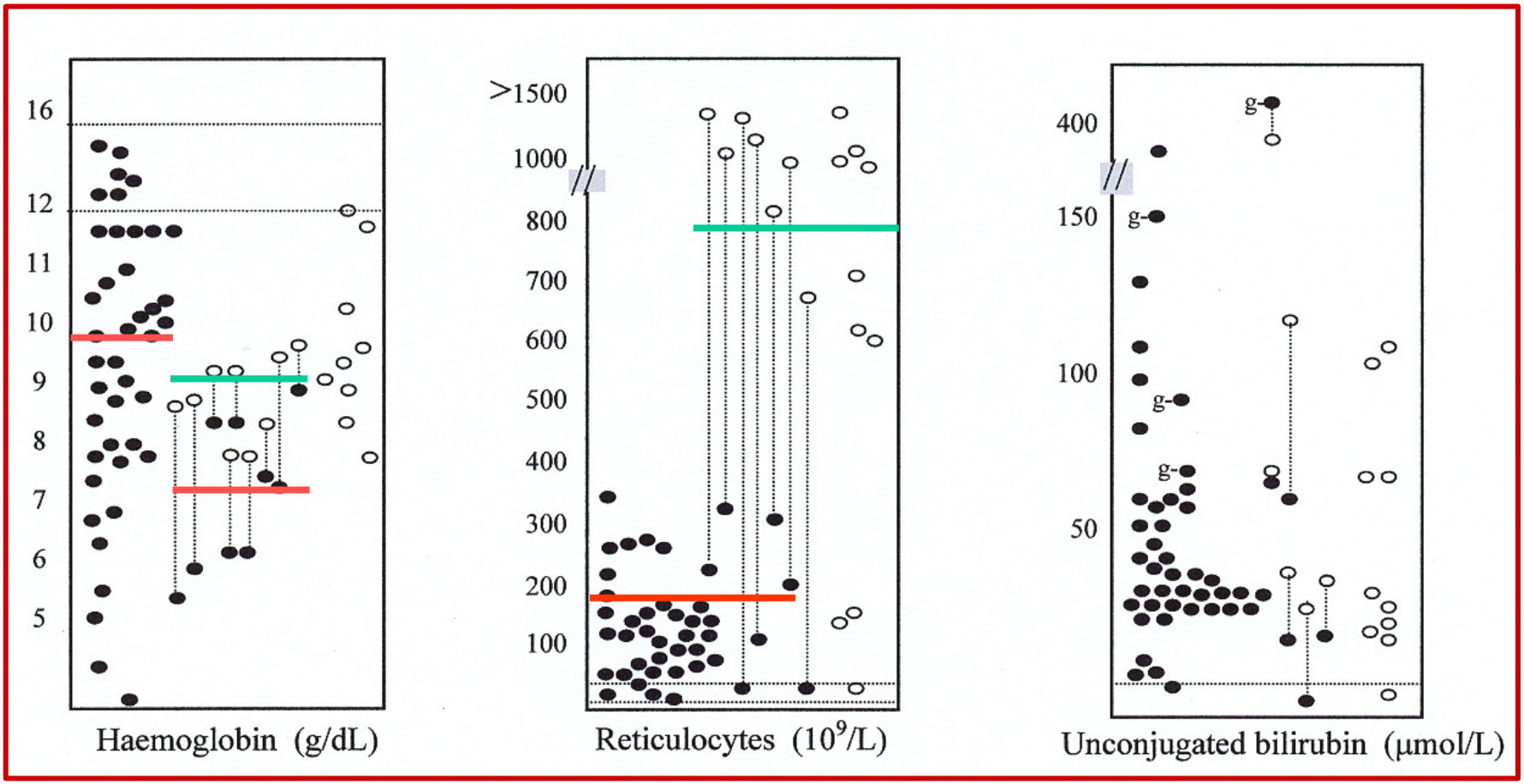
| 1310 | haematologica | 2008; 93(9)

In the splenectomized patients, the hemoglobin levels were normal in all cases but one (who had severe spectrin deficiency), and markers of hemolysis were significantly reduced as compared to those in non-splenectomized subjects.

Table 1. Hematologic and biochemical data of non-splenectomized and splenectomized HS patients.

| | *Non-splenectomized (n=259)* | | | *Splenectomized (n=41)* | |
|---|---|---|---|---|---|
| Hematologic parameters[a] | | | | | |
| Hemoglobin (g/dL) | 12 | (6-18.9) | $p<0.001$ | 14.8 | (9.2-18.4) |
| MCV (fL) | 86 | (68-112) | $p<0.03$ | 90 | (76-112) |
| MCHC (g/dL) | 35.5 | (27.6-39.9) | | 35.6 | 29.4-38.8) |
| Spherocytes (%) | 7 | (0-56) | | 10 | (0-44) |
| Markers of hemolysis[a] | | | | | |
| Reticulocytes ($\times 10^9$/L) | 244 | (9-909) | $p<0.0001$ | 78 | (37-439) |
| Unc. bilirubin (I.U.) | 30.8 | (5.1-215.4) | $p<0.0001$ | 13.7 | (3.4-66.7) |
| Defective protein[b] | | | | | |
| Band 3 | 139 | (54) | | 19 | (46) |
| Spectrin | 81 | (31 | | 17 | (41) |
| Ankyrin or combined spectrin/ankyrin | 9 | (3) | | 4 | (10) |
| Band 4.2 | 2 | (1) | | 0 | (0) |
| Undetected | 28 | (11) | | 1 | (3) |

# Some haematological parameters in 61 PK deficient patients




- **Anaemia** (in not-S or before S pts): severe (17), mod-mild (31), compensated (6)
- **Median Hb** = 9.8 g/dL in unsplenectomised and 7.3 in candidates to splenectomy
- **Median Hb increase after splenectomy** = 1.8 g/dL (0.4-3.4)
- **Median Retics** =166x$10^9$/L in unsplenectomised and 796x$10^9$/L in splenectomised

Zanella *et al*, 2005

# Splenectomy in CDA II

Splenectomised patients: 9/36

| | | | |
|---|---|---|---|
| CM ♀ | : **Hb** ↑ | +2.3 g/dL | (9.0- 11.3) |
| BV ♀ | : **Hb** ↑ | +1.2 g/dL | (8.0- 9.2) |
| MA ♂ | : **Hb** ↑ | +2.1 g/dL | (10.6- 12.7) |
| MuA ♂ | : **Hb** ↑ | +2.8 g/dL | (8.4- 11.2) |
| FG ♀ | : **Hb** ↑ | +1 g/dL | (8.7- 9.7) |
| CR ♀ | : **Hb** ↑ | + ? | (?- 10.5) |
| ZR ♀ | : **Hb** ↑ | + ? | (?- 9.9) |
| FML ♀ | : **Hb** ↑ | + ? | (?- 10.0) |
| GM ♀ | : **Hb** ↓ | -1g/dL | (11.4- 10.4) |

# Terapia

- **Somministrazione di acido folico**
- **Emotrasfusioni**
- **Splenectomia**
- **Ferrochelazione**

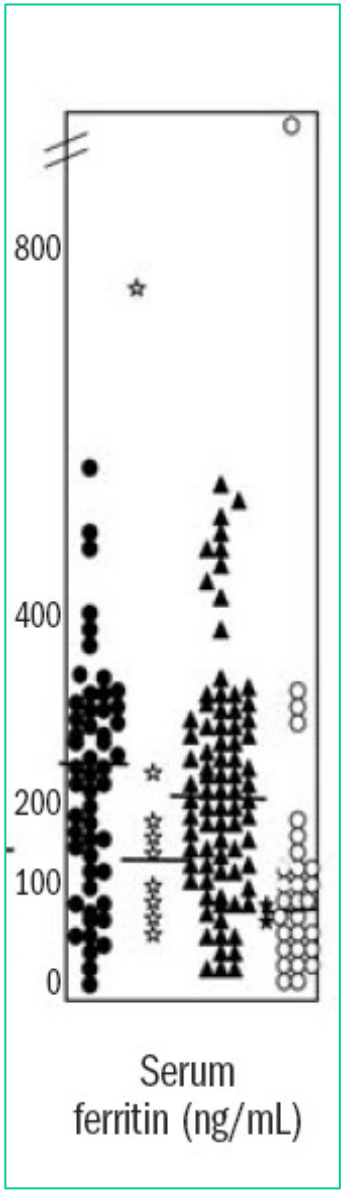
# Iron status in HS

**Table 1.** Hematologic and biochemical data of non-splenectomized and splenectomized HS patients.

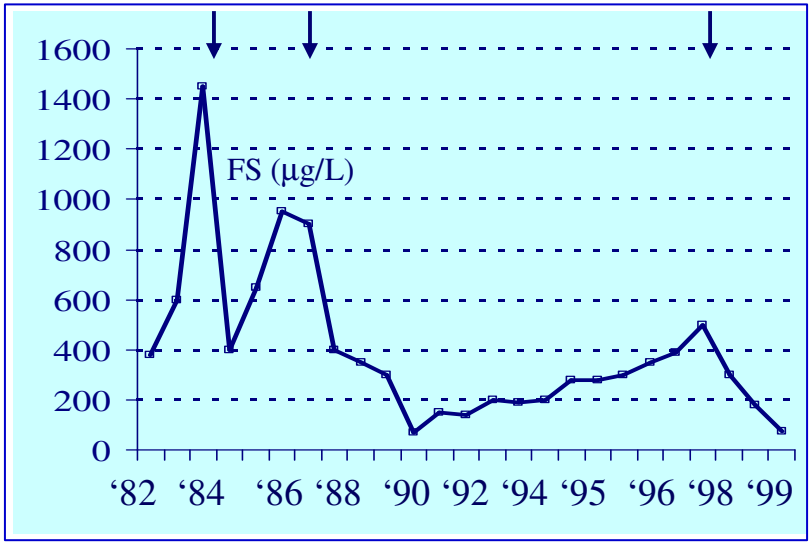
| | *Non-splenectomized (n=259)* | | *Splenectomized (n=41)* | |
|---|---|---|---|---|
| Iron status parameters[a] | | | | |
| Transferrin saturation (%) | 29 | (8-93) | 33 | (0.3-85) |
| Serum ferritin (ng/mL) | 115 | (3-1403) | 133 | 12-1617) |

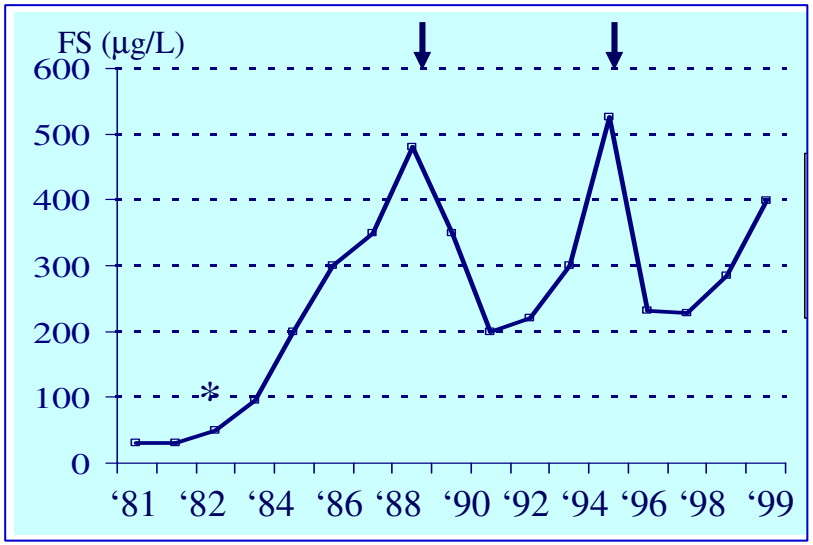
**Table 2.** Hematologic data of band 3- or spectrin- deficient HS patients grouped according to whether they had or had not been splenectomized.

| | *Band 3 deficiency* | | | | *Spectrin deficiency* | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *Non-splenectomized (n=139)* | | *Splenectomized[a] (n=27)* | | *Non-splenectomized (n=81)* | | | *Splenectomized[a] (n=26)* | |
| Iron status parameters[b] | | | | | | | | | |
| Transferrin saturation (%) | 29 | (10-79) | 34 | (1-61) | 34 | (12-93) | | 39 | (10-85) |
| Serum ferritin (ng/mL) | 145 | (7-1296) | 107 | (11-844) | 177 | (3-1403) | $p$=0.03 | 143 | (13-1617) |




A serum ferritin concentration >500 ng/mL was detected in 8 out of 189 non-splenectomized and never transfused patients; three of these eight patients had both increased serum ferritin concentration and transferrin saturation, and were heterozygous for the HFE mutation His63>Asp.




| | | |
|---|---|---|
| **Age (yr) / Sex** | **55 / M** | **30 / F** |
| **Transfusions** | **No** | **No** |
| **Spleen** | **In** | **Out** |
| **Hb (g/dL) pre / post splenectomy** | **12.6** | **7.8 / 9.1** |
| **Liver siderosis (grade)** | **3** | **4** |
| **Liver Fibrosis (grade)** | **2** | **3** |
| **HFE genotype** | **His63Asp/wt** | **His63Asp/Cys282Tyr** |
| **Ineffective Iron Turnover (ref. range 1-17)** | **69 %** | **nd** |

A. Zanella, P. Bianchi, A. Iurlo, C. Boschetti, E. Taioli, C. Vercellati, M. Zappa, E. Fermo, D.Tavazzi, M. Sampietro.

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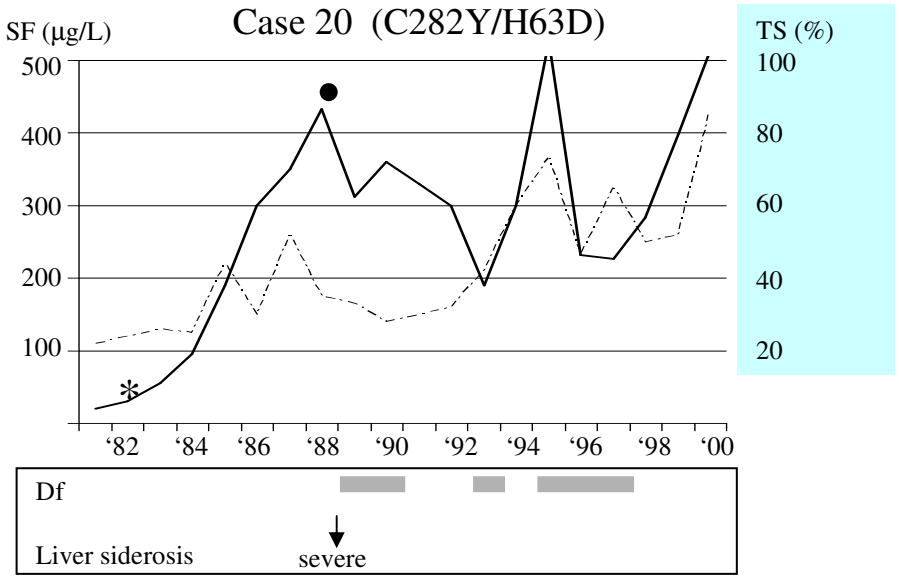


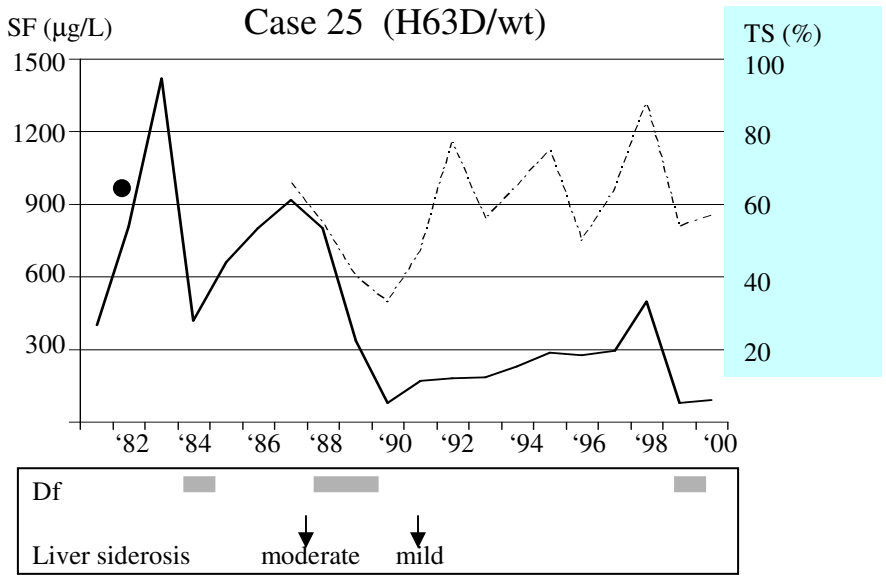


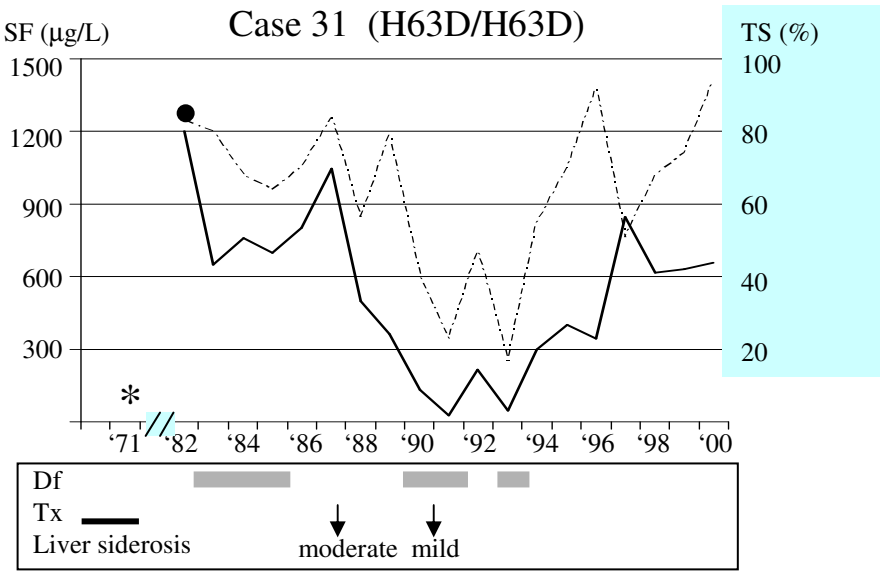


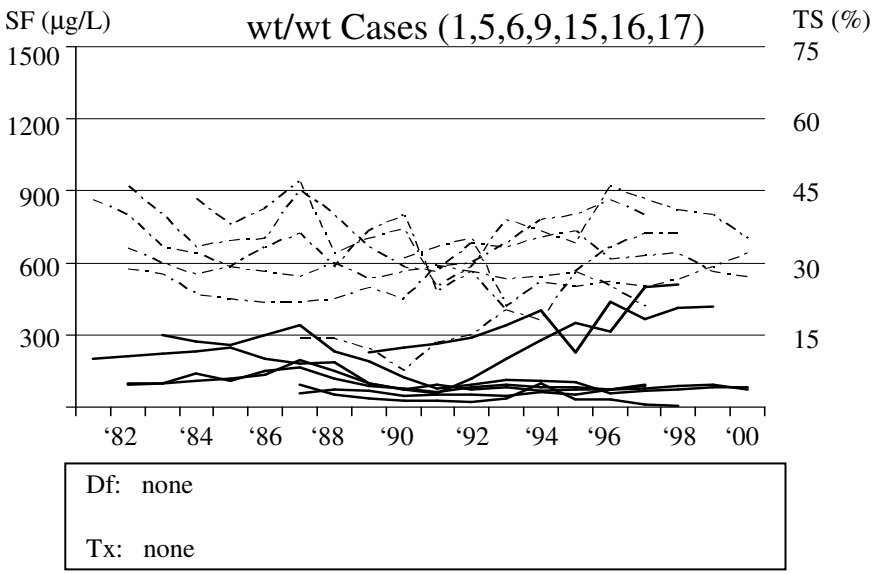

FINE

# Indications for Splenectomy

A multitude of factors aff ect the decision to do splenectomy, including the risk of postsplenectomy infection, the emergence of penicillin resistant pneumococci, access to medical care, and the increased risk of ischaemic heart disease, cerebral stroke, pulmonary hypertension, and thrombosis later in life
(Troendle et al, 2007; Jardine & Laing, 2004; Schilling et al, 2006)

A reasonable approach would be to splenectomise all patients with moderately severe and severe hereditary spherocytosis and all those who have symptomatic haemolytic anaemia, growth retardation, skeletal changes, leg ulcers, or extramedullary haemopoietic tumours. Other candidates for splenectomy are older patients with hereditary spherocytosis who have vascular compromise of the vital organs or, for cosmetic reasons, adult patients with pronounced visible jaundice due to the combination of mild to moderate hereditary spherocytosis and Gilbert's syndrome

Whether patients with moderate disease and compensated, asymptomatic anaemia should be splenectomised remains controversial.

Treatment of patients with mild to moderate hereditary spherocytosis and gallstones is also debatable,

bjh guideline

# Guidelines for the diagnosis and management of hereditary spherocytosis

P. H. B. Bolton-Maggs[1], R. F. Stevens[2]†, N. J. Dodd[3], G. Lamont[4], P. Tittensor[5] and M.-J. King[6] on behalf of the General Haematology Task Force of the British Committee for Standards in Haematology

**INDICATIONS FOR SPLENECTOMY**

Table III. Classification of spherocytosis and indications for splenectomy (modified from Eber, S.W., Armbrust, R. & Schroter, W. Variable clinical severity of hereditary spherocytosis: relation to erythrocytic spectrin concentration, osmotic fragility and autohemolysis. *Journal of Pediatrics*, 177, 409–411 (copyright 1990, with permission from Elsevier).

| Classification | Trait | Mild | Moderate | Severe |
|---|---|---|---|---|
| Haemoglobin (g/dl) | Normal | 11–15 | 8–12 | 6–8 |
| Reticulocyte count % | Normal (<3%) | 3–6 | >6 | >10 |
| Bilirubin (μmol/l) | <17 | 17–34 | >34 | >51 |
| Spectrin* per erythrocyte (% of normal) | 100 | 80–100 | 50–80 | 40–60 |
| Splenectomy | Not required | Usually not necessary during childhood and adolescence | Necessary during school age before puberty | Necessary – delay until 6 years if possible |

# Splenectomy: recommendations

**There is no evidence that one surgical approach is superior to another, and the choice of the laparoscopic route would be dependent on the availability of appropriately trained surgeons, and suitable equipment, although it can result in a shorter hospital stay and less pain.**

**In children undergoing splenectomy for symptoms of cholelithiasis, the gall bladder should be removed. In children who require cholecystectomy for symptoms of gallstones, the spleen should always be removed as well, otherwise the risk of stones persists**

**Partial splenectomy may be of benefit in very young children with severe disease, but it is likely that further surgery may need to be undertaken for either recurrence of haematological problems or symptomatic cholelithiasis**

**Where clinical suspicion exists, it may be useful to serologically document infection with parvovirus B19. Some children with HS and parvovirus infection may require blood transfusion, but this should be kept to a minimum and be guided by clinical features, as complete recovery usually occurs within 10–14 d.**

**There is no indication for extended thrombosis prophylaxis after splenectomy in patients with HS.**

It is particularly important to rule out stomatocytosis, where splenectomy is contraindicated because of the thrombotic risk (Delaunay et al 1999)

# Complications of splenectomy

- A post splenectomy mortality rate of 0.05-0.30/100 persons/years of follow-up has been reported (Davies et al, Clin Med 2002)

- The serious long term complication is overwhelming post-splenectomy infection with encapsulated bacteria, mostly *Streptococcus Pneumoniae* and, in same geographic regions, parasitic infections (Hansen and Singer, Pediatr Dev Pathol 2001)

- Because the risk of postsplenectomy infection is very high in infancy and early childhood, splenectomy should be delayed until 6–9 years of age if possible, but should not be done before 3 years of age, even if chronic transfusion is needed in the interim. Further delay might be harmful because the risk of cholelithiasis increases greatly in children after 10 years of age. (Perrotta, Lancet 2008)

# Vaccination and Antibiotic Profilaxis

Update of guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen

JM Davies, R Barnes and D Milligan

Clinical Medicine Vol 2 No 5 September/October 2002

**Table 1. Key recommendations for immunisation in hyposplenic individuals.**

| Vaccine | Timing | Revaccination schedule | Comments |
|---|---|---|---|
| Pneumococcal vaccine polyvalent | Administer at least 2 weeks pre-splenectomy if possible or 2 weeks post-splenectomy | 5 years | Immunity may decline rapidly in certain patient groups<br>Monitoring of antibody levels may be useful |
| Pneumococcal vaccine conjugate | Not known | Not known | May complement polyvalent vaccine in the near future |
| Haemophilus influenza B conjugate | Administer at least 2 weeks pre-splenectomy if possible or 2 weeks post-splenectomy | Not currently recommended | Use in previously unvaccinated individuals |
| Meningococcal C vaccine conjugate | Administer at least 2 weeks pre-splenectomy if possible or 2 weeks post-splenectomy | See text | Use only in unimmunised individuals |
| Meningococcal A & C polyvalent | Administer at least 2 weeks pre-splenectomy if possible or 2 weeks post-splenectomy | See text | Recommended only for short-term protection for at risk individuals undertaking overseas travel |
| Influenza vaccine | Administer as soon as practicable pre- or post-splenectomy to afford seasonal protection | Yearly | |

The use and duration of prophylactic antibiotics after splenectomy is controversial, especially since the worldwide emergence of penicillin-resistant pneumo cocci. Scientific justification for any specific regimen does not exist—eg, first 3–5 years after surgery versus lifelong, and expert opinions diff er widely on the use of different regimens. (Kaplinsky and Spirer 2006)

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# INDICATIONS FOR SPLENECTOMY

**Risks and benefit should be assessed carefully before splenectomy is done. A multitude of factors affect the decision to do splenectomy, including the risk of postsplenectomy infection and the emergence of penicillin resistant pneumococci, access to medical care, and the increased risk of ischaemic heart disease, cerebral stroke, pulmonary hypertension, and thrombosis later in life (Troendle et al, 2007; Jardine & Laing, 2004; Schilling et al, 2006)**

**A reasonable approach would be to splenectomise all patients with moderately severe and severe hereditary spherocytosis and all those who have symptomatic haemolytic anaemia, growth retardation, skeletal changes, leg ulcers, or extramedullary haemopoietic tumours. Other candidates for splenectomy are older patients with hereditary spherocytosis who have vascular compromise of the vital organs or, for cosmetic reasons, adult patients with pronounced visible jaundice due to the combination of mild to moderate hereditary spherocytosis and Gilbert's syndrome**

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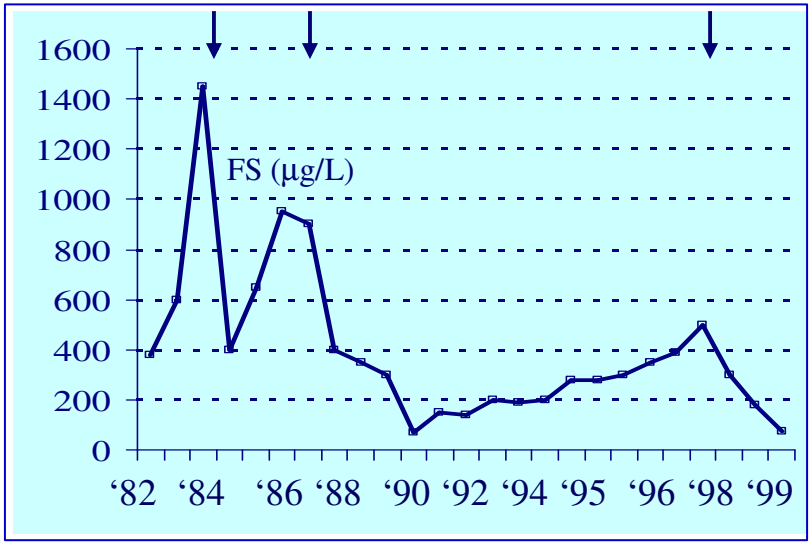
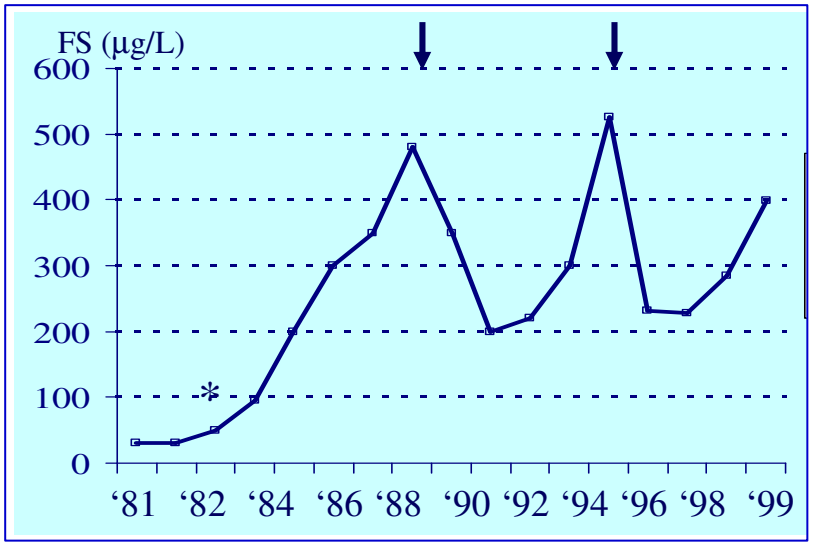
# PK TERAPIA

# Treatment of PK deficiency

- No specific therapy is available
- Red cell transfusions
  - in severely anaemic cases
  - particularly in the first years of life
  - intercurrent infections, pregnancy
  - based on the clinical conditions rather than on Hb levels
- Splenectomy
  - does not arrest haemolysis
  - increase of 1-3 g/dL in haemoglobin
  - often reduces or even eliminates transfusion requirement
  - reserved to severely affected, young patients who need regular blood transfusions, and to patients who do not tolerate anaemia
  - aplastic or haemolytic crises may still occur
- Iron chelation
  - desferroxamine/deferiprone
- Erythropoietin
  - treatment of iron overload in one patient
- Bone marrow transplantation

Tanaka & Paglia, 1971; Dacie, 1985; Zanella *et al*, 1993, 2001; Vukelja, 1994; Tanphaichitr *et al*, 2000; Watanabe *et al*, 2002; Eber *et al*, 2002; Marshall *et al,* 2003




| | | |
|---|---|---|
| **Age (yr) / Sex** | **55 / M** | **30 / F** |
| **Transfusions** | **No** | **No** |
| **Spleen** | **In** | **Out** |
| **Hb (g/dL) pre / post splenectomy** | **12.6** | **7.8 / 9.1** |
| **Liver siderosis (grade)** | **3** | **4** |
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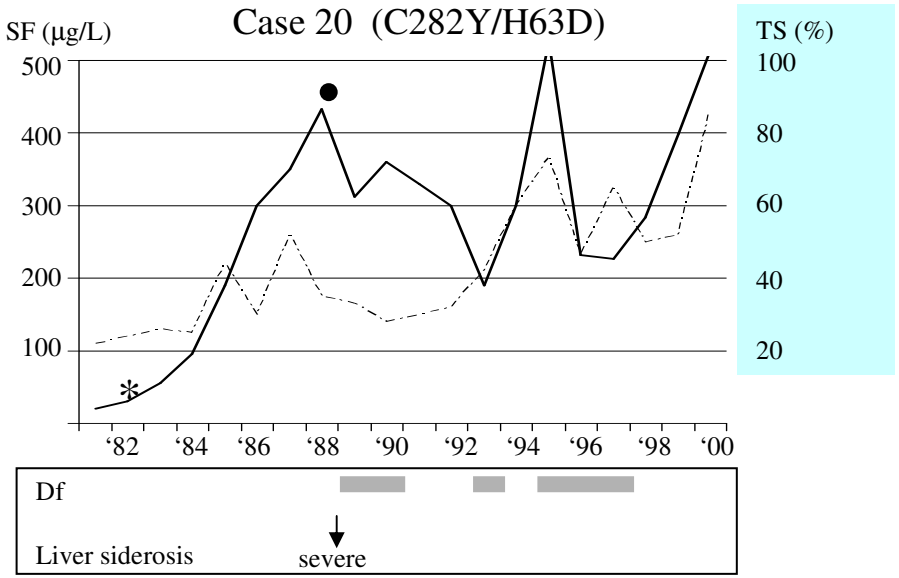


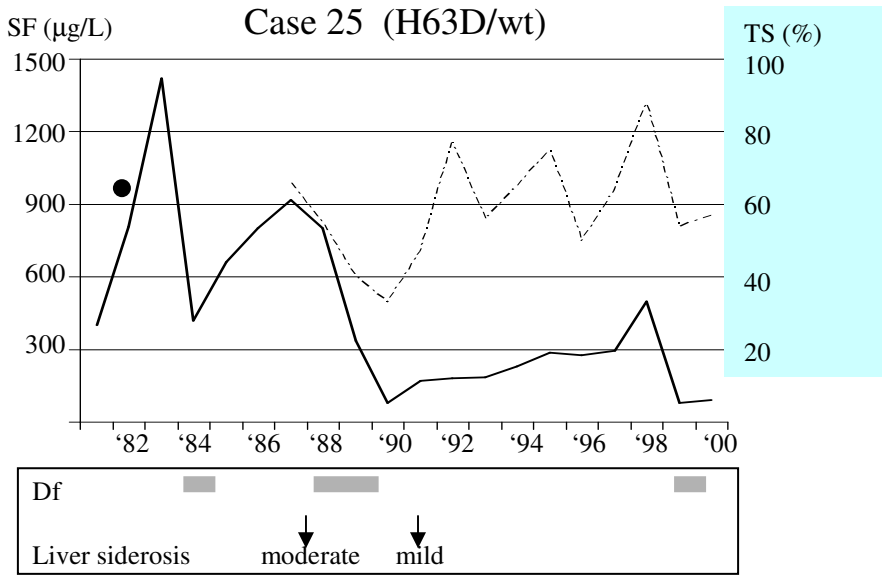


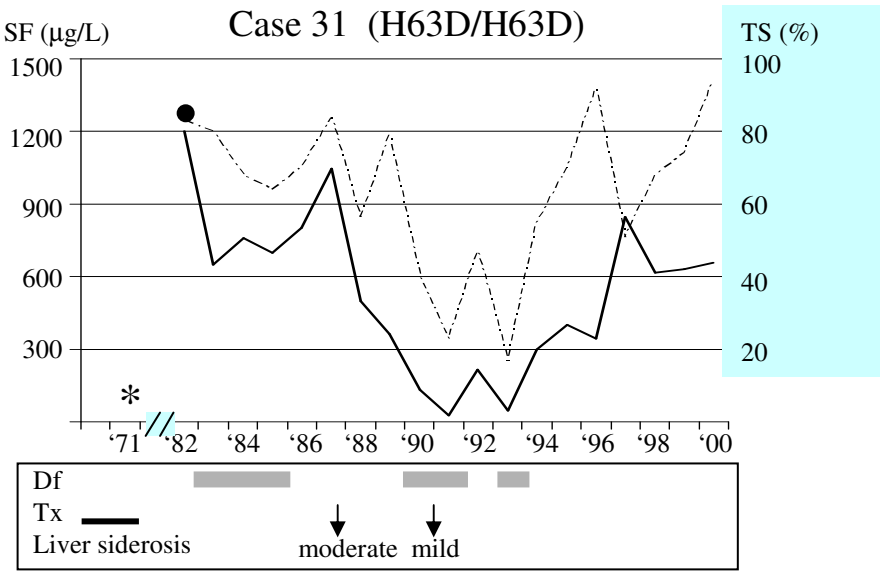


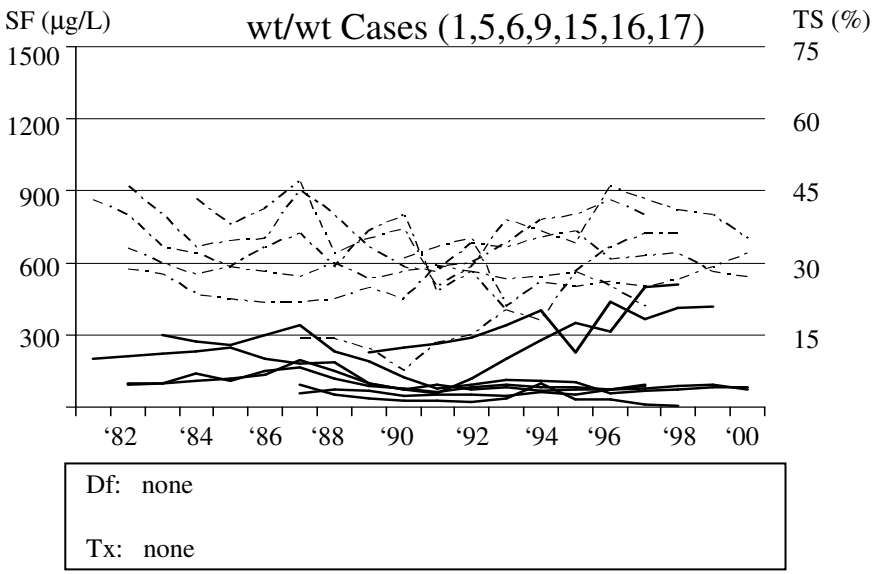

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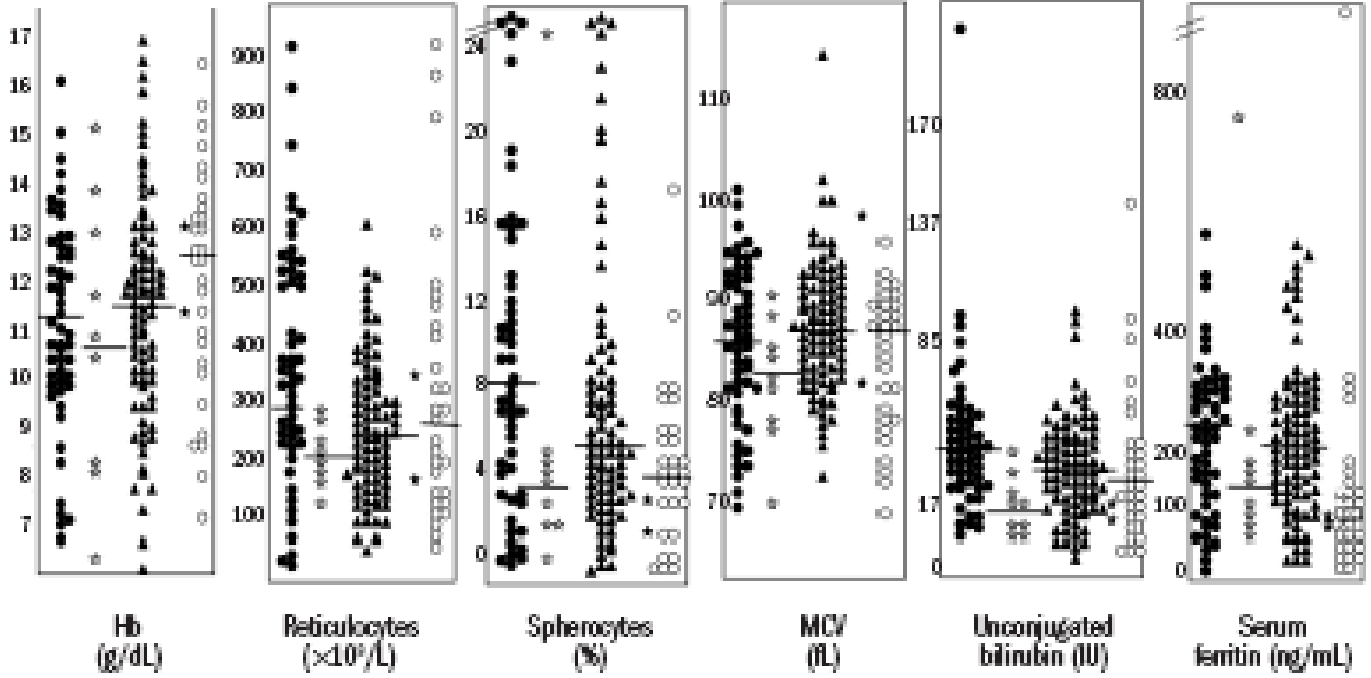


Figure 2. Hematologic parameters of 259 non-splenectomized HS patients grouped according to the results of SDS-PAGE analysis. ▲ band 3 deficiency, ● spectrin deficiency, ☆ ankyrin and combined ankyrin and spectrin deficiency, ★ band 4.2 deficiency, · unclassified membrane defect. Horizontal bars indicate median values.

• No significant differences were observed among the various groups, although haemoglobin levels were slightly lower, and median spherocyte number and haemolysis markers slightly higher in spectrin than in band 3 and 4.2 deficient patients.

•HS presented as **trait, mild, moderate, and severe in 42%, 38%, 11%, 9%** of spectrin/ankyrin deficient patients, and in 50%, 30%, 16%, 4% of band 3 deficient cases, respectively.

## Haematological and biochemical data of 21 HS patients before and after splenectomy

| | Pre-splenectomy | | Post-splenectomy | |
|---|---|---|---|---|
| *Haematological parameters* | | | | |
| **Hb (g/dL)** | 10.8 | (7.6-15.1) | 13.9 | (12.6-18.8) |
| **MCV (fL)** | 84 | (68-106) | 84 | (73-95) |
| **MCHC (g/dL)** | 35.4 | (28.3-38.8) | 34.8 | (33.3-37.1) |
| **Spherocytes (%)** | 9 | (1-32) | 4 | (3-16) |
| **Reticulocytes (x109/L)** | 337 | (96-640) | 51 | (11-118) |
| **Unc. bilirubin (mg/dL)** | 1.9 | (0.7-8.9) | 0.7 | (0.35-1.83) |

- **Increase of median haemoglobin levels (from 10.8 g/dL, to 13.9 g/dL)**
- **Decrease of reticulocytes (from 337x$10^9$/L to 51x$10^9$/L) and unconjugated bilirubin (from 32.5 IU to 12 IU).**
- The effect of splenectomy was comparable in young (n=6) and adult patients.
- Splenectomy allowed the identification of the membrane defect in all the previously unclassified cases (4 spectrin, 3 spectrin/ankyrin, and 1 band 3 deficiency).

# SPLENECTOMY- Complications

**The serious long term complication is overwhelming post-splenectomy infection with encapsulated bacteria, mostly Streptococcus Pneumoniae and, in same geographic regions, parasitic infections** (Hansen and Singer, Pediatr Dev Pathol 2001)
**A post splenectomy mortality rate of 0.05-0.30/100 persons/years of follow-up has been reported (Davies et al, Clin Med 2002)**

**The risk is not completely eliminated by currently recommended pre-splenectomy vaccination against pneumococcus, haemophilus and meningococcus. There remain many unanswered questions: How long does pneumococcal immunity last? Which is the best vaccine?**

**Because the risk of postsplenectomy infection is very high in infancy and early childhood, splenectomy should be delayed until 6–9 years of age if possible, but should not be done before 3 years of age, even if chronic transfusion is needed in the interim. Further delay might be harmful because the risk of cholelithiasis increases greatly in children after 10 years of age** (Perrotta, Lancet 2008).

**The use and duration of prophylactic antibiotics after splenectomy is controversial, especially since the worldwide emergence of penicillin-resistant pneumo cocci. Scientific justification for any specific regimen does not exist—eg, first 3–5 years after surgery versus lifelong, and expert opinions differ widely on the use of different regimens. (**Kaplinsky and Spirer 2006)