Management of jaundice

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Introduction
Physiology
History
Testing
Level to treat
Why treat
Treatment options
Current management
Introduction

- Neonatal jaundice common
- > 50% healthy term infants
- Re-emergence of kernicterus
- AAP guidelines - July 2004
Physiology

- In utero bilirubin handled by placenta and mother's liver

- After birth, neonate must cope with increase in bilirubin production and decreased ability to clear bilirubin

- Course of adjustment uncertain
Why are neonates prone to jaundice?

- Increased bilirubin load
  - Red cell life span shorter & turnover higher

- Increased bilirubin production
  - Racial groups
  - Blood group compatibility
  - Increased enterohepatic circulation of bilirubin
● **Feeding**
  - Breast milk: competitive inhibitor of UDGT
    - Increases bilirubin reabsorbed from gut
  - Inadequate nutrition
    - Limits newborns capacity to excrete bilirubin in stools
    - Breast Feeds typically established 96 hours after birth
    - Greatest risk for hyperbilirubinemia is 3-5 days
    - Dehydration contribute to onset and progression of jaundice
HEME

Red Blood Cell

Heme oxygenase

CO
Fe \( ^{2+} \)

Bilirubin

Biliverdin

Biliverdin reductase

UGT

Bilirubin

Digluconide

Excretion in stool

Enterohepatic recirculation
Why is bilirubin dangerous?

- Bilirubin must be bound to carrier protein to be transported
- Free bilirubin-
  - Not bound to albumin
  - Crosses blood brain barrier
  - Neurotoxicity
- Risk of neurotoxicity increases with
  - Decreased binding
  - Decreased albumin
History
18th century

1724

- "true jaundice, and, on the other hand, the icteric tinge which may be observed in infants, immediately after birth......
  the latter, is of no account and disappears spontaneously after meconium has been passed"
  - Juncker

1737

- “I do not remember many practical authors. . . . who have taken notice of the jaundice in infants; nevertheless, many die of it for want of proper and seasonable helps; and most people are so stupidly ignorant that they imagine because the poor child grows yellow-consequently it must die, and therefore they will not look out for help”
  - Bracken - The Midwives Companion
TRAÎTÉ
DE
L'ICTÈRE OU JAUNISSE
DES ENFANTS DE NAISSANCE;
Ouvrage couronné en 1785 par la Faculté
de Médecine de Paris.
PAR M. BAUMES,
Professeur de Pathologie et de Néuropathie à l'École de Médecine de Montpellier, et ci-devant Professeur de Médecine
et de Clinique de l'Université de Médecine de cette ville;
ex-Président et Secrétaire perpétuel de la Société de Médecine-pratique de Montpellier; Associé de la Société de l'École
de Médecine de Paris; Membre de l'Académie de Médecine,
de la Société départementale de Médecine, de la Société médicale d'Éternité, de la Société académique des Sciences
et de la Société galénique de Paris; des Sociétés de Médecine de Bordeaux, de Marseille, de Nancy, de Bruxelles,
de Namur; des Sociétés des Sciences de Montpellier, de Dijon,
de Vaucouleurs, du Gard, etc. etc.
SECONDE ÉDITION.

À PARIS,
Chez MÉQUIGNON l'aîné, Libraire de l'École et de la
Société de Médecine, rue de l'École de Médecine, n° 3
ou 9, vis-à-vis la rue Hauteville.

M. DCCC. VI.
1905 “…… In some jaundice persists for weeks……from a deficiency of intestinal juices. The feeding during this period must be carefully watched, and it will usually be found safer to give the increase in food every second or every third day”

John Zahorsky

1908 “Occurrence of icterus neonatorum …between 15% and nearly all infants”

Shaw and Fetra. The Diseases of Children

1921 Icterus neonatorum- - “yellow colouration of the skin is at first hidden…..can only be seen when blood is pressed out of a portion of skin e.g. tip of the nose…”

Dr August Ritter von Reuss. The diseases of the newborn
"jaundice...lasting for an unusually long time...may be due to some catarrhal condition consequent upon chilling.....he has just come from an environment where the temperature was 99° or more, now he lies naked, or in the sorry protection of a flimsy shawl, in a room with a temperature of 65° or less, while he awaits the attentions of a nurse who is perhaps none too careful to avoid chill in washing him...."
1930

Icterus is “much less common in private than in hospital patients, suggesting with care and the better condition of the patient at birth, it is less likely to occur”

“on this account, slight chills are regarded by some as the cause”

Donald Paterson. Sick Children Diagnosis and Treatment
Incidence

○ > 50% healthy term infants

○ Incidence of jaundice varies from one nursery
  ● Lab standards, feeding policies, drugs
  ● Intensity and duration of illumination in the nursery


○ Prevention of rhesus incompatibility

○ Newborn hyperbilirubinemia- commonest readmission diagnosis

○ **Testing**

- **1994-AAP**
  - Aim to reduce unnecessary testing and treatment

- **Universal screening**


- **Cost vs benefit**
1. Inspection

- Initial diagnosis

- Unreliable

- SBR 119-136 µmol - visible

- Face and trunk, not extremities SBR= 204
  

- Intraobserver agreement about jaundice only marginally better than chance alone!
  
Kramer’s rule

- jaundice starts on the head
- extends towards the feet as the level rises

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<th>1</th>
<th>2</th>
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<tr>
<td>SBR</td>
<td>100</td>
<td>150</td>
<td>200</td>
<td>250</td>
<td>&gt;250</td>
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<td>umol/L</td>
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2. Transcutaneous bilirubinometers

- Acceptable correlation between TcB and SBR

- Variable accuracy
  - Skin pigmentation
  - SBR > 257
  - < 35/40

- Easy, non-invasive, repeatable

- Predischarge screening tool SBR > 95th C
3. End tidal Carbon Monoxide

Direct measurement of rate of heme catabolism and rate of bilirubin production

Correct for ambient carbon monoxide
4. Serum bilirubin

- SBR = bilirubin produced - bilirubin eliminated
- Severe haemolysis not essential for imbalance to occur
- Mainstay of management of neonatal jaundice
- Need high precision, reproducibility, accuracy
- Large inter-laboratory variability

5. Bilirubin:albumin ratio

- correlates to unbound bilirubin
  - ability of bilirubin to bind
  - amount of albumin

- if bilirubin load exceeds binding capacity → free bilirubin

- SBR (mg/dl) : Serum albumin (g/dl)
- Ratio > 0.63 may be associated with ABR changes
What level to treat

- 1952
  - kernicterus
    - 50% babies $SBR > 31$
    - 18% $SBR 16-30$
  - recommended $SBR kept < 20$

- 1959
  - 54 term babies, no isoimmunization, $SBR > 20$
  - No exchanges. All normal at follow up

- 1972
  - "at present would not treat any full term infant with exchange transfusion regardless of degree of hyperbilirubinaemia....after excess hemolysis excluded....risk of exchange far greater than kernicterus..."

- 1983
  - Vigintiphobia
Bhutani nomogram
hour specific SBR values

- hour specific SBR values
- 2840 near-term and term babies
- no obvious evidence of haemolytic disease
- at discharge or 48 hours, SBR has not yet reached its peak
- allows prediction of risk of hyperbilirubinaemia

Why treat?

- **kernicterus**
  - Yellow kern = nuclear region
  - pathological diagnosis
  - interchangeable with acute or chronic bilirubin encephalopathy

- **AAP 2004**
  - acute- toxicity in first week of life
  - kernicterus- chronic and permanent sequelae
Kernicterus

- Frequency declined - prevention of rhesus disease
- 1971-1991
  - no published reports in healthy full term babies
  - less aggressive approach to jaundice and notion that kernicterus would not occur in previously healthy babies
- since then... re-emergence of problem
- 1970- length of stay 3.9 days

- Today- shorter stay, cost, public pressure for natural childbirth

- early discharge before bilirubin peak?

- Earlier discharge - responsibility for observing babies in high-risk period shifted
Incidence

- Pilot kernicterus registry USA
  - 1992-2001  80 infants
  - all discharged pre 72 hours
  - 75% readmitted in first week
  - 95% breast fed
  - severe kernicterus sequelae in 80%

- BPSU
  - unconjugated hyperbilirubinemia SBR > 510µmol/l
  - 1st year of study- 38 infants met criteria
  - 6 cases of bilirubin encephalopathy

Donal Manning, Wirral Hospital, Merseyside
What can hyperbilirubinemia do?

- Study 30,000 full term infants
  - If SBR kept < 20 (340)- no adverse effects on IQ, neuro examination or hearing


- Moderate HB (205-340 in term babies)
  - behavioural and learning difficulties
  - dose - response relationship

Clinical signs of severe hyperbilirubinaemia

- **acute**
  - hypertonia- extensor muscles
  - opisthotonus
  - poor feeding
  - high pitched cry

- **chronic**
  - extrapyramidal movement disorders
  - gaze abnormalities
  - sensorineural hearing loss
  - intellectual deficit

Volpe JJ. Neurology of the newborn
- neuropathic features of bilirubin induced brain injury/kernicterus well known
- limited understanding of neuronal injury and cell death
- chronologic evolution of injury and predictive value to long term disability poorly defined
- MRI patterns recognized
Treatment

- **1908** - “medical intervention in cases of icterus neonatorum is in no sense indicated....”

- **1909** - “icterus neonatorum is usually so evanescent a phenomenon that it calls for no treatment beyond- and I fancy this may be of importance- keeping the baby warm”

- “if the jaundice has not disappeared by the end of the second week, give grey powder. Hyd. Cum.creta gr 1/4, sod.bicarb.gr.j 3 x day...”
Blood exchange transfusion

- Hart - 1925
  - first exchange transfusion - erythroblastosis fetalis
  - successful, but ignored for next 20 years

- Wiener, Wexler and Gamrin - 1944
  - failed

- Wallerstein - 1946
  - 3 successful exchange transfusions - erythroblastosis fetalis.
  - saggital sinus for blood withdrawal and peripheral vein for infusion
Definitive technique described by Diamond in 1947
- introduced umbilical vein use for exchange transfusion


- mainstay of treatment 1970s

- mortality 0-7%

- morbidity
  - blood products
  - metabolic derangement
  - cardiorespiratory
  - catheter complications
Study 1997
- No mortality in healthy infants
- 20% died in sick infant group
- 14% permanent sequelae

As Exchange Transfusion becomes less frequently carried out
- ? Risk of higher morbidity and mortality
Light treatment

- 1958 Cremer et al, Lancet
- Sunlight

Fig. 5—Sunshine treatment of an icteric infant with jaundice of prematurity (case 6)
• Artificial light- same result
• Found better drops in bilirubin with intermittent PTX
• Specimens left in daylight lose up to 30% bilirubin in 1 hour
  - Sample transportation issue

○ How does it work?
  ● Photochemical reactions occur
  ● Formation of E-isomers and lumirubin - water soluble

○ Efficacy
  ● Light intensity wavelength
  ● Body surface exposed
  ● Dose delivered
    ○ Power of light
    ○ Distance from baby
- **Intermittent v continuous**
  - Conflicting results
  - Theoretically no plausible rationale for intermittent PTX

- **Bronze baby**
  - Cholestatic jaundice
  - May be related to accumulation of porphyrins
  - Presence of direct hyperbilirubinaemia not C/I

- **Contra-indication**
  - Congenital porphyria / FH - severe photosensitivity and blistering
Side effects?

- **DNA modifying properties**

- **Cerebral blood flow**
  - Peak systolic blood flow increased with overhead PTX cf bilibeds.
  - Small number trial n=30
    Hammerman C, Kaplan M Biol Neonate 2004

- **Loose stools, dehydration, skin rashes**
TREATMENT OPTIONS

HEME

Red Blood Cell

CO
Fe \(^{2+}\)

Bilirubin Biliverdin

biliverdin reductase

Bilirubin

UGT

Bilirubin Diglucuronide

Excretion in stool

Enterohepatic recirculation

INCREASE CONJUGATION

BILIVERDIN REDUCTASE INHIBITORS

DECREASE ENTEROHEPATIC RECIRCULATION

HO INHIBITORS

heme oxygenase

INCREASE CONJUGATION

BILIVERDIN REDUCTASE INHIBITORS

DECREASE ENTEROHEPATIC RECIRCULATION
Inhibition of heme degradation

1. **Metalloporphyrins**
   - Heme oxygenase rate limiting step in bilirubin production
   - Inhibitors of HO
   - Inhibit bilirubin production
   - Also affect lipid peroxidation
Tin

- Non-biocompatible metal
- Very high potency
- Photosensitization, induce mRNA
- Neonatal trials
  - PTX decreased by 76%
  - i.m. injection
  - No long term effects at 18/12

Zinc
- Biocompatible metal
- Orally absorbable
- Chimps only


Chromium
- Biocompatible metal
- No phototoxicity
- Orally absorbable

Ideal treatment combo
- Narrow spectrum blue light 450-480nm + metalloporphyrin
2. D penicillamine

○ Europe but not USA
○ Chelating agent
○ Does not displace bilirubin from albumin

• Historical trial for ABO incompatibility
  ↓ exchange transfusions- not stat significant

Side effects
○ Adults- fatal with aplastic anaemia, thrombocytopenia, myasthenia

○ Potential effects- ↓ Ca$^{2+}$ influx, ↓ myocardial contractility
3. Peptide inhibitors of Heme Oxygenase

- Imunosuppressive
- No human studies
- Mice- upregulation of HO mRNA
Inhibiting biliverdin reductase

- Potentially useful
- Enzyme that converts biliverdin to bilirubin
- Biliverdin
  - Water soluble
  - Excretable
- No studies yet
- Side effect – green babies!
Increase bilirubin conjugation

1. Phenobarbitol
   - Enhances UPGT, improves conjugation
   - Given last weeks of pregnancy
     - ↓ incidence of severe jaundice
     - Need for exchange ↓ by factor of 6
   - Side effects
     - sleepiness, stupor, breathing ↓
2. Clofibrate

- Antilipidaemic agent
- Reduces VLDL and cholesterol
- ↑ bilirubin conjugation and excretion
  - Lower SBR, shorter duration of jaundice
  - ↓ use of PTX
- Side effects
  - Nausea (adults), muscle cramps, pruritis, leukopenia
  - Neonatal study- no side effects but no long term follow up
3. Herbal remedies

“where there’s tea, there’s hope” Sir Arthur Pinero 1855

- Artemesia (yin-chen), Huang-lin (coptis chinesis)
- Hepatoprotective
- ? Antioxidant effect

- Constitutive androstane receptor related
  - Bilirubin clearance
  - Herbal teas in mice → accelerated clearance of bilirubin, need CAR to do so

Decrease enterohepatic recirculation of bilirubin

**Oral feeding**
- Early feeds
- Fluid supplementation will not prevent ↑ SBR

**Oral charcoal**
- Reduces SBR

**Agar**
- Can bind to bilirubin in GI tract
- ↓ duration of PTX

Davis DR, Yeary RA. Dev Pharmacol Ther 1987;10(1):12-20
Others

**Albumin**
- $↑$ bilirubin binding
- prevents free bilirubin entry into brain
- Pre - exchange
  - Conflicting results re efficacy

**Bilirubin oxidase**
- Oxidation of bilirubin $→$ water soluble and excretable
- Side effects- enzyme derived from fungus, allergic reactions possible

AAP guidelines 2004 (>35/40)

- Prevention
- PTX
  - Direct/conjugated should not be subtracted from total bilirubin
- Haemolysis
  - I.V. gammaglobulin 0.5-1g/kg over 2 hours
- Albumin
  - If serum albumin < 30
- Exchange
  - In any infant with signs of encephalopathy even if SBR falling
○ Parent info
  ● Written and verbal

○ Follow-up
  ● by health care professional

<table>
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<th>Infants discharged</th>
<th>should be seen by age</th>
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<tr>
<td>&lt; 24 hours</td>
<td>72 hours</td>
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<tr>
<td>24 - 48 hours</td>
<td>96 hours</td>
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<tr>
<td>48 - 72 hours</td>
<td>120 hours</td>
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Earlier or more frequent follow-up if risk factors.
**SUMMARY**

**TREATMENT OPTIONS**

1. PHOTOTHERAPY
2. EXCHANGE TRANSFUSIONS

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**HEME**

**Red Blood Cell**

CO Fe $^{2+}$

**bilineirin reductase**

**3. HO INHIBITORS**

**UGT**

**Bilirubin**

**Biliverdin**

**Excretion in stool**

**Enterohepatic recirculation**

**5. INCREASE CONJUGATION**

**Bilirubin Diglucuronide**

**4. BILIVERDIN REDUCTASE INHIBITORS**

**6. DECREASE ENTEROHEPATIC RECIRCULATION**
Summary

- Kernicterus still rare
- Need to be more aware
- Remember high risk babies
- More frequent follow up
- Future research-
  - Tin MP
  - ETCO