CARDIOVASCULAR THERAPY IN NEONATAL AND PEDIATRIC SEPSIS

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FROM
EVIDENCE BASED MEDICINE
TO
DAILY PRACTICE

PRIMARY ENDPOINT

MORTALITY OR MORBIDITY: WHAT´S THE PRIMARY ENDPOINT?

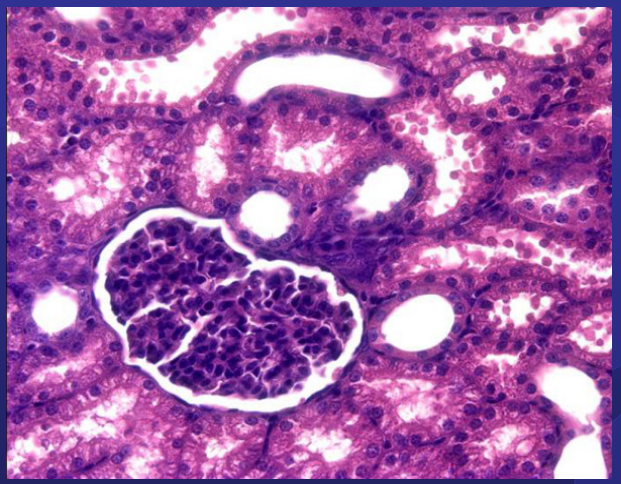
22nd ESPNIC Medical § Nursing Annual Congress
Hannover Germany, Tibboel D. 2011

- MYOCARDIAL DYSFUNCTION:
  78% IN PEDIATRIC SEPSIS, *Ceneviva 1998*
- MORTALITY RATE:
  1-3% IN PREVIOUSLY HEALTHY
  7-10% IN CHRONICALLY ILL CHIDREN, *Brierley 2009*

EXPERIMENTAL MODEL

SEPSIS - INDUCED ACUTE KIDNEY INJURY *Seely 2011*

HISTOLOGICAL IMAGE OF A CONTROL AND A SEPTIC KIDNEY



Chvojka 2008

HEART FAILURE

„AN INADEQUATE
VOLUME OF BLOOD AND OXYGEN
AT A RATE APPROPRIATE TO THE BODY´S METABOLIC DEMAND“

NOW CONSIDERED:

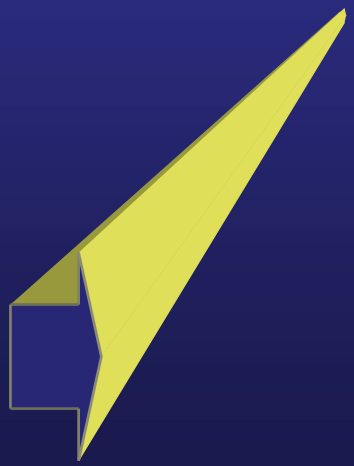
„ MORE
A CARDIOCIRCULATORY DISORDER
THAN A SIMPLY DISEASE
OF THE HEART“

Zalzstein, Gorodischer 2005

PRINCIPLES OF PHARMACOLOGY

SUPPORT OF COMPENSATORY MECHANISMS

↑RENAL SALT AND WATER RETENTION
↑CATECHOLAMINE RELEASE
CARDIAC REMODELING



- ↑PRELOAD
- ↓AFTERLOAD
- ↑CARDIAC OUTPUT
- ↑CONTRACTILITY + ↑HEART RATE
- TO INHIBIT, EVEN TO REVERSE CARDIAC REMODELING

Greenberg 2001

MECHANISMS OF DRUG ACTION

- DRUGS →THE WORKLOAD OF THE HEART

VENOUS RELAXANTS
ARTERIOLAR VASODILATORS
MIXED VASODILATORS
ACE INHIBITORS

- DRUGS →INOTROPICS

CATECHOLAMINES
INHIBITORS - PDE III
CALCIUM -SENSITIZING AGENTS

- DRUGS → DIURETICS

SPIRONOLACTONE

Table 1: SUMMARY OF TARGETS FOR CARDIOVASCULAR DRUGS (*Turner 2011*)

MEDICINE	PHARMACOLOGY	MAIN ACTIONS
DOPAMINE ↑systolic volume	D1 D2 β1 β2 AGONIST	↑CO + ↑SVR LOW VS.HIGH DOSE INOCONSTRICTOR
DOBUTAMINE ↑systolic volume	PREDOMINANT β1 AGONIST	↑CO + ↑SVR ↑CHRONOTROPY INODILATOR
EPINEPHRINE *COLD shock* ↑*SVRI*	α1 α2 β1 β2 AGONIST β> α α1 α2 AGONIST	↑CO+↑SVR ↑HR LOW vs HIGH DOSE INOCONSTRICTOR
NOREPINEPHRINE *WARM shock* ↓*SVRI*	> α	
VASOPRESSIN ↓*SVRI*	ADH AGONIST art.	↑BASAL VP
MILRINONE ↑*SVRI* ↑*diastolic volume*	PDE III INHIBITOR	↑CO INODILATOR LUSEOTROPIC EF.

PHARMACODYNAMICS

„2/3 OF SEPTIC CHILDREN PRESENTED WITH LOW CARDIAC OUTPUT NEEDING INOTROPES“

Ceneviva 1998

NEONATAL AND PEDIATRIC SEPTIC SHOCK

Epidemiologic data:

- COLD SHOCK: ↓CO + SVRI ↑ (2/3)
- WARM SCHOCK-I: ↑CO + SVRI ↓ (1/5)
- WARM SCHOCK-II: ↓CO + SVRI ↓ (1/5)

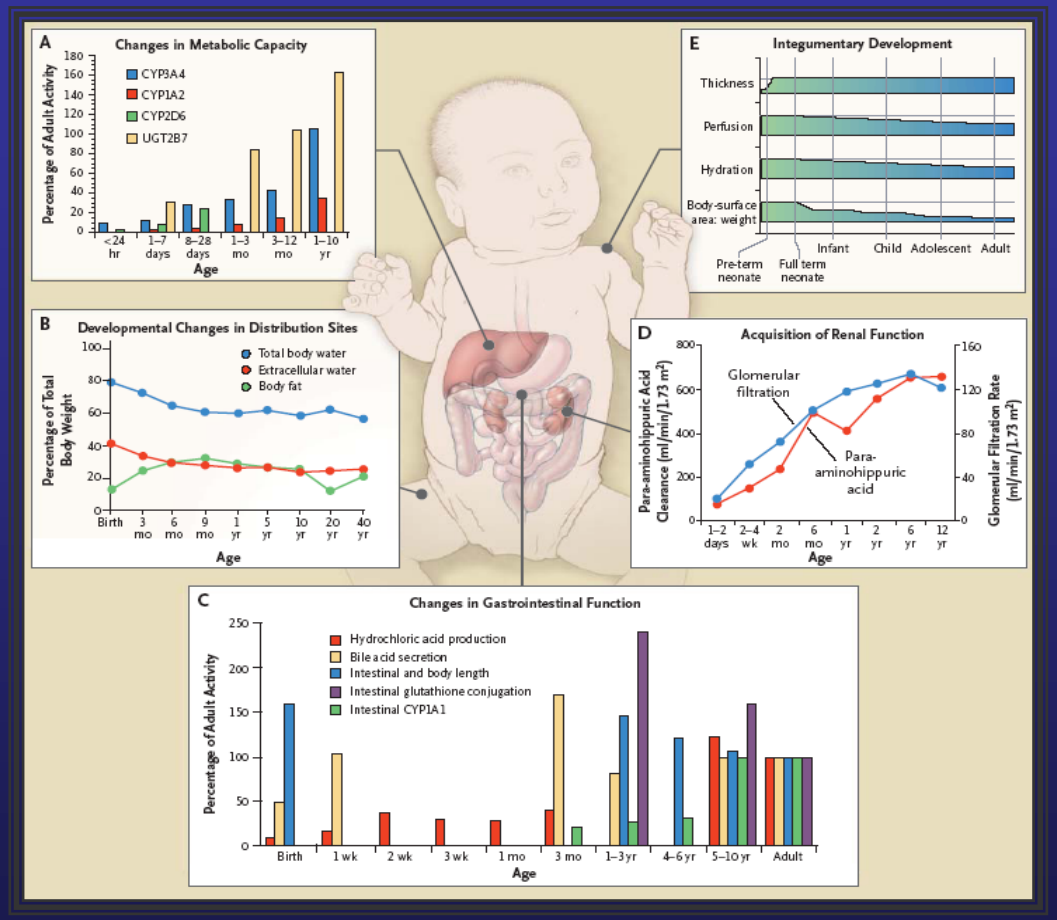
RETROSPECTIVE STUDY

Table 2: Treatment for circulatory failure: results from NICU/PICU Department of Pediatrics Charles University in Prague 2006 – 2011, retrospective study (n=447)

MEDICATION	NICU/PICU (N)	NICU/PICU (%)
DOPAMINE	320	71
DOBUTAMINE	302	67
DOPA+DOBU	263	59
EPINEPHRINE	20	4
NOREPINEPHRINE	35	8
VASOPRESSIN	3	1
MILRINONE	3	1
HYDROCORTISONE	234	52

DEVELOPMENTAL PHARMACOKINETICS

Kearns et al. NEJM 2003, J. N. van den Anker et al. 2011



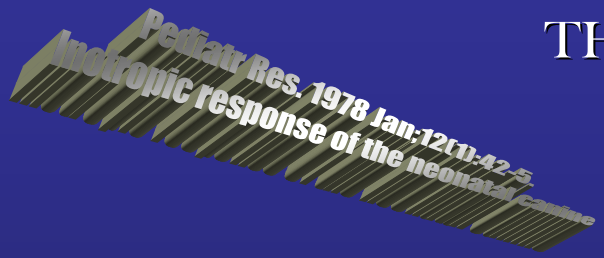
THE INFLUENCE
OF AGE
and MATURATION

ON

PK/PD
DRUG DISPOSITION
and RATIONAL THERAPY

CHILDREN vs. ADULTS I

„MORE LIMITED FASHION TO INTOTROPIC DRUGS“



DUE TO:
THE BIOLOGIC IMMATURITY
OF THE MYOCARDIUM
Driscoll 1978, Friedman 1985

- RESTRICTED FUNCTIONAL RESERVE
  Rudolph 1985
- UNDERDEVELOPED CARDIAC SYMPATHETIC NERVES
  Geis 1975
- DIFFERENCES IN METABOLISMS OF THE MYOCARDIUM
  Bataglia 1978

CHILDREN vs. ADULTS II

COVARIATES I
„THE EFFECT OF INFLAMMATION ON DRUG METABOLISM: A FOCUS ON PEDIATRICS“

Possible PK/PD relationship during inflammatory diseases *Vet at al 2011*

COVARIATES II
„PHARMACOGENOMICS OF ADRENORECEPTORS“
Flordellis 2004

Effects of common polymorphisms in the *a*1A-, *a*2B-, *b*1- and *b*2-adrenoreceptors on haemodynamic responses to adrenaline
Snapir 2003

CLASSICAL INOTROPIC DRUGS

DOPAMINE

„↓INOTROPIC RESPONSE TO DOPAMINE
ON THE IMMATURE MYOCARDIUM,
↑WITH ADVANCING AGE“
Steinberg 1994

D1, D2 ACTION IN PRETERM
Osborn 2002

DOSAGE: 0.5 -10 – 20 μg/kg/min i.v.
VD-EF: 2 - 5 μg/kg/min (added)
α-EF: ≥10 μg/kg/min i.v.

CLASSICAL INOTROPIC DRUGS

DOBUTAMINE

„ ↑CHRONOTROPIC EFFECT
IN YOUNG CHILDREN vs ADULTS “ *Habib 1992*

„ ↑ C-PL 40 -190 µL/mL correlated to
↑CARDIAC IMPROVEMENT
IN ADULTS“ *Leier 1983*

WIDE PK/PD VARIABILITY
IN CHILDREN

DOSAGE: 2.5 -10 - 20 µg/kg/min i.v.

CLASSICAL INOTROPIC DRUGS

EPINEPHRINE

„ THE MYOCARDIUM
IS SENSITIVE TO EPINEPHRINE
WITH VARIOUS EFFECT
ON REGIONAL
BLOOD FLOW AND TOXICTY
IN CHILDREN“

0.5-0.8 μg/kg/min i.v.↓PVR

≥0.8 μg/kg/min i.v. ↑PVR

DOSAGE-NICU: 100-300 ng/kg/min
DOSAGE-PICU: 0.1-1.5 μg/kg/min
OPTIMAL: 0.05-0.3 μg/kg/min i.v.

VASOPRESSORS

NOREPINEPHRINE

NO RCTs EXIST WITH DOCUMENTED EFFECTS
ON RENAL PERFUSION
IN CHILDREN
Bellomo 2001

EFFECTIVE TISSUE PERFUSION
0.4-0.5 µg/kg/min i.v

Tourneux 2007

DOSE LD: 20-100 ng/kg/min

MD: 0.1-1.0 µg/kg/min i.v.

OTHER INOTROPIC DRUGS

MILRINONE (AMRINONE)

„INOTROPIC EFFECT OF AMRINONE IS AGE DEPENDENT“

↓CL -NEONATES, HEART HEPATIC FAILURE
Allen-Web 1994

↓PVR WITHOUT SYSTEMIC HYPOTENSION

LD: 0.75 μg/kg/min - 3H i.v.
MD-NICU: 0.2 μg/kg/min i.v.
MD-PICU: 0.25-0.5 μg/kg/min i.v

OTHER INOTROPIC DRUGS

MILRINONE

„THERE ARE A LIMITED NUMBER
OF RTc IN CHILDREN THAT SUGESST A BENEFICAL
EFFECT OF MILRINONE IN SEPTIC SHOCK“
Meyer 2011

„ POPULATION PK MODELLING
IN THE PRETERM
HAS ESTABLISHED AN OPTIMAL REGIMEN
FOR MILRINONE“
Paradisis 2007

LD: 0.75 μg/kg/min - 3H i.v.
MD-NICU: 0.2 μg/kg/min i.v.
MD-PICU: 0.25-0.5 μg/kg/min i.v

NEW INOTROPICS

LEVOSIMENDAN

DOSE: LD 6 -12 μg/kg/10min i.v.
MD 0.05-0.1 μg/kg/min - 24h i.v.

Pinto 2008

VASOPRESSORS

VASOPRESSIN (AVP)

Vasopressin in catecholamine-refractory shock in children
S. Meyer 2007

The use of AVP/TP as a rescue therapy should be considered on an individual basis.

DOSE: 0.018-0.12 UNITS/kg/h

MIXED VASODILATORS

NITROPRUSSIDE

„↑CARDIAC INDEX STIMULATE
THE TACHYPHYLAXIS
IN HYPERTENSIVE CHILDREN“
Rouby 1982

BENEFIT
IN CHILDREN WITH
COLD SHOCK AND NORMAL BP
Lodha 2011

LD: 0.3 - 0.5 μg/kg/min i.v.
MD: 3 - 8 - 10 μg/kg/min i.v.

EVIDENCE BASED THERAPY

TRANSITORIAL CIRCULATION

NEONATAL SEPSIS

- FLUID REFRACTORY SCHOCK 15min → COLD SHOCK INOTROPY
- DOPAMINE RESISTANT SCHOCK → COLD vs WARM SHOCK INOTROPY MICROCIRCULATION
- CATECHOLAMINE RESISTANT SCHOCK 60min → SvcO2≥ 70% nBP vs lowBP LV/RV function SVC flow 40ml/kg/min CI=3.3-6.0 L/min/m^2
- REFRACTORY SCHOCK

FLUID REFRACTORY SCHOCK

DOPAMINE: 5-9 μg/kg/min
DOBUTAMINE: 10 μg/kg/min
(lowCO, nBP, nSVRI/ ↑)

DOPAMINE - RESISTANT SCHOCK

EPINEPHRINE: reverse
0.05-0.3 μg/kg/min

CATECHOLAMINE-RESISTANT SCHOCK

COLD SHOCK RV vs LV
→ MIL , iNO, ILOPROST
(lowCO, lowBP)
WARM SHOCK
→ VASOPR (lowCO, lowBP)

HYROCORTISONE: 2.5 mg/kg/6H

REFRACTORY SCHOCK

ECMO

EVIDENCE BASED MEDICINE

PEDIATRIC SEPSIS

FLUID REFRACTORY SCHOCK 15min

COLD vs WARM SHOCK

CATECOLAMINE RESISTANT SCHOCK 60min

COLD vs WARM SHOCK

PERSISTENT CATECHOLAMINE RESISTANT SCHOCK

COLD vs WARM SHOCK
SvcO2 70%
nBP vs lowBP
CI=3.3-6.0 L/min/m^2

REFRACTORY SCHOCK

FLUID REFRACTORY SCHOCK

DOPA, DOBU: 5-9 µg/kg/min
EPINEPHRINE:0.05-0.3 µg/kg/min reverse
NOREPINEPHRINE: 0.1- 1.0 µg/kg/min reverse

CATECOLAMINE - RESISTANT SCHOCK

HYDROCORTISONE: 1 mg/kg/6H i.v.

PERSISTENT CATECHOLAMINE-RESISTANT SCHOCK

COLD SHOCK
SvO2 >70% → EPI
SvO2 <70% → MIL, LEVO
COLD (low BP)
SvO2>70% → NOR
SvO2<70%: → DOBU, MIL, LEVO
WARM SHOCK (low BP):
SvO2>70% NOR→ (low BP)+ VASOPRESSIN
SvO2<70% LOW DOSE EPI

REFRACTORY SCHOCK

ECMO

CONCLUSION I

THE UPDATED 2007 GUIDELINES CONTINUE:

- TO EMPHASIZE EARLY USE OF AGE – SPECIFIC THERAPIES:

LARGER FLUIDS
INOTROPE AND VASODILATOR THERAPIES
HYDROCORTISONE
AND ECMO

- ADEQUATE MONITORING OF DRUG RESPONSE IS RECOMMENDED (PD VARIABILITY)

CONCLUSION II

PERSPECTIVES FROM THE UPDATED 2007 GUIDELINES?

- THE ROLE OF CLINICAL PHARMACOLOGY (PD):

THE POTENTIAL ROLE
OF NEW SEPSIS-AND
TISSUE PERFUSION BIOMARKERS
IN DAILY PRACTICE
TO EVALUATE
DRUG ADJUSTMENT
OR
DRUG DOSAGE

- THE ROLE OF PHARMACOGENOMICS?

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PERSPECTIVES ?

Děkuji Vám za pozornost