

TYROSINEMIA

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TYROSINEMIA

- ◆ Autosomal – recessive trait
- ◆ Heterozygous are asymptomatic
- ◆ Québec (Saguenay region) { 1 out of 20 is a carrier
1 out of 1,846 newborn
is affected
- ◆ Genotype – phenotype correlations (?)

TYROSINEMIA

Laboratory findings

- ◆ ↑ Tyrosine
(↑ Phenylalanine)
- ◆ * ↑ Succinylacetone (in blood and urine)
- ◆ FAH activity (lymphocytes, erythrocytes, liver tissue)
- * This is « pathognomonic of tyrosinemia »

TYROSINEMIA

Prenatal diagnosis

- ◆ Succinylacetone in amniotic fluid
- ◆ FAH assay in cultured amniocytes or chorionic virus cells
- ◆ Molecular screening (known mutation)

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Neonatal screening

- ◆ Succinylacetone detection

- ◆ Tyrosine measurements 
 - False (+)
 - False (-)

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Clinical features

◆ Hepatocellular necrosis

◆ Cirrhosis

◆ Hepatic failure

◆ Rickets

◆ Tubulopathy

◆ Neurological symptoms



before 2 years of age

TYROSINEMIA

Clinical features (liver failure)

- ◆ Coagulopathy
- ◆ Odor resembling boiled cabbage
- ◆ Ascitis – Anasarca
- ◆ Jaundice appears in terminal cases
- ◆ ↑ aminotransferases (moderate)
- ◆ ↑ α -foetoprotein
- ◆ Aminoaciduria

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Differential Diagnosis

- ◆ Galactosemia
- ◆ Hereditary fructose intolerance
- ◆ Wilson's disease
- ◆ Lactic acidosis
- ◆ GSD type 1

TYROSINEMIA

Clinical features (chronic course)

- ◆ All patients developed CIRRHOSIS
- ◆ Neurological crisis
- ◆ Hepatocarcinoma

TYROSINEMIA

Clinical features (chronic course)

Case report :

S.Y. 14 years old, girl

Normal growth & development

Hepato-splenomegaly

ALT-AST and GGT = (N)

α -foetoprotein = 35.000 U/L

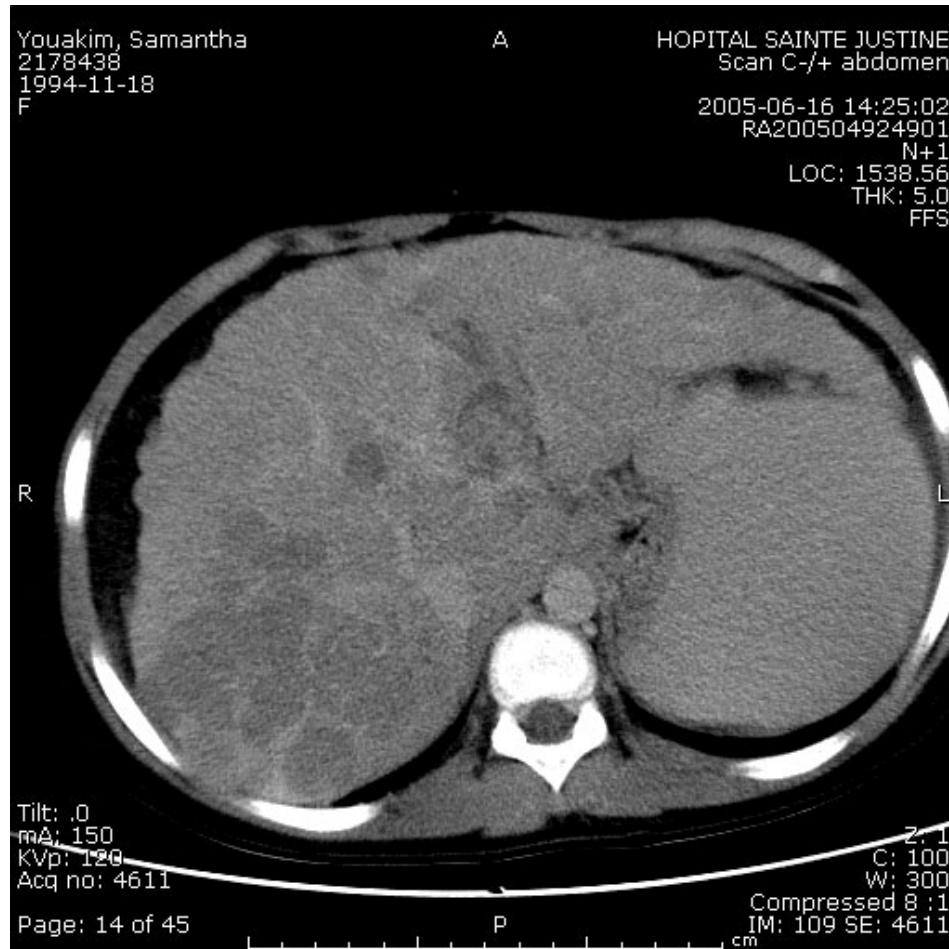
Ultrasound = Hepatic « nodules »

Biopsy = **HCC**

URINE SUCCINYLLACETONE = (+)

TYROSINEMIA

Hepatocarcinoma



TYROSINEMIA

Hepatocarcinoma

TABLE 29.1. CHILDREN WITH TYROSINEMIA UNDERGOING LIVER TRANSPLANTATION WHO HAD NOT RECEIVED PREVIOUS NTBC TREATMENT

Patient	Age at OLT (yr)	Nodules/HCA and/or Dysplasia ^a	Outcome
1	1½	-/dysplasia grade 1	Death, primary nonfunction
2	8	-/-	A&W
3	9	-/-	A&W
4	3½	+/HCA and dysplasia grade 3	A&W
5	2	+/dysplasia grade 3	A&W
6	10	+/-	A&W
7	1½	+/dysplasia grade 1	A&W
8	12	+/-	A&W
9	1½	-/dysplasia grade 1	A&W
10	17	-/-	Liver/kidney, A&W
11	6	+/dysplasia grade 2	A&W
12	3	-/dysplasia grade 2	A&W
13	2	-/dysplasia grade 1	A&W
14	½	+/dysplasia grade 2	Death, primary nonfunction
15	9½	+/dysplasia grade 3	A&W
16	1	+/dysplasia grade 3	A&W
17	2½	+/dysplasia grade 1	A&W
18	2½	+/dysplasia grade 1	A&W
19	11	+/HCA and dysplasia grade 3	A&W
20	½	+/dysplasia grade 2	A&W
21	3	+/dysplasia grade 1	A&W
22	11/12	+/dysplasia grade 3	A&W
23	2	+/dysplasia grade 2	A&W

^aDysplasia classified as in Ferrell et al. (59).

A&W, alive and well; OLT, orthotopic liver transplantation; HCA, hepatocarcinoma.

TYROSINEMIA

Renal disease

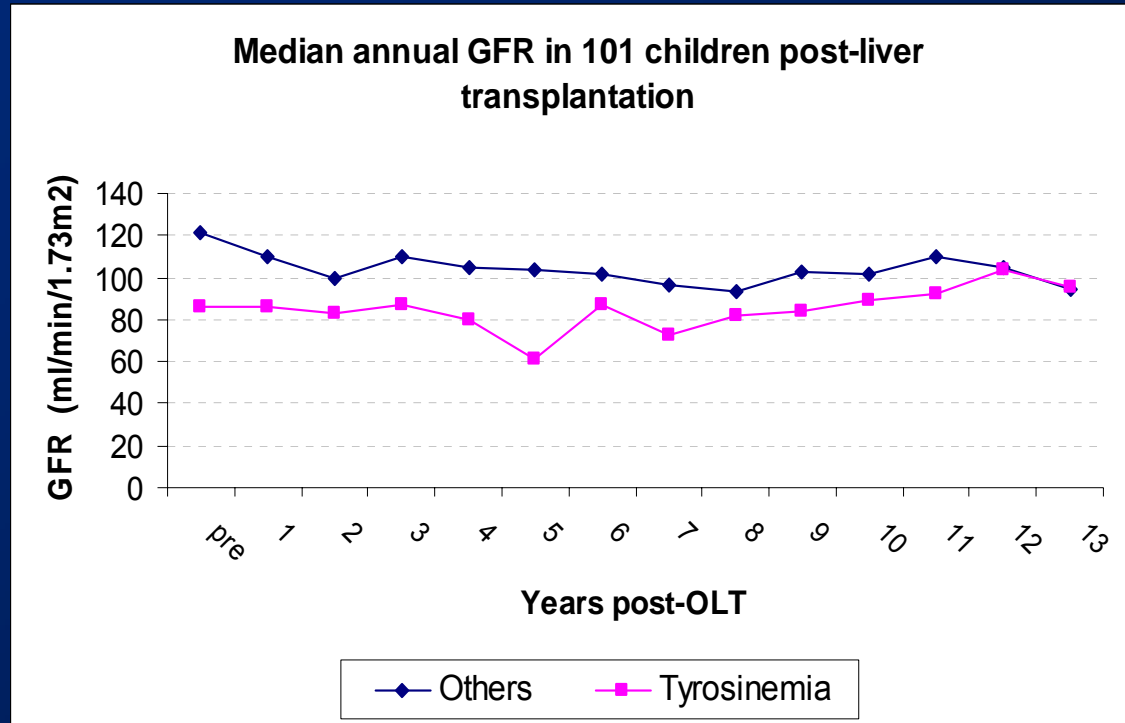
TABLE 29.2. EVALUATION OF RENAL DISEASE IN 37 PATIENTS WITH TYROSINEMIA

Patient	Age (yr)	Nephromegaly	Nephrocalcinosis	GFR Pretransplantation ^a (mL/min/1.73/m ²)
1	0.7	+	+	40
2	8	+	-	69
3	9	+	-	137
4	3.5	+	+	142
5	1.5	+	-	105
6	9.7	+	-	47
7	1.5	+	-	64
8	18	+	+	34
9	8	+	+	36
10	12	+	-	83
11	2.0	+	-	108
12	18	+	+	27
13	6	+	-	52
14	2.0	-	-	173
15	2.5	-	-	73
16	2.8	+	-	ND
17	3.5	+	-	ND
18	1.9	-	-	ND
19	8	+	+	ND
20	1.8	+	-	ND
21	9	+	+	117
22	0.3	+	-	82
23	4	+	+	93
24	6	+	+	65
25	2.0	+	-	86
26	0.7	+	-	182
27	0.9	+	+	155
28	2.0	-	-	147
29	2.0	+	+	125
30	0.5	-	-	141
31	2.0	+	-	107
32	9	-	-	124
33	2.0	+	+	90
34	2.5	-	-	116
35	4	+	-	128
36	1.0	-	+	120
37	3.0	-	-	128

^aDTPA method. GFR, glomerular filtration rate; ND, not determined.

TYROSINEMIA

Treatment



Year	Pre	1	2	3	4	5	6	7	8	9	10	11	12	13
Others (range)	121 (194)	110 (118)	99 (128)	110 (118)	105 (163)	104 (132)	101 (133)	96 (79)	93.5 (88)	103 (69)	101 (89)	109 (48)	105 (38)	94 (55)
Tyrosin- emia (range)	86.5 (108)	86 (130)	83 (85)	87 (96)	80 (108)	61 (91)	87.5 (93)	73 (61)	82 (81)	84 (77)	89 (55)	92 (33)	104 (58)	95.5 (29)
Patient number	91	88	80	70	67	60	54	41	38	30	24	15	11	7

TYROSINEMIA

Treatment

NITISINONE (NTBC)

Dose = ≥ 1.0 mg/kg/d = Plasma NTBC ≥ 50 $\mu\text{mol/l}$

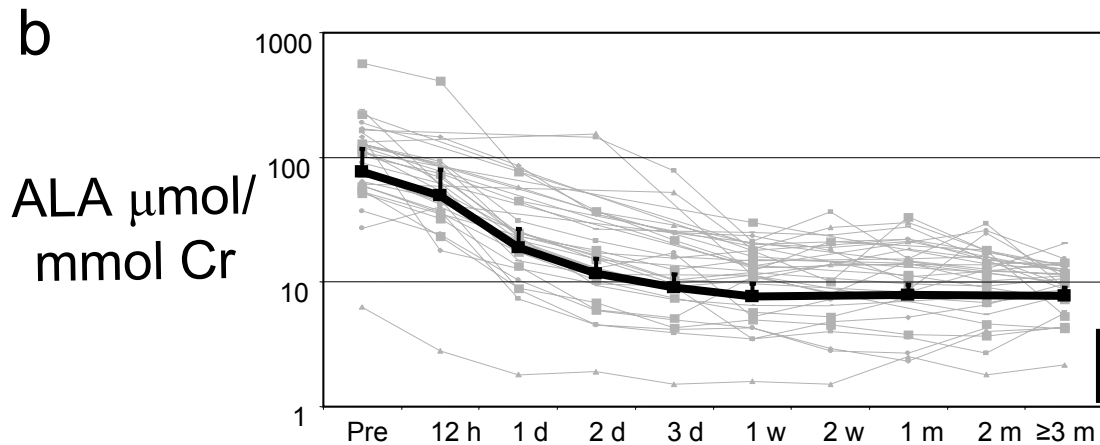
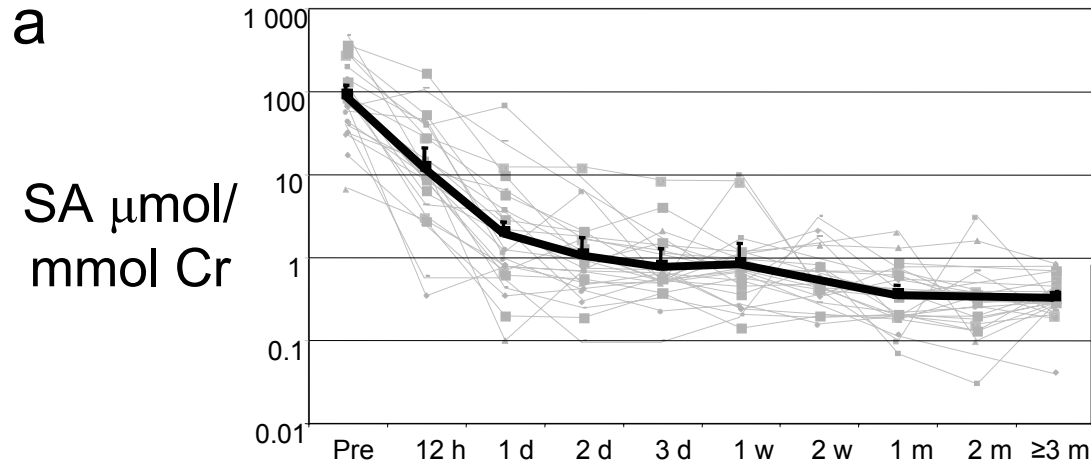
Side effects : Ocular crystals (tyrosine)* = Photophobia

Hypoglycemia?

(\uparrow) ALT ?

* Tyrosine = ≤ 400 $\mu\text{mol/l}$ (diet)

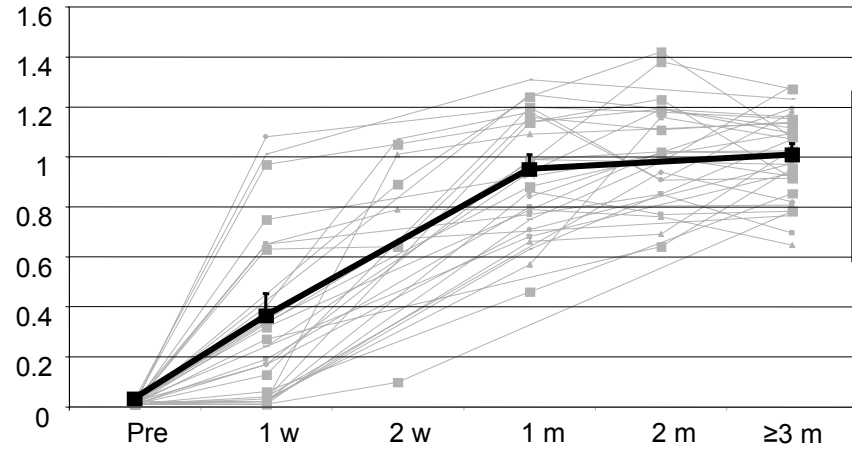
TYROSINEMIA - *Treatment*



TYROSINEMIA - Treatment

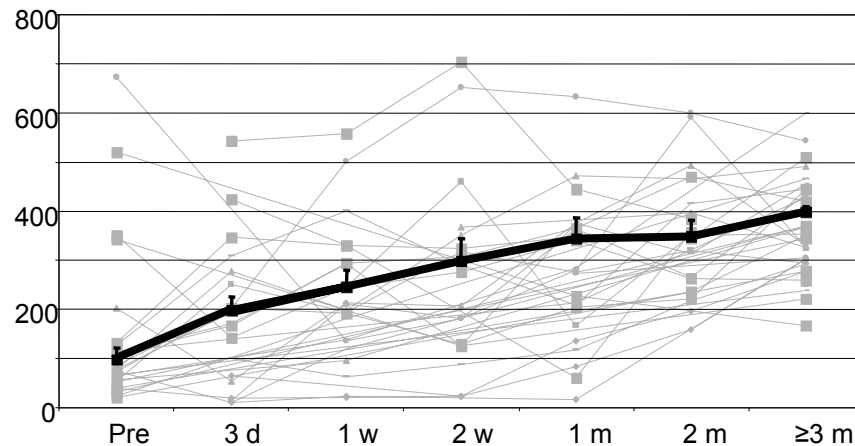
C

PBG-S
nkat/g Hb

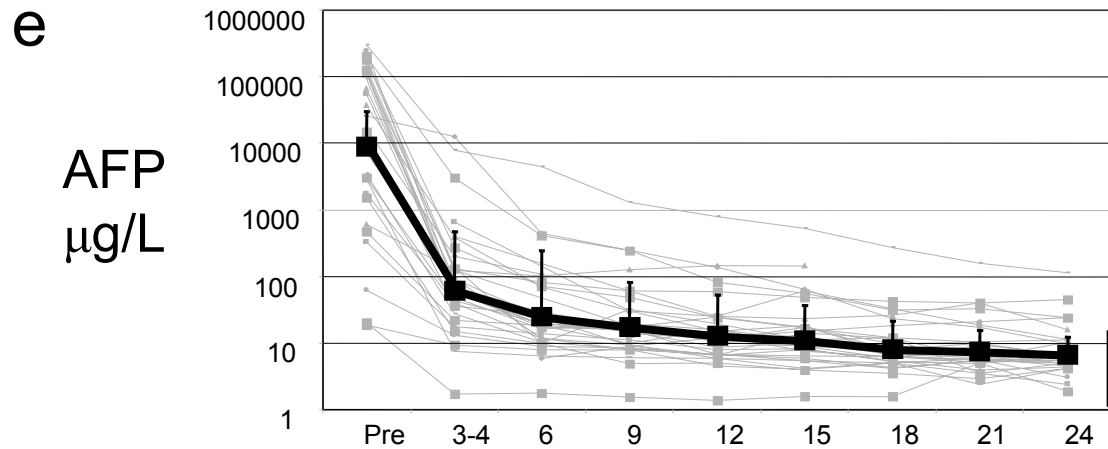


d

Tyr
 $\mu\text{mol/L}$



TYROSINEMIA - *Treatment*



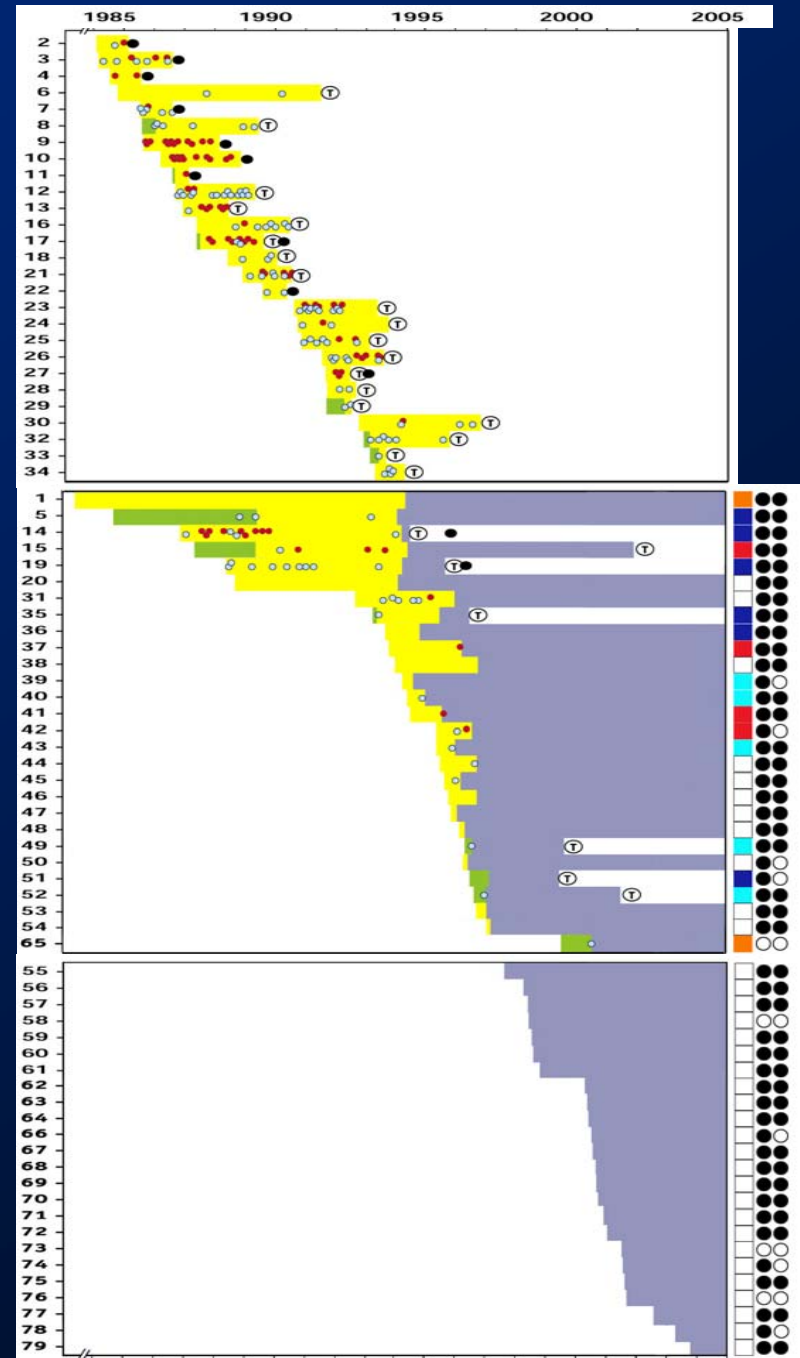
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Treatment

A : Non-nitisinone

B : Late-nitisinone

C : Early-nitisinone



TYROSINEMIA

Treatment

NITISINONE (NTBC) started at 1st month of life :

- ◆ No liver « nodules »
- ◆ No (↓) GFR
- ◆ No neurological symptoms

TYROSINEMIA

Treatment

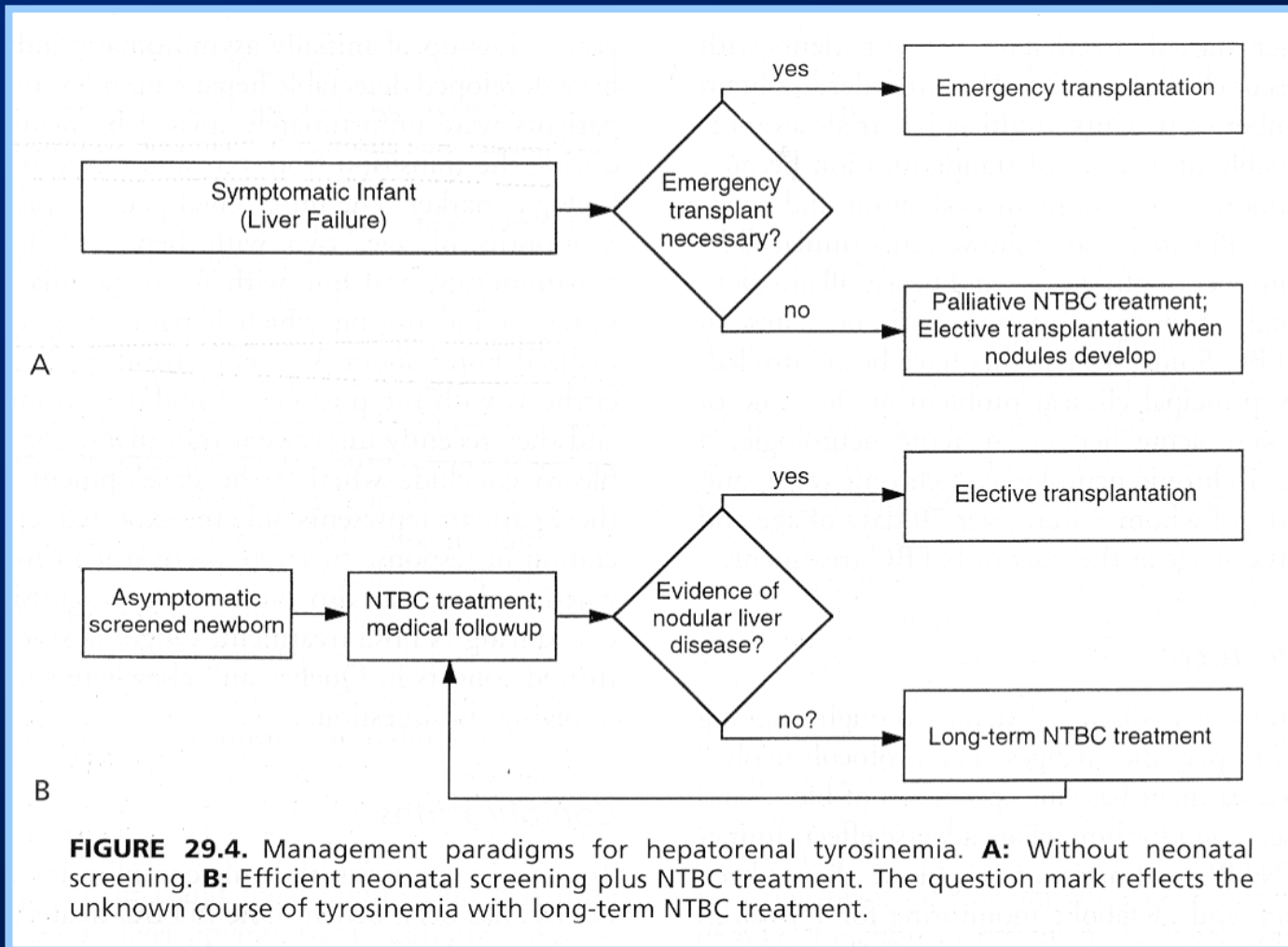
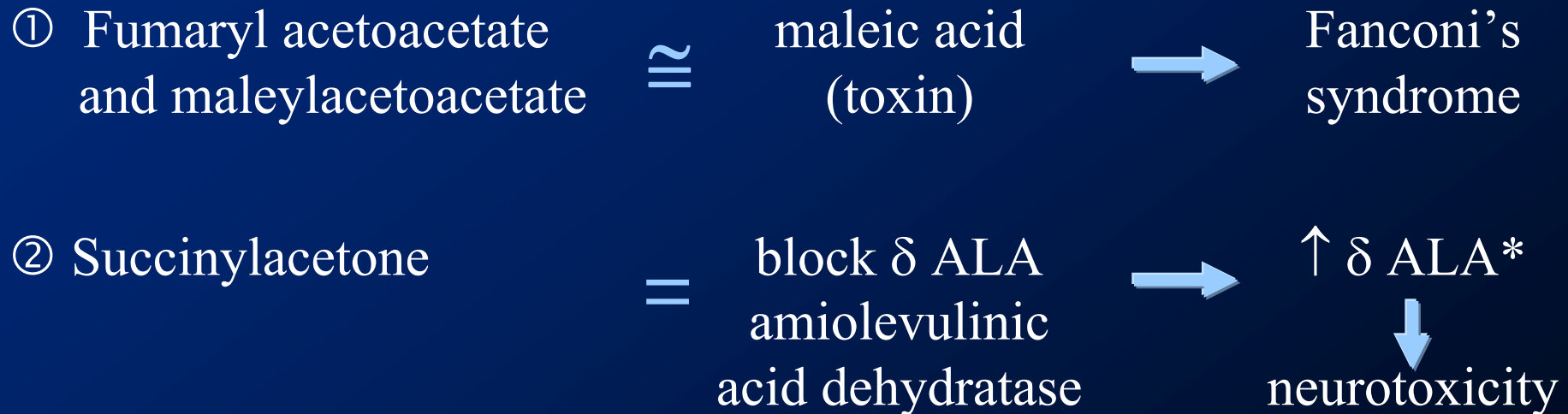


FIGURE 29.4. Management paradigms for hepatorenal tyrosinemia. **A:** Without neonatal screening. **B:** Efficient neonatal screening plus NTBC treatment. The question mark reflects the unknown course of tyrosinemia with long-term NTBC treatment.

TYROSINEMIA

Mechanism of hepatic and renal symptoms



* Accumulation in genetic deficiency of δ ALA dehydratase and in lead poisoning.

