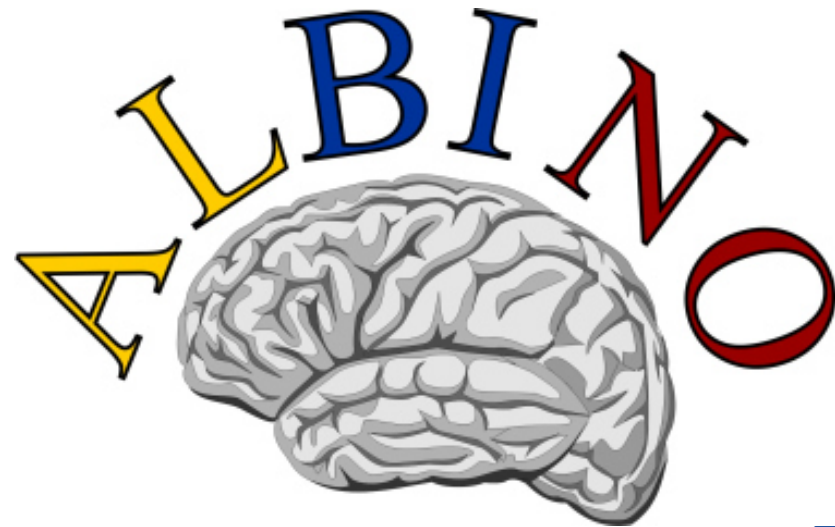
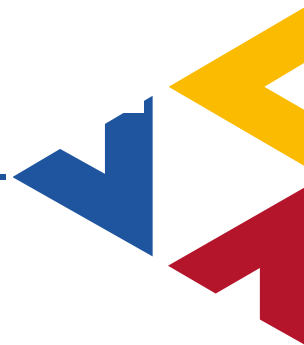


Effect of **AL**lopurinol in addition to hypothermia for hypoxic-ischemic **Brain Injury** on **Neurocognitive Outcome**



Axel Franz, Tübingen



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Hypoxic-ischemic encephalopathy



- ▶ 1-2 / 1000 newborn suffer from moderate to severe HIE
- ▶ 700-1.500 neonates / year in Germany
5.000-10.000 neonates /year in Europe
(... worldwide up to 1 Mio. infants /year)
- ▶ Therapeutic hypothermia is the only established treatment for HIE
- ▶ Despite therapeutic hypothermia,
40% of infants with moderate HIE suffer from death or severe disability

Hypoxic-ischemic encephalopathy



- ▶ 1-2 / 1000 newborn suffer from moderate to severe HIE
- ▶ 700-1.500 NG / year in Germany
5.000-10.000 NG / year worldwide
(... worldwide 100.000-200.000 infants /year)
- ▶ Therapeutic hypothermia is the only treatment for HIE
- ▶ Despite therapeutic hypothermia, 40% of affected infants suffer from death or severe disability

There is an urgent need for additional treatment options !!!



Hypoxic-ischemic encephalopathy

Pathophysiology: phases of HIE evolution



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Kelen and
Robertson
EHD 2010
CPCS
Kinderklinik
Tübingen

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Reperfusion-injury
(O₂-radicals,
inflammation)
and excitatory injury
result in
**2° energy failure
and apoptosis**

Johnston et al.,
Lancet Neurol 2011

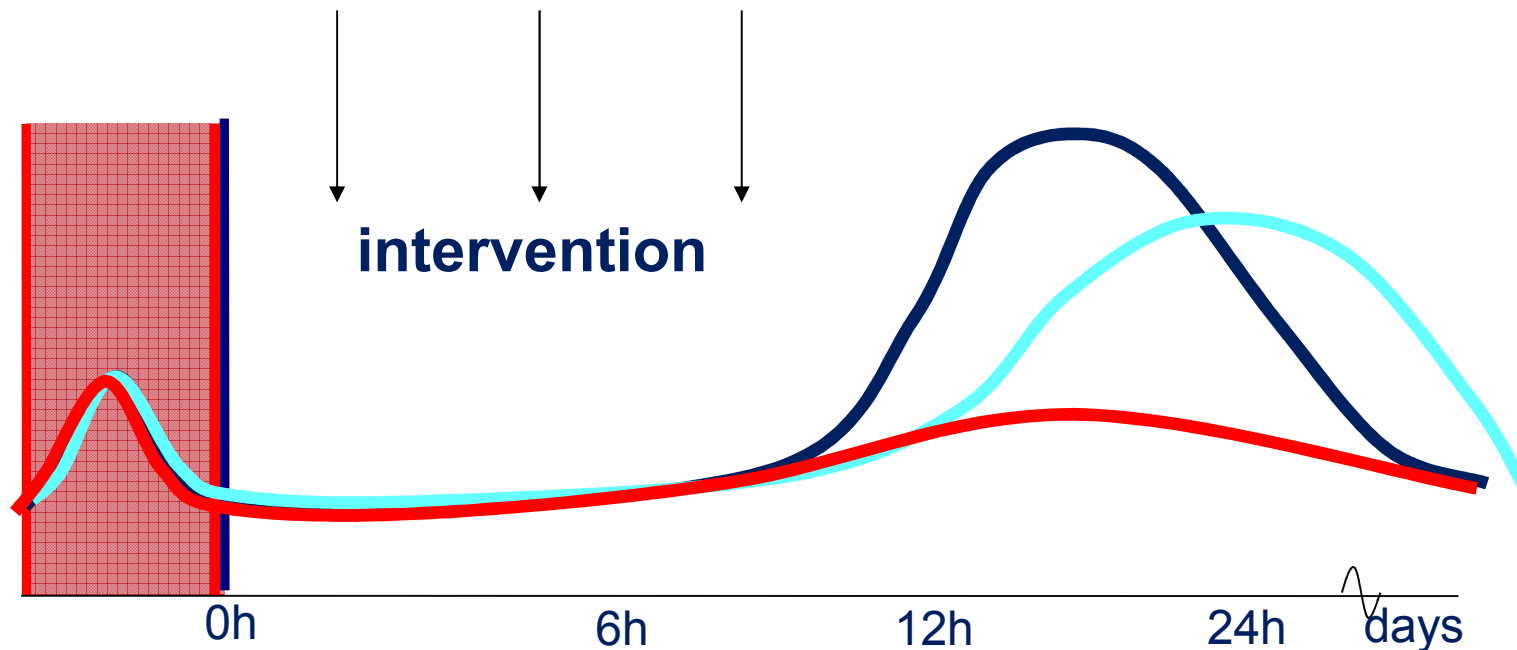


Treatment strategies

Birth
asphyxia



reperfusion/ reoxygenation/
excitatory /inflammatory damage



hypothermia

+ further (pharmacological) intervention(s)

F.v.Bel,
Utrecht

HIE - Pharmacological cocktail-therapy



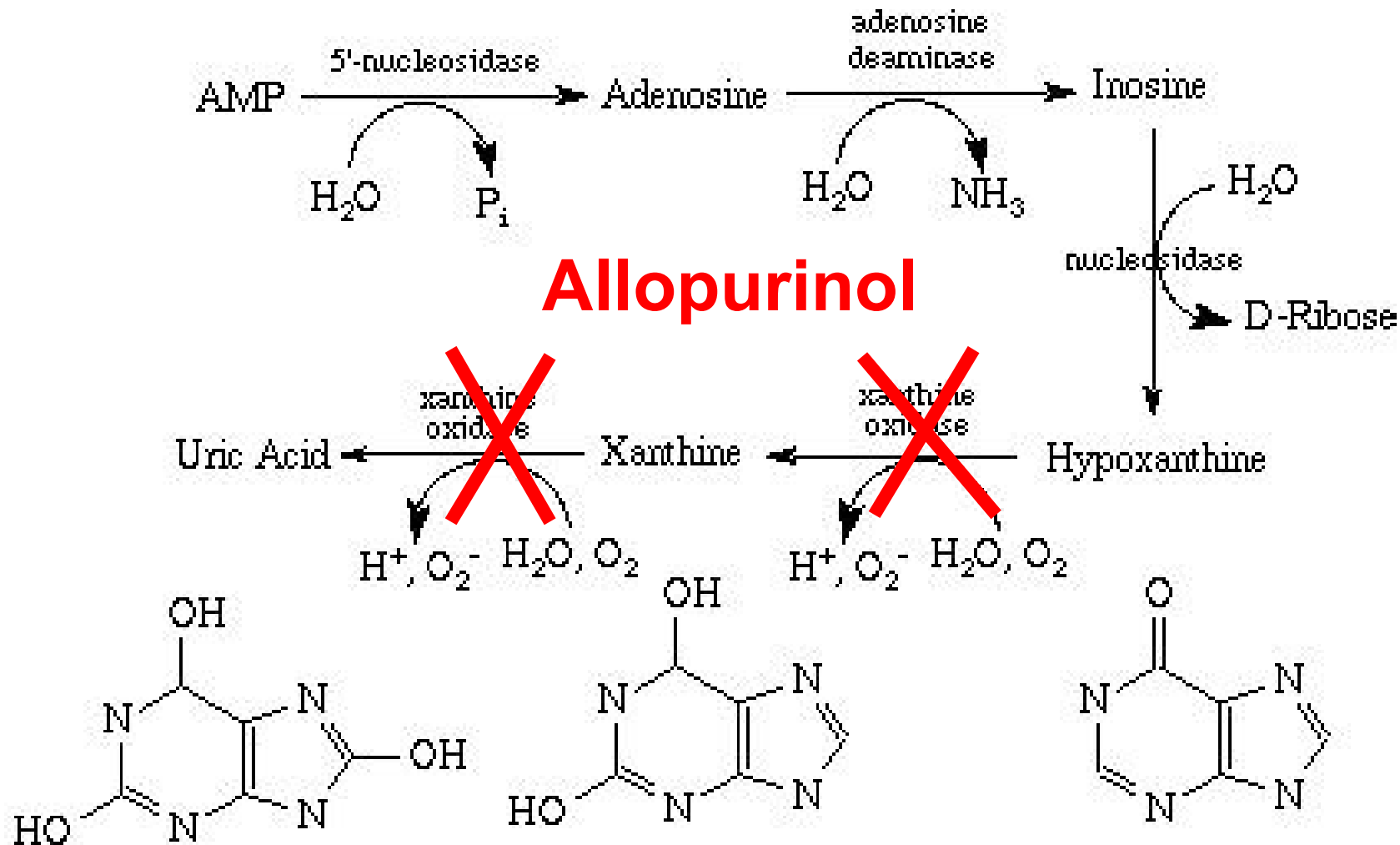
Further treatment options in addition to hypothermia currently investigated:

- ▶ **Xenon (anti-excitatory)**
- ▶ **Erythropoietin (anti-apoptotic)**
- ▶ **Melatonin (antioxidative?)**

Any additional treatment options ?



Origine of Oxygen Radicals in HIE



Animal data supporting Allopurinol for HIE



- ▶ Xanthine-oxidase mediated oxygen radical injury largely occurs *early after* ischemia
- ▶ Allopurinol administered after inducing hypoxia-ischemia reduces brain injury in 7-day-old rats [Palmer, Pediatr Res 1993].
- ▶ Vasogenic edema (MRI) was reduced [Peeters-Scholte, Pediatr Res 2003]
- ▶ Cerebral energy state was preserved in allopurinol-treated piglets [Peeters-Scholte, Exp Brain Res 2004].

Clinical Data supporting Allopurinol for HIE



Metaanalysis of 3 RCTs [Chaudhari, Cochrane 2008]
[vanBel, Paediatrics 1998, Benders, Arch Dis Child 2006,
Gunes, Pediatr Neurol 2007]

P: Neonates with HIE (together n=114)

I: Allopurinol (up to 4h after birth)

C: Standard / Placebo (without hypothermia)

O: death or disability (2 studies)

T: at 1-2 years of age

**Reduction of death/disability from 65% to 25% in
allopurinol-group in infants with moderate HIE
[Kaandorp, Arch Dis Child 2012].**



CPCS
Kinderklinik
Tübingen

Favorable risk/benefit-ratio



No evidence of severe harm from allopurinol:

- ▶ in 138 neonates following antenatal allopurinol
- ▶ in 58 neonates following postnatal allopurinol
- ▶ In 155 infants undergoing cardiac surgery

„The available data have not raised major safety concerns related to use in newborn infants.“

[Cochrane Rev 2008]

Key Challenge with ALBINO study

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Xanthine oxidase-mediated production of superoxide radicals occurs within minutes of reperfusion

[Ono Brain Res 2009]



The ALBINO project

Aims to investigate:

P: In (near) term infants with severe
acidosis and/or asphyxia

I: the effect of **very**
after birth) **How could that be realized?**
in ad... **Can parents give informed consent within**
... **that time frame??** ... **emin**

C: ... placebo

O: ... neurodevelopmental impairment

T: ... assessed at 2 years of age



Deferred Consent for the ALBINO-study



- ▶ Anticipated potential benefit from early administration
- ▶ Favorable risk/benefit-ratio
- ▶ Minimal burden from study–driven examinations
- ▶ Impossible to get meaningful consent before administration of study medication

§30 Declaration of Helsinki (2014)



“Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.”.

Community Engagement



Press release: inform community by mass media

Basic Information: inform parturients in pre-natal clinics/ obstetric practices / delivery units etc. (Flyer / Poster including link to study homepage and full parent information)

Verification that opt-out was *not* chosen

Before opening the container with study medication investigators shall verify:

- that the parents understand the local language (or English),
- that they have been informed about the study
- that had *not* expressed the wish of non-participation after having received the information

Deferred Consent for the ALBINO-study



Formal written informed consent after 1st dose

(written information + oral explanation +
time for reflection + signature of both
parents (if applicable) as usual)

Planned Recruitment for the ALBINU-study



We aim:

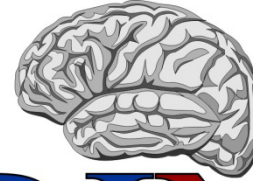
- to involve 60-80 study centers in Europe
- to screen 1200 infants with umbilical arterial pH<7.0 or need for resuscitation
- to recruit 846 infants
- to assess at least 684 infants at 2 years
- within 2 years

The ALBINO team



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**ALBINO-Coordinator
for Poland:
Jan Mazela
University of Poznan**



ALBINO

Effect of **AL**lopurinol on neuroprotection and hypothermia
for **AL**lopathy in the **AL**lopathy Brain **AL**lopathy
Neurocognitive **AL**lopathy Outcome

**We seek NICUs throughout Europe
who might be willing to participate !!!**

