Introduction to Critical Care Neurology

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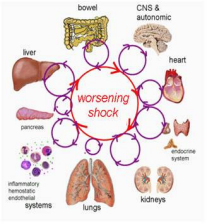
Major issues of ICU care

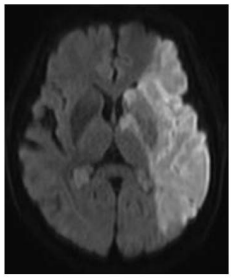
- **Primary Neurologic cause**
  - Severe stroke
  - Status epilepticus
  - Head trauma
  - ICP issues
- **General critical care**
  - Sepsis
  - Severe aspiration pneumonia
  - For CRRT
  - Hemodynamic and ventilator



General critical care:

Infection & sepsis

Case

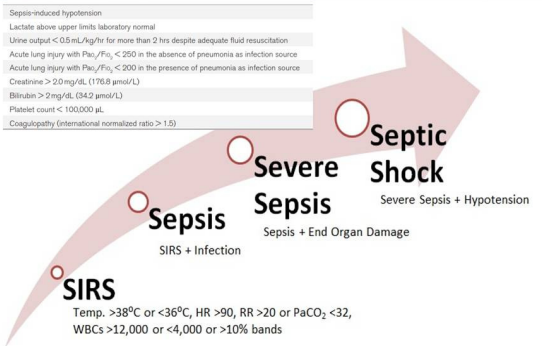


F/ 89
Sudden aphasia, Rt. Side weakness

Next day
- Fever up to **38.3**
- CRP: 8.6
- CPA: unremarkable

Antibiotics ?
Early sepsis?

Sepsis

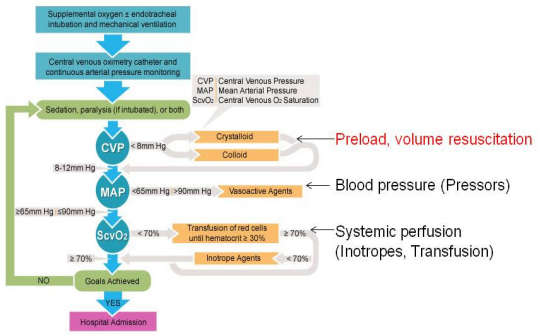


Sepsis treatment

- Drotrecogin Alfa (Activated) in Adults with Septic Shock 2012
  - CONCLUSIONS
  - DrotAA did not significantly reduce mortality at 28 or 90 days, as compared with placebo, in patients with septic shock. (Funded by Eli Lilly; PROWESS-SHOCK ClinicalTrials.gov number, NCT00604214.)
- Hydrocortisone Therapy for Patients with Septic Shock 2008
  - CONCLUSIONS
  - Hydrocortisone did not improve survival or reversal of shock in patients with septic shock, either overall or in patients who did not have a response to corticotropin, although hydrocortisone hastened reversal of shock in patients in whom shock was reversed. (ClinicalTrials.gov number, NCT00147004.)
- **Early Goal directed therapy**
  - 46.5% -> 30.5% : 16% improvement

첫 6시간 안에 resuscitation

EGDT: early goal directed therapy



1. Fluid resuscitation

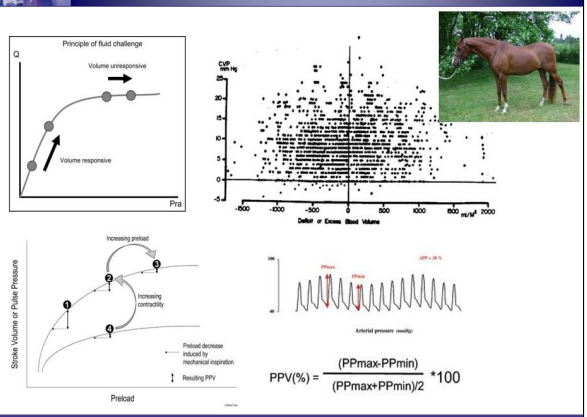
A. Initial Resuscitation

1. Protocolized, quantitative resuscitation of patients with sepsis- induced tissue hypoperfusion (defined in this document as hypotension persisting after initial fluid challenge or blood lactate concentration ≥ 4 mmol/L). Goals during the first 6 hrs of resuscitation:
   a) Central venous pressure 8–12 mm Hg
   b) Mean arterial pressure (MAP) ≥ 65 mm Hg
   c) Urine output ≥ 0.5 mL/kg/hr
   d) Central venous (superior vena cava) or mixed venous oxygen saturation 70% or 65%, respectively (grade 1C).
2. In patients with elevated lactate levels targeting resuscitation to normalize lactate (grade 2C).

G. Fluid Therapy of Severe Sepsis

1. Crystalloids as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B).
2. Against the use of hydroxyethyl starches for fluid resuscitation of severe sepsis and septic shock (grade 1B). Voluven
3. Albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids (grade 2C).
4. Initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemia to achieve a minimum of 30 mL/kg of crystalloids (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients (grade 1C).
5. Fluid challenge technique be applied wherein fluid administration is continued as long as there is hemodynamic improvement either based on dynamic (eg, change in pulse pressure, stroke volume variation) or static (eg, arterial pressure, heart rate) variables (UG).

1. Fluid resuscitation : CVP 8-12 mmHg



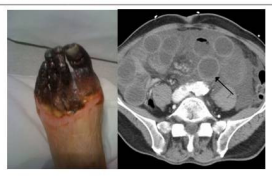
2. Pressors

H. Vasopressors

1. Vasopressor therapy initially to target a mean arterial pressure (MAP) of 65 mm Hg (grade 1C).
2. Norepinephrine as the first choice vasopressor (grade 1B).
3. Epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure (grade 2B).
4. Vasopressin 0.03 units/minute can be added to norepinephrine (NE) with intent of either raising MAP or decreasing NE dosage (UG).
5. Low dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension and vasopressin doses higher than 0.03-0.04 units/minute should be reserved for salvage therapy (failure to achieve adequate MAP with other vasopressor agents) (UG).
6. Dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (eg, patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (grade 2C).
7. Phenylephrine is not recommended in the treatment of septic shock except in circumstances where (a) norepinephrine is associated with serious arrhythmias, (b) cardiac output is known to be high and blood pressure persistently low or (c) as salvage therapy when combined inotrope/vasopressor drugs and low dose vasopressin have failed to achieve MAP target (grade 1C).
8. Low-dose dopamine should not be used for renal protection (grade 1A).
9. All patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available (UG).

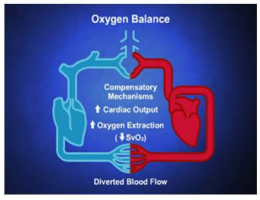
Pressors

Outcomes	Illustrative Comparative Risks[a] (95% CI) Assumed Risk	Corresponding Risk	Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)	Comments
	Dopamine	Norepinephrine				
Short-term mortality	530 per 1000	Study population 482 per 1000 (440 to 524)	RR 0.91 (0.83 to 0.99)	2043 (6 studies)	⊕⊕⊕⊖ moderate[b,c]	
Serious adverse events —Supraventricular arrhythmias	229 per 1000	Study population 82 per 1000 (34 to 195)	RR 0.47 (0.38 to 0.58)	1931 (2 studies)	⊕⊕⊕⊖ moderate[b,c]	
Serious adverse events —Ventricular arrhythmias	39 per 1000	Study population 15 per 1000 (8 to 27)	RR 0.35 (0.19 to 0.66)	1931 (2 studies)	⊕⊕⊕⊖ moderate[b,c]	

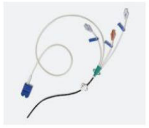


Too much vasopressin

3. Tissue perfusion



Target ScvO2 > 70%



Perfusion
Oxygen delivery:

$$DO_2 = CaO_2 \bullet CO$$

Dobutamine. Milrinone

Transfusion, if needed (HCT <30)

$$CaO_2 = [(SaO_2 \bullet 1.39 \times Hb) + (0.0031 \bullet PaO_2)]$$

Goal

SURVIVING SEPSIS CAMPAIGN BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:
1) Measure lactate level
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad spectrum antibiotics
4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥4mmol/L

TO BE COMPLETED WITHIN 6 HOURS:
5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation ($ScvO_2$)*
7) Remeasure lactate if initial lactate was elevated*

Antibiotics and culture

C. Diagnosis

1. Cultures as clinically appropriate before antimicrobial therapy if no significant delay (> 45 mins) in the start of antimicrobial(s) (grade 1C). At least 2 sets of blood cultures (both aerobic and anaerobic bottles) be obtained before antimicrobial therapy with at least 1 drawn percutaneously and 1 drawn through each vascular access device, unless the device was recently (<48 hrs) inserted (grade 1C).

D. Antimicrobial Therapy

1. Administration of effective intravenous antimicrobials within the first hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1C) as the goal of therapy.

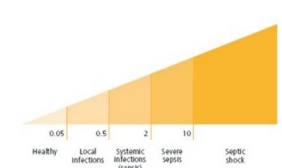
2a. Initial empiric anti-infective therapy of one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis (grade 1B).

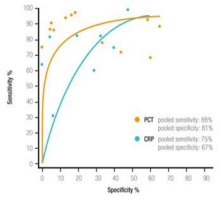
2b. Antimicrobial regimen should be reassessed daily for potential deescalation (grade 1B).

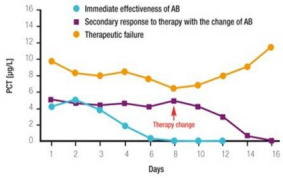
3. Use of low procalcitonin levels or similar biomarkers to assist the clinician in the discontinuation of empiric antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection (grade 2C).

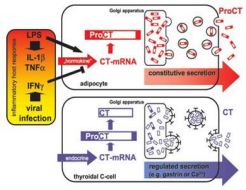
4a. Combination empirical therapy for neutropenic patients with severe sepsis (grade 2B) and for patients with difficult-to-treat, multidrug-resistant bacterial pathogens such as *Acinetobacter* and *Pseudomonas* spp. (grade 2B). For patients with severe infections associated with respiratory failure and septic shock, combination therapy with an extended spectrum beta-lactam and either an aminoglycoside or a fluoroquinolone is for *P. aeruginosa* bacteremia (grade 2B). A combination of beta-lactam and macrolide for patients with septic shock from bacteremic *Streptococcus pneumoniae* infections (grade 2B).

Procalcitonin









General critical care:
Ventilator

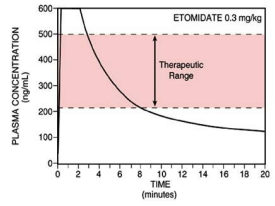
Pitfalls

- M/75, Lt. MCA infarction, M1 severe stenosis
- ABGA 7.24 – 55 – 66 – 92%, RR 28 BP 90/60
- Intubation : Choice of drug ?
  - 1) Midazolam
  - 2) Propofol
  - 3) Valium
  - 4) Etomidate
  - 5) 생튜베이션

Midazolam

	Diazepam	Midazolam
Cmax (ng/ml)	28.8	13.3
Cmax (ng/ml)	161.8	64.6
Half-life (hours)	21.5	2.2
%F (∞)	99.4%	97.9%

Midazolam: prolonged effect
Hemodynamic effect
Hypotension

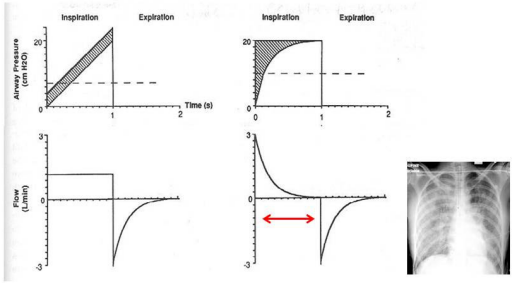


Etomidate
Hemodynamic stability
- No hypotension

Time course

- Controlled ventilation: AC-PC/ AC-VC
- SIMV or PSV
- CPAP
- T-piece

Volume controlled vs. Pressure controlled



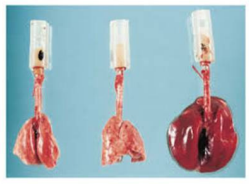
Flow * time = Volume

Flow controlled,
volume cycled

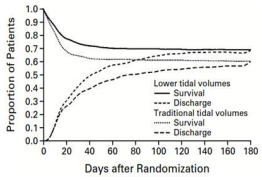
Pressure controlled,
time cycled

More ideal transition to PSV
Long time – even alveolar distribution

Ventilator induced lung injury



High volume, high pressure



6ml/kg, Pplat < 30cmH2O

IBW (kg) Males:
50 + 2.3(height in inches – 60)
or 50 + 0.91(height in cm – 152.4)

IBW (kg) Females:
45.5 + 2.3(height in inches – 60)
or 45.5 + 0.91(height in cm – 152.4)

M/75, 170cm, 75kg, Initial setting TV?

1) 365ml 2) 450ml 3) 700ml 4) 1200ml

TV should be based on IBW, not actual BW

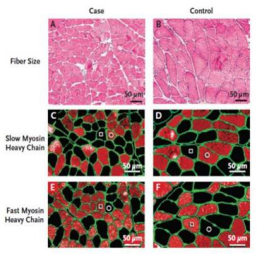
Diaphragm

Rapid Disuse Atrophy of Diaphragm Fibers in Mechanically Ventilated Humans

N Engl J Med 2008;358:1327-35.

Table 2. Summary of Ventilator Settings, Arterial Blood Gas Measurements, and Vital Signs for Control and Case Subjects.*

Measurement	Control Subjects (N=8)	Case Subjects (N=14)	P Value
Ventilator settings and related measurements			
Tidal volume (ml/kg of body weight)	7.5±1.3	8.0±2.0	0.47
Ventilation frequency (breaths/min)	11±1.7	14±3.0	0.02
PEEP (cm H_2O)	0.0±0.0	6.0±1.0	<0.001
FiO_2 (%)	—	52±0.11	—
SaO_2 (%)	99±2.0	—	—
PaO_2 (mm H_2O)	—	147±88	—
$PvCO_2$ (mm Hg)	31±3.8	—	—
$PaCO_2$ (mm Hg)	—	34±6.0	—
Arterial pH (units)	—	7.39±0.05	—
PaO_2/FiO_2 †	—	412±167	—
Vital signs			
Systolic pressure (mm Hg)	115±10	125±20	0.20
Diastolic pressure (mm Hg)	62±6.0	70±10	0.08
Heart rate (beats/min)	72±9.0	105±18	<0.001
Body temperature (°C)	35.7±0.3	36.4±1.1	0.06



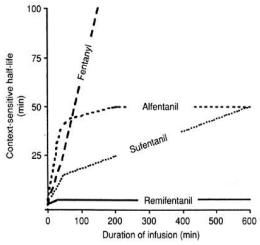
Even within 18hrs of controlled ventilation

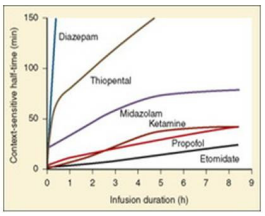
Continuous sedation

- For medical reasons
  - Lung , sepsis, irritability etc.
  - Several days after stopping sedation
  - Patient won't regain consciousness, no response
  - What is wrong?

Continuous sedation

- Midazolam or fentanyl





Context sensitive half life prolongation

Neurologic critical care

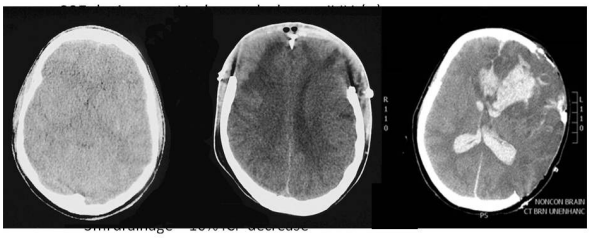
ICP management

Stepwise approach

Revised Columbia Stepwise ICP Protocol

7. PENTOBARBITAL
6. HYPOTHERMIA
5. HYPERVENTILATION
4. OSMOTHERAPY
3. CPP OPTIMIZATION
2. SEDATION
1. SURGICAL DECOMPRESSION

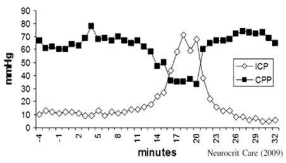
Step 1: Decompression



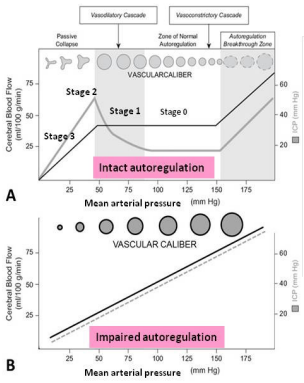
- Craniectomy: more definitive
  - Bifrontal : Traumatic brain injury
  - Hemicraniectomy

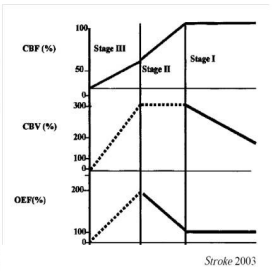
Step 2: proper sedation

- Reversible sedation to allow repeated neuro-examination
- Drugs : Decrease brain metabolism -> decrease ICP
  - Fentanyl
  - Precedex : 0.4mcg/Kg/h – dose titration
  - Midazolam : 0.05-0.2mg/Kg/h
  - Propofol : propofol infusion syndrome, infection, hypotension

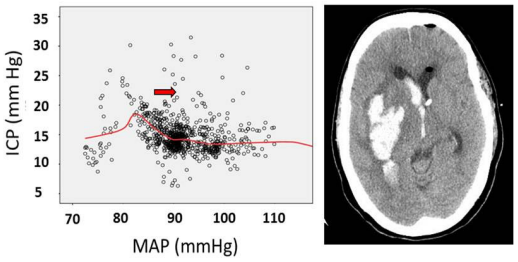


Step 3: CPP/MAP optimization



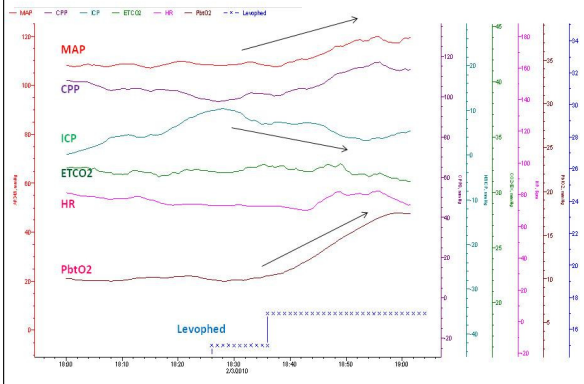


Step 3: CPP/MAP optimization



- ICP / MAP scatterplot -> intact cerebral autoregulation
- MAP should be maintained > 90 mm Hg

Step 3: CPP/MAP optimization



Step 4: Osmotic agents (1)

- **Mannitol:** 184KD sugar
  - Osmotic diuresis
  - Rapid onset: within minutes
  - Last up to 5 hrs (Peak 2hrs)
  - Form: **15% -25%** g/100ml

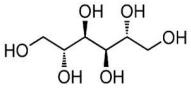
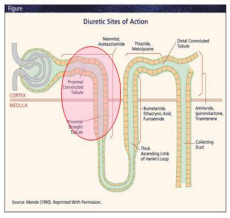


Table 1. Comparison of Osmotic Agents

Solution Concentration	Sodium Concentration (mEq/L)	Osmolarity (mOsm/L)
Ringer's lactate	130	275
0.009	154	308
0.02	242	684
0.03	513	1062
Mannitol 20%	n/a	1098
Mannitol 25%	n/a	1375
0.075	1283	2566
0.234	4004	8008



Step 4: Mannitol (2)

MAJOR CLINICAL AND PHYSIOLOGICAL BENEFITS OF EARLY HIGH DOSES OF MANNITOL FOR INTRAPARENCHYMAL TEMPORAL LOBE HEMORRHAGES WITH ABNORMAL PUPILLARY WIDENING: A RANDOMIZED TRIAL

TABLE 3. Early improvement of bilateral pupillary widening in the two groups of patients[a]

Pupillary improvement	No. of patients		
	HDM group	CDM group	Total
Yes	10	3	13
No	5	10	15

TABLE 4. Early improvement of unilateral pupillary widening in the two groups of patients[a]

Pupillary improvement	No. of patients		
	HDM group	CDM group	Total
Yes	44	29	73
No	13	27	40

- [illegible] : little effect and unpredictable results
- Higher dose (1.4 g/kg) was more powerful than 0.7 g/kg in TBI RCT

Neurosurgery 2002

Stopping point

- Mannitol Stopping point S-osm < 320 (?) : No strong evidence !!!

Osmolality and osmotic gap

Timing of Measurement	No MI-ARI*	MI-ARI*	p Value†
osmolality (mOsm/kg)			
baseline	301 ± 9	303 ± 4	0.556
before MI-ARI	320 ± 22	322 ± 23	0.481
peak	320 ± 22	344 ± 25	0.025

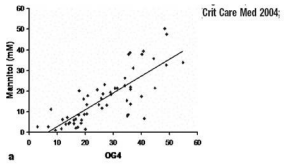
Variable	B Coefficient	SE	p Value	Exp (B)	95% CI for Exp (B) Lower	Upper
APACHE II score	0.116	0.046	0.013	1.123	1.025	1.229
congestive heart failure	2.417	1.147	0.035	11.215	1.183	106.291
constant	−4.626	1.158	0.000	0.010		

Mechanism of Renal injury

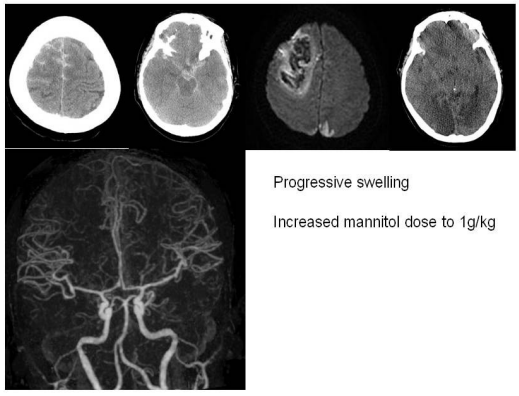
- Direct Mannitol effect
  - Not merely due to hypersomolarity
    - Hypertonic saline: much fewer RF
  - Acute tubular necrosis
  - Pre-renal type injury
    - Euvolemia : mandatory

Step 4: Mannitol (3)

- **Osmolar gap** : Measured osm – Calculated osm
  - Well correlated with Mannitol concentration

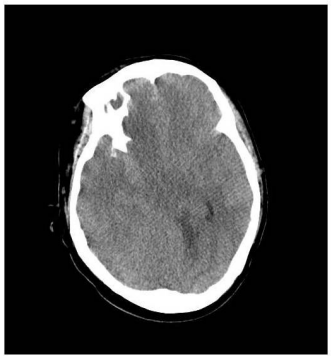


  - **OG > 55 mOsm**
    - Retrospective analysis:
      - Mannitol induced RF (+): OG > 65 mOsm
      - Mannitol induced RF (-): OG < 55 mOSm



Progressive swelling

Increased mannitol dose to 1g/kg



Bilateral pupil dilatation
Coma
No pain response

What to do?

1) More mannitol
2) Give up
3) Decompressive surgery

Step 4: Hypertonic saline (1)

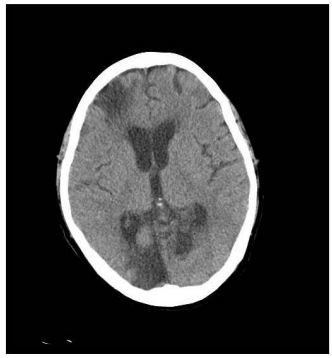
- HTS: 3% - 23.4%
  - 0.9% Normal saline : **308 mEq/L**
  - Dose: **23.4% - 30cc** or equivalent amount of osmolarity
  - 우리나라: 11.7% **NACL4IP** : 40mEq/20cc - 60cc IV shooting

Table 1. Comparison of Osmotic Agents

Solution Concentration	Sodium Concentration (mEq/L)	Osmolarity (mOsm/L)
Ringer's lactate	130	275
0.009	154	308
0.02	242	684
0.03	513	1062
Mannitol 20%	n/a	1098
Mannitol 25%	n/a	1375
0.075	1283	2566
0.234	4004	8008

HTS

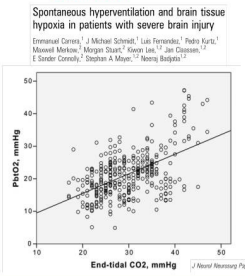
- Side effect / complication
  - Too rapid infusion -> hypotension over 10min
  - Electrolyte imbalance, hypernatremia
  - Serum osmolarity increase, ARF
  - CPN
  - Tissue necrosis -> prefer central line

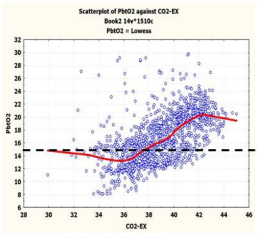


Survived ICP crisis

Step 5: Hyperventilation

- Decrease $PaCO_2$ -> Vasoconstriction -> decrease CBV -> ICP ↓
- Side effect : brain hypoxia, **even PaCO2 around 30 mm Hg**
  - Fixed degree of hyperventilation without brain oxygen monitoring can be harmful

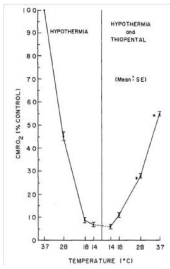




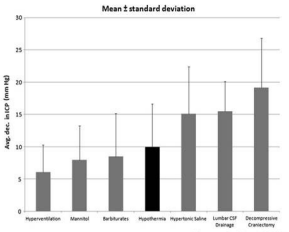
Patient with ICH

Step 6: Hypothermia

- Mechanism
  - Decreases metabolism
  - Coupled decrease in CBF
- Target temperature
  - CA: 33 (32-34)
  - For ICP: < 35.5 (35)

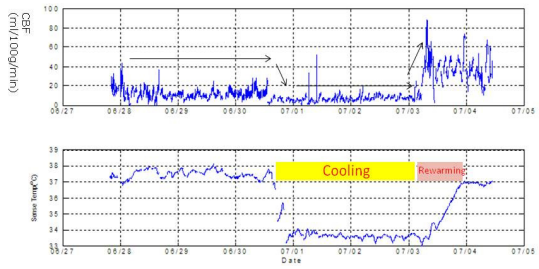


6% / 1°C



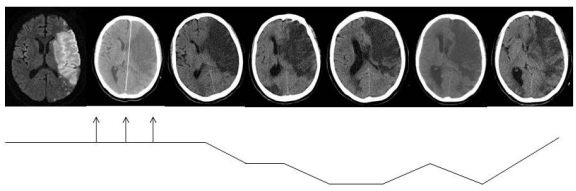
Neurocrit Care (2009)

Step 6: Hypothermia

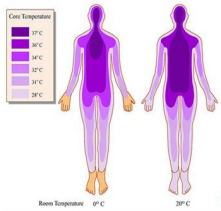


Cooling decreases CBF (ICP decrease)
Rewarming -> rebound ICP/CBF increase

Ko et al. 2010 NY Conference of Neurologic Emergency

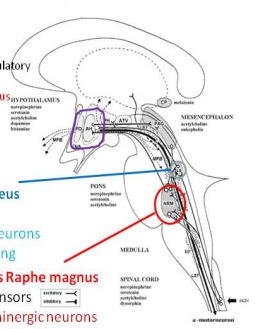


Thermoregulation



Core body Temperature: 37
Peripheral T : 2-4 °C lower

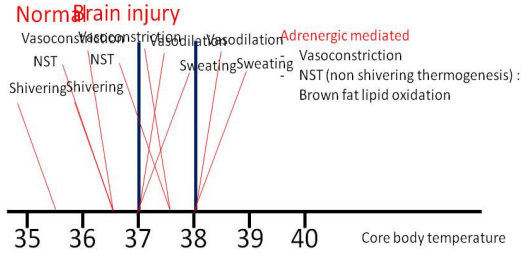
Main thermoregulatory center:
Ant. Hypothalamus



Locus subcoeruleus
Cold sensors
Noradrenergic neurons
Promotes shivering

Nucleus Raphe magnus
Heat sensors
Serotoninergic neurons
Inhibits shivering

Physiological response

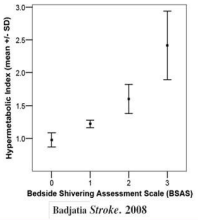


Adrenergic mediated Vasoconstriction
NST (non shivering thermogenesis) : Brown fat lipid oxidation

Shivering

- BSAS

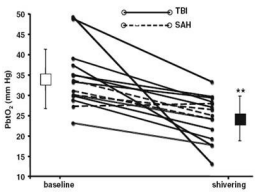
Score	Definition
0	**None:** no shivering noted on palpation of the masseter, neck, or chest wall
1	**Mild:** shivering localized to the neck and/or thorax only
2	**Moderate:** shivering involves gross movement of the upper extremities (in addition to neck and thorax)
3	**Severe:** shivering involves gross movements of the trunk and upper and lower extremities



Badjatia *Stroke*. 2008

Effect of Shivering on Brain Tissue Oxygenation During Induced Normothermia in Patients With Severe Brain Injury

Mauro Oddo · Suzanne Frangos · Eileen Maloney-Wilensky · W. Andrew Kofke · Peter D. Le Roux · Joshua M. Levine



Columbia anti-shivering protocol

Prevention of Shivering During Therapeutic Temperature Modulation: The Columbia Anti-Shivering Protocol

H. Alex Choi · Sung Rae Ko · Mary Presciutti · Luis Fernandez ·

Step		Intervention	Dose
0	Baseline	Acetaminophen	650–1000 mg Q 4–6 h
		Buspirone	30 mg Q 8 h
		Magnesium sulfate	0.5–1 mg/h IV Goal (3–4 mg/dl)
		Skin counterwarming	43°C/MAX Temp
1	Mild sedation	Dexmedetomidine	0.2–1.5 mcg/kg/h
		or	Fentanyl starting dose 25 mcg/h
		Opioid	Meperidine 50–100 mg IM or IV
2	Moderate sedation	Dexmedetomidine and Opioid	Doses as above
3	Deep sedation	Propofol	50–75 mcg/kg/min
4	Neuromuscular blockade	Vecuronium	0.1 mg/kg IV