

Shock

Fellow Core Curriculum
2018

Case Presentation

- 42 yo female transferred to ICU with shock following primary admission for catatonia
- BP 71/42, HR 83, RR 32, SaO₂ 98% 2L NC, 38.8

Case Presentation

- Quickly apparent that she is most likely in septic shock
- C.dif resulted positive day of transfer to ICU

Case Presentation

- Stabilizes following volume resuscitation
- Started on IV flagyl, enteral vanc
- Low-dose NE (0.08-0.15 mcg/kg/min)
- Bedside US - OK cardiac indices

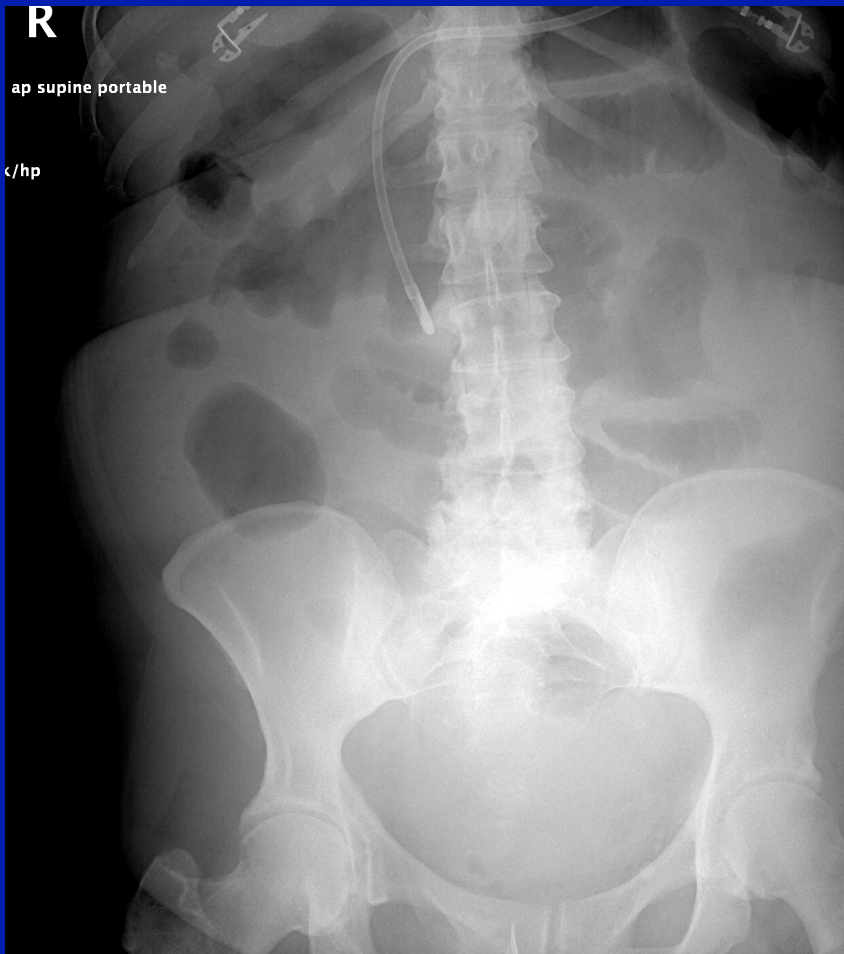
Case Presentation

- Stabilizes following volume resuscitation
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- Bedside US OK cardiac indices

Progression





	6:30 PM	7:00 PM	7:30 PM	8:00 PM	8:15 PM
				Regular	
	38	28		46	
				Shallow...	
	81/53	74/44	71/45	68/45	65/44
	61	54	54	53	50
				NIBP	
				Large A...	
m				Right Arm	
	94	95		95	
				Finger	

Progression



- Rapid deterioration with marked increase in abd size and tension
- Intubated for mixed resp failure
- Volume resuscitation and vasopressor
- Emergent ex-lap

Progression

IV Drips					
 EPINEPHrine 16 mg [0.1 mcg/kg/min] + NS (wt requ...	Rate	mL/hr			
	EPINEPHrine	mcg/kg/min			
			34.58	34.58	34.58
			0.4	0.4	0.4
  fentaNYL 2500 mcg/NS 100 mL Premix 2,500 mcg [50 mcg/hr] + P...	Rate	mL/hr			
	fentaNYL	mcg/hr			
norepinephrine + 468 mL Sodium Chloride 0.9% intr...	Rate	mL/hr			
	norepinephrine	mcg/kg/min			
			129.66		
			1.5		
 vasopressin 40 Unit(s) [0.04 unit(s)/min] + NS (wt require...	Rate	mL/hr			
	vasopressin	unit(s)/min			
					4.8
					0.08

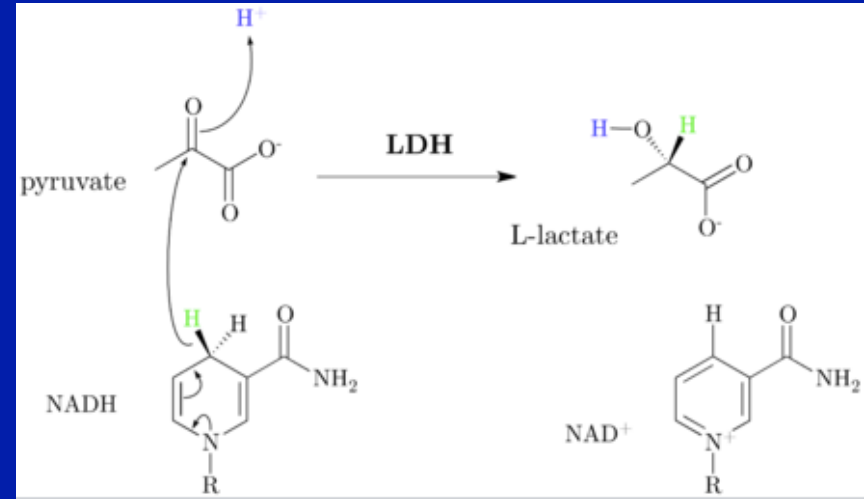
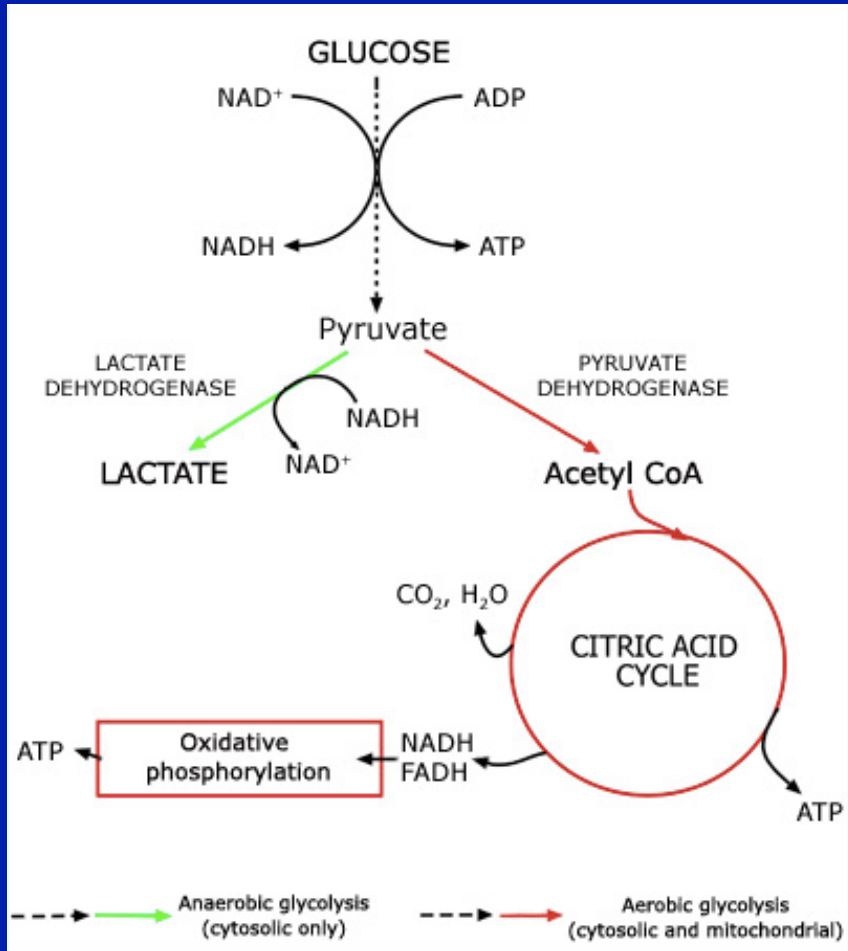
Lactic acid levels ranging from 6-15 last 10 hours; pH 7.17-7.28
 BP hovering at 90/50 (MAP 60)
 Has received 13L crystalloid, no colloid

Things I Mean to Know...

About Shock

- What do we do with a lactate?
- What about bicarb?

Lactate – anaerobic metabolism



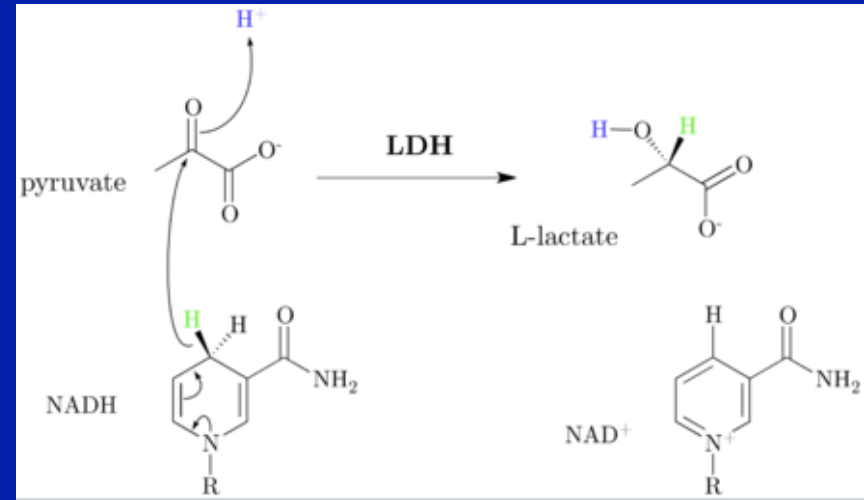
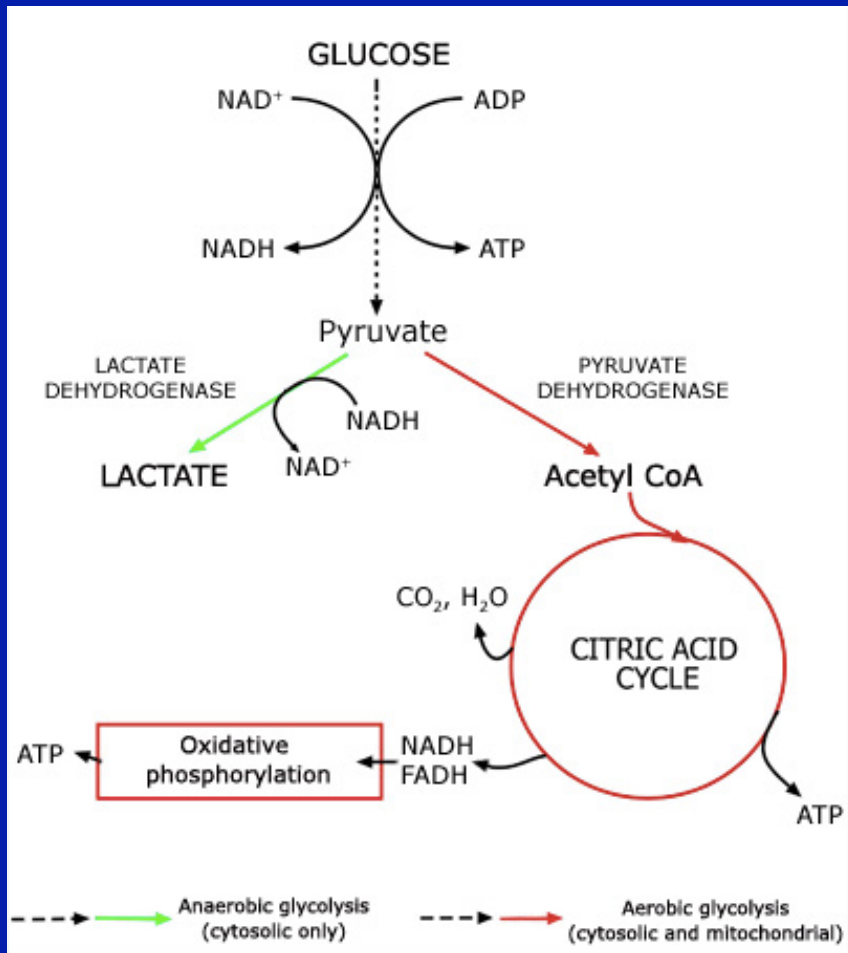
Glucose to CO₂ and H₂O via TCA cycle gets 38 ATPs from each glucose.

Anaerobic pathway gets 2 ATP

When limited O₂ to support aerobic glycolysis, pyruvate metabolism shifts to anaerobic pathway (thus lactate produced)

Typical lactate:pyruvate ratio is 10:1

Lactic Acidosis



ATP hydrolyzed to ADP – H is byproduct

When TCA cycle running, H ions are used during ox phos.

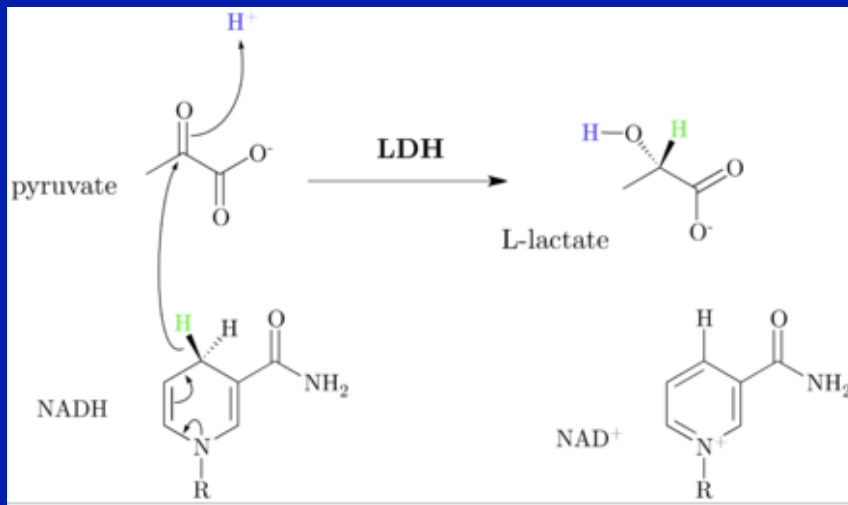
The milieu that predisposed to anaerobic glycolysis in the shock state usually associated with mitochondrial dysfunction (no ox phos), and H ions abound. Thus acidosis.

Lactate Consumption

- Primarily metabolized in liver (60%) and kidney (30%)
- Major use is gluconeogenesis (Cori cycle)

Lactate Consumption

- The relationship between lactate and pyruvate is bidirectional (lactate can be oxidized back to pyruvate)

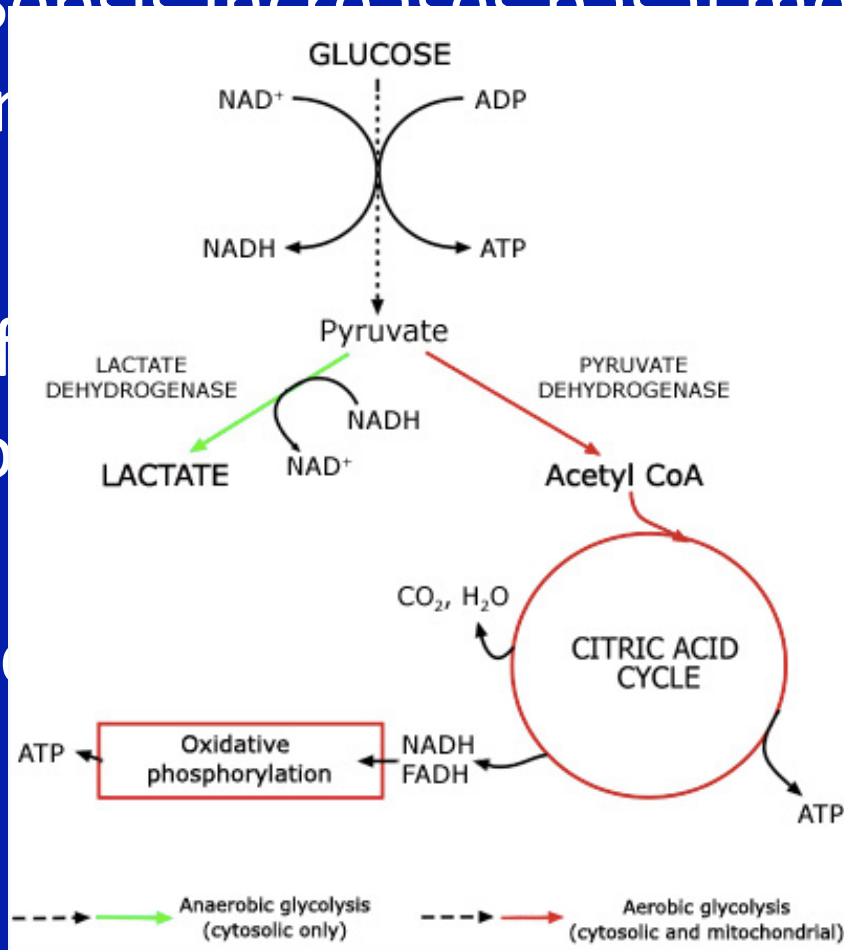


Lactate Transport (Shuttle)

- Allow consumption of lactate in mitochondria of target organs at a distant site
- MCTs move lactate (and protons) across membranes – MCTs are most prevalent in skeletal muscle, cardiac myocytes, and liver, also brain. LDH also present in these sites.
- Cardiac myocytes and liver import lactate, convert back to pyruvate, which may then be consumed by mitochondria (or gluconeogenesis in liver)
- Suggests lactate production is important adaptive response – i.e alternative fuel

Sepsis and glycolysis

- Sepsis increases basal metabolic rate, and increases glycolytic flux”



- If oxygen is scarce (hypoxia), pyruvate will be converted to lactate (anaerobic glycolysis) (may not always be the case in sepsis environment)

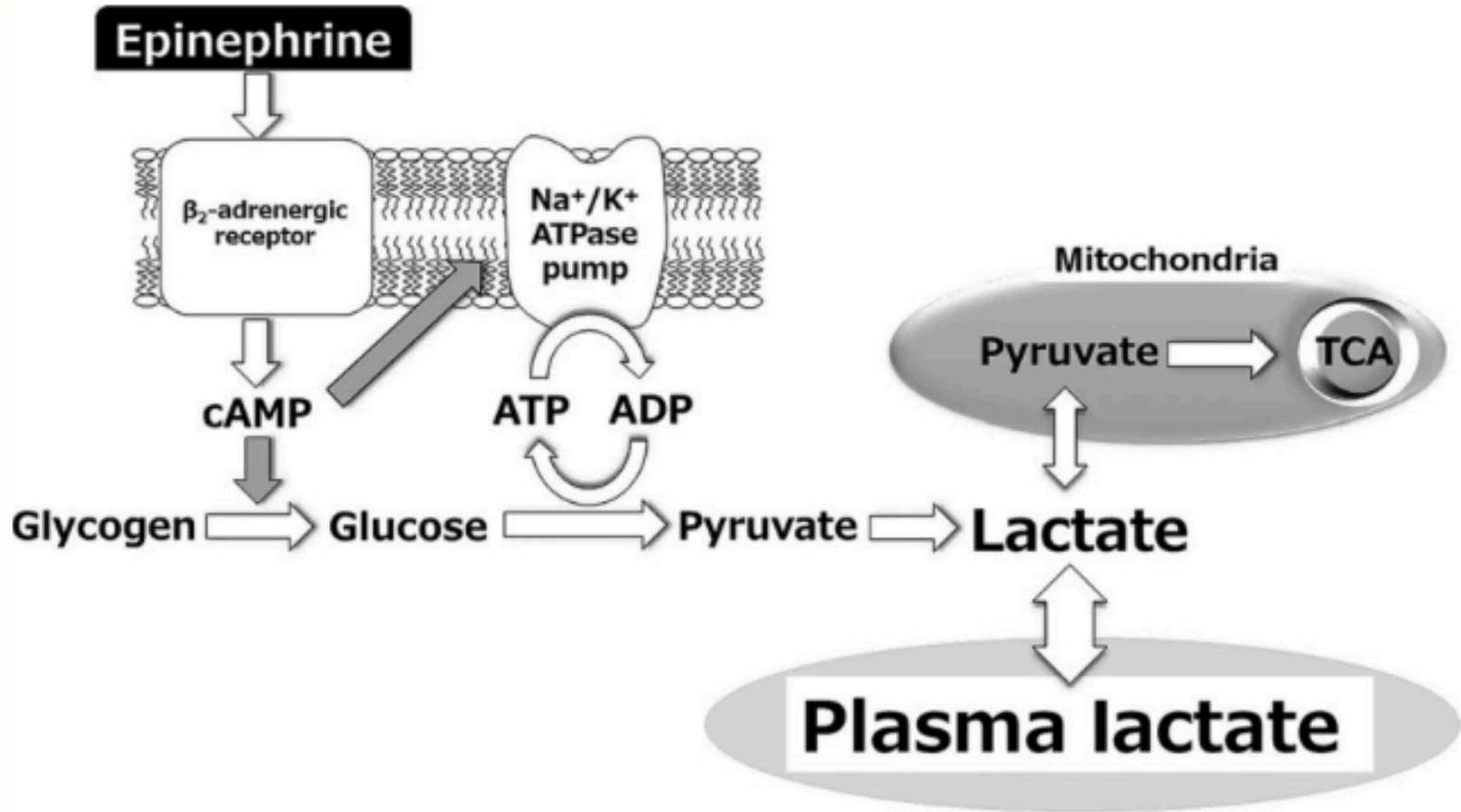
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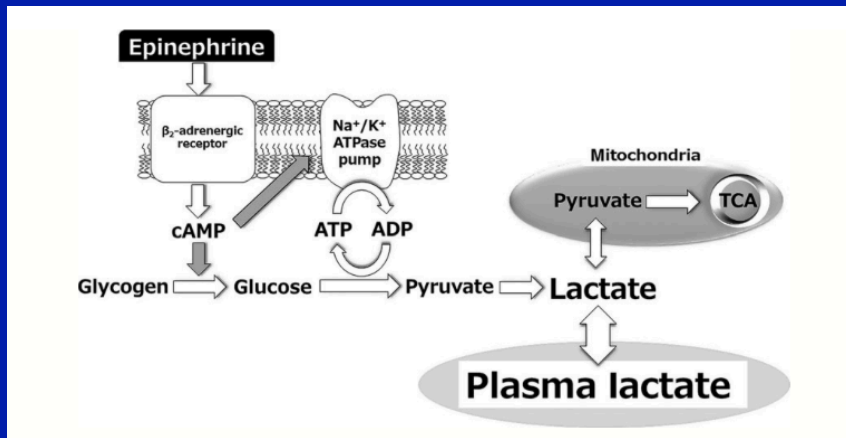
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Glycolytic Flux in skeletal muscle markedly increased by catecholamines

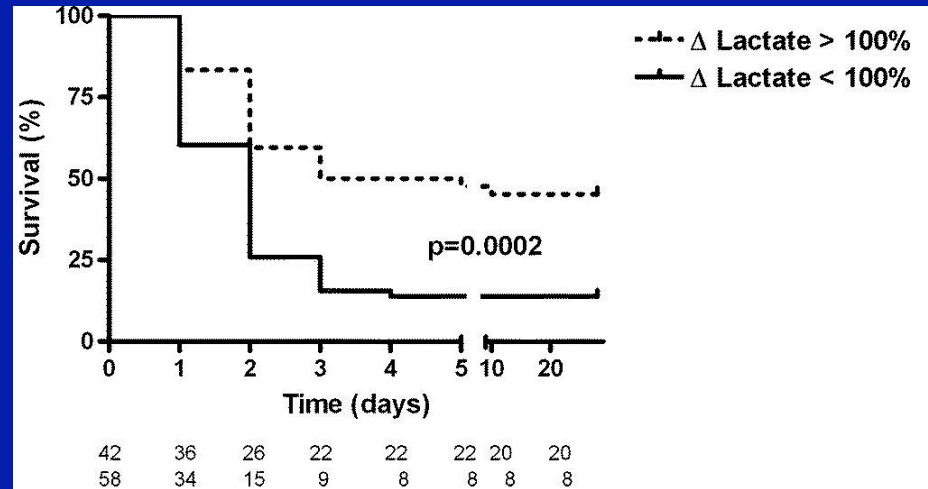
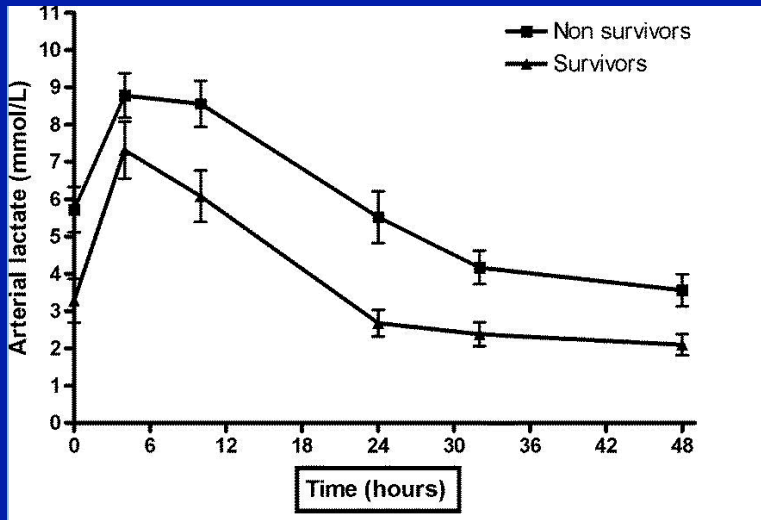


Glycolytic Flux in skeletal muscle markedly increased by catecholamines



- Suggestion that increased lactate in setting of stress (or catechol infusion) may represent intact cytosol function and adaptive mechanism
- Lactate rise with epi (or sepsis) may not represent tissue ischemia

Lactate response to epinephrine



Retrospective study of 100 patients with shock on epi – analyzed change in lactate before and 4 hours after initiation of epi infusion. In MV analysis, patients whose lactates went UP had a lower risk of death (52% versus 85%)

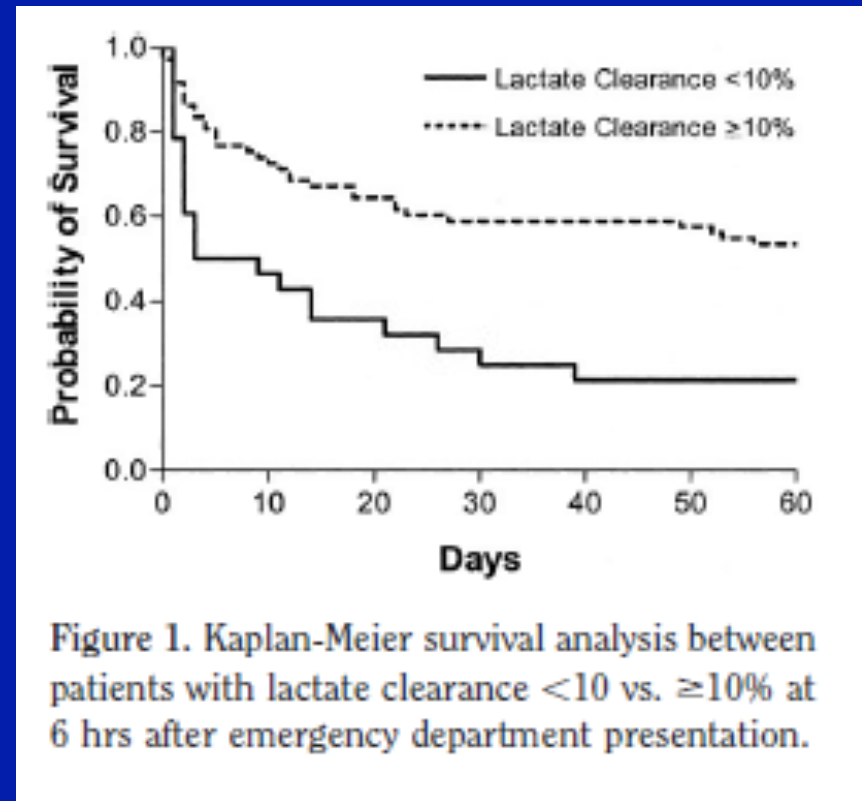
Wutrich Y, Barraud D, Conrad M et al. Early increase in arterial lactate concentration under epinephrine infusions is associated with a better prognosis during shock. Shock 2010.

Lactate Clearance

- SEP-1 requires measurement of serial lactate in septic shock (notwithstanding evidence from PROCESS, PROMISE, and ARISE) as part of 3 hour bundle
- This measure was largely based on Surviving Sepsis Guidelines targetting bundle treatment for septic shock, including those defined by lactate > 4.0

What was the evidence base?

- Index Study: Nguyen 2004
- Prospective obs
- enrolled severe sepsis & septic shock
- n = 111, overall hosp mortality 42%
- Lactate measured at index and hour 6
- Many caveats

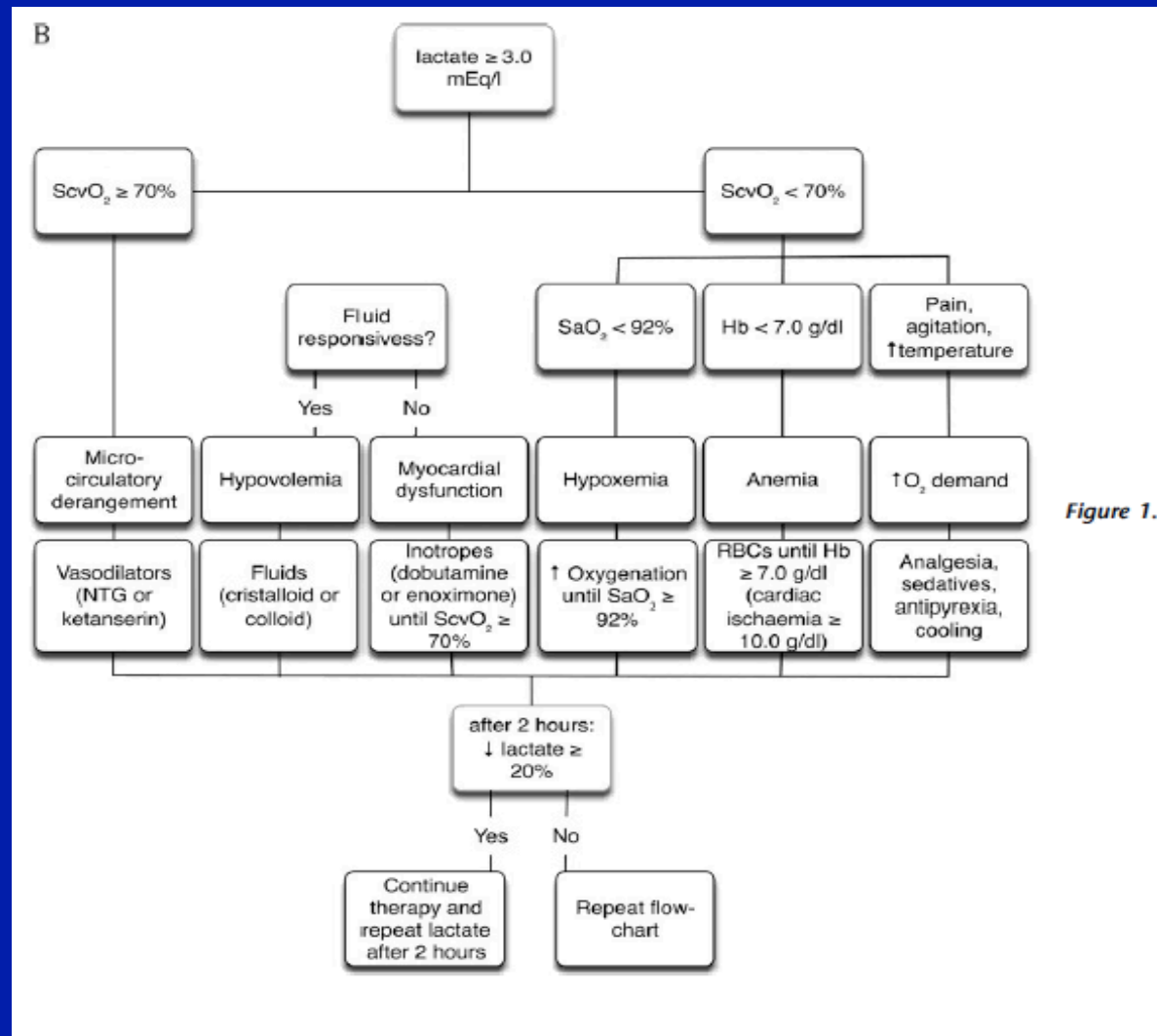


What was the evidence base?

- Best RCT: Jansen 2010
- Enrolled ICU admissions with lactate > 3 (excluded liver failure)
- $n = 348$
- Most were septic shock
- Essentially testing usual care with only an index lactate, or EGDT with lactate Q2H, with explicit goal of serial 20% reductions

Jansen TC, van Bommel J, Schoonderbeek FJ, et al; LACTATE study group: Early lactate-guided therapy in intensive care unit patients: A multicenter, open-label, randomized controlled trial. *Am J Respir Crit Care Med* 2010; 182:752–761

Jansen AJRCCM 2010: Lactate Clearance RCT



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TABLE 2. BLOOD LACTATE LEVELS

Hours after Start of Therapy	Lactate Level (mEq/L)		P Value
	Control Group	Lactate Group	
Baseline (0 h)	4.7 (3.9–5.5)	4.6 (3.9–5.4)	0.75
8	2.7 (2.3–3.2)	2.6 (2.2–3.1)	0.59
0–8	3.3 (2.8–3.9)	3.2 (2.7–3.8)	0.80
9–72	1.7 (1.4–2.0)	1.6 (1.3–1.9)	0.17

The adjusted mean values (95% confidence interval) were obtained from mixed model analysis. Lactate levels are expressed as geometric means. *P* values were calculated after logarithmic transformation of lactate levels.

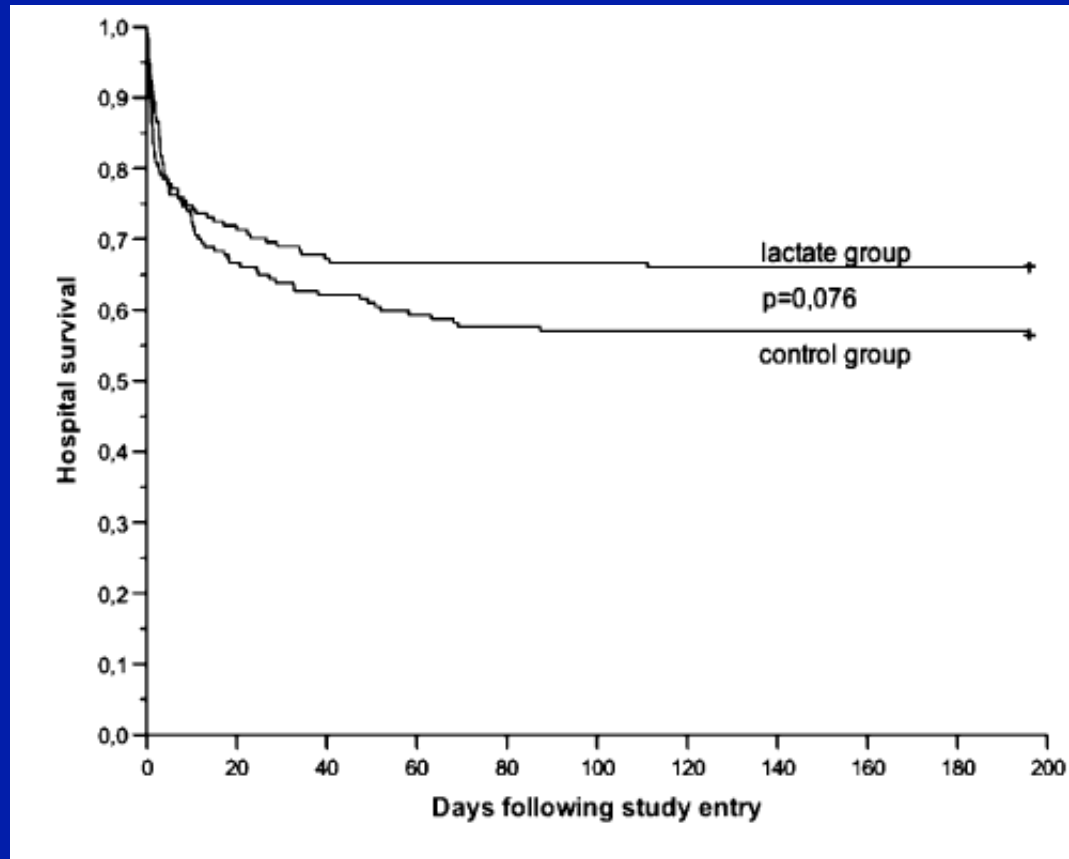
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TABLE 3. FLUIDS AND VASOACTIVE MEDICATION USE DURING THE INITIAL TREATMENT PHASE AND UP TO 72 HOURS

Treatment	Control Group	Lactate Group	P Value
Fluids, ml*			
0–8 h [†]	2,194 ± 1,669	2,697 ± 1,965	0.011
9–72 h [‡]	10,043 ± 6,141	8,515 ± 4,987	0.055
Red blood cell transfusion, ml			
0–8 h [†]	196 ± 495	322 ± 1037	0.15
9–72 h [‡]	345 ± 667	423 ± 1300	0.59
Any inotropic agent, % [§]			
0–8 h [†]	32.9	40.1	0.17
9–72 h	44.2	35.2	0.12
Any vasodilator, % [¶]			
0–8 h [†]	20.2	42.5	<0.001
9–72 h	27.1	43.2	0.005
Any vasopressor, % ^{**}			
0–8 h [†]	63.6	69.5	0.25
9–72 h	63.7	71.4	0.16

Jansen TC, van Bommel J, Schoonderbeek FJ, et al; LACTATE study group: Early lactate-guided therapy in intensive care unit patients: A multicenter, open-label, randomized controlled trial. *Am J Respir Crit Care Med* 2010; 182:752–761

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Recent Data

- Ryoo 2018
- retrospective study from prospective registry
- multicenter enrolling patients with septic shock (lactate > 2 and vasopressor[NE]) who received bundle-guided resuscitation.
- 1060 patients, 28D mortality 25%.

Ryoo 2018 Registry Data

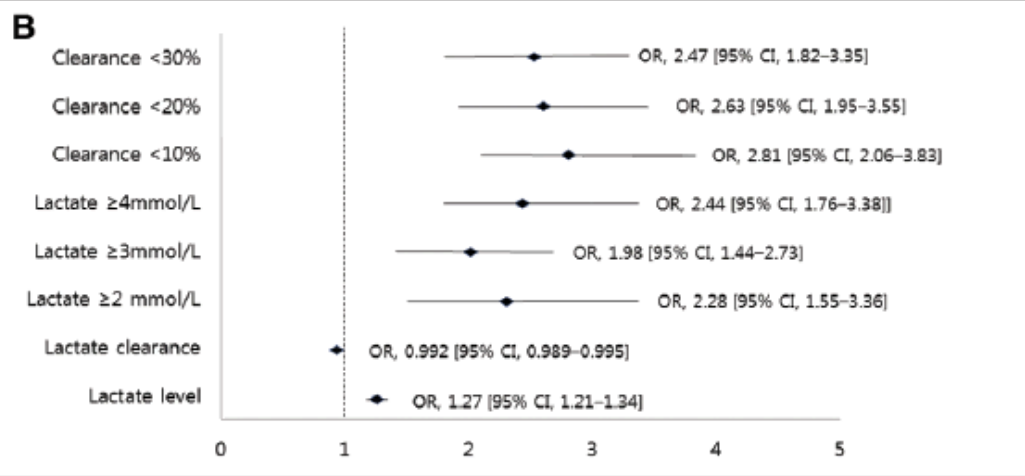
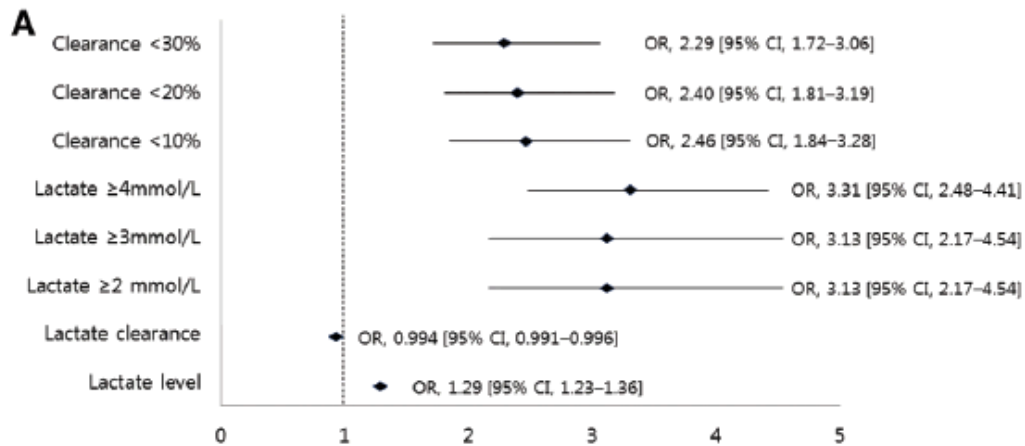


Figure 3. Logistic regression analysis of raw lactate levels and lactate clearance 6 hr after septic shock recognition for predicting 28-d mortality rates. **A**, Unadjusted odds ratio (OR) and 95% CI. **B**, Adjusted OR and 95% CI; adjusted for initial lactate levels and Sequential Organ Failure Assessment score.

So it's a marker, may not be any better than single measure of lactate at 6 hours (in fact 6 hour lactate looked better on ROC than clearance – neither was great).

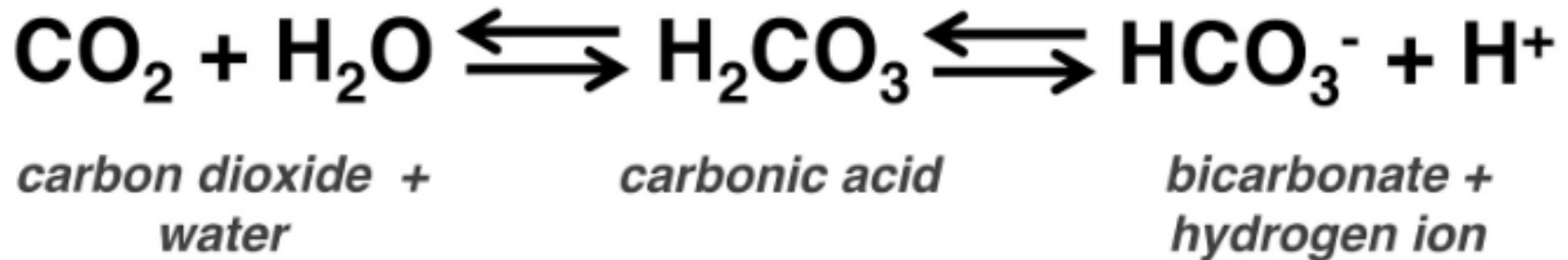
Not clear which interventions toward this marker actually impact outcome.

Things I Mean to Know...

About Shock

- What do we do with a lactate?
- What about bicarb?

The problem with bicarb ...



- Adequate ventilation can blow off the CO₂, but some CO₂ will diffuse across membranes and worsen intracellular pH
- Really?

2 human studies usually cited to support intracellular acidosis theory

Goldsmith 1997

- Measured intracellular pH in leukocytes from healthy volunteers
- Worsening intracellular milieu after alkalination of ECF with NaHCO_3

Levrant 2001

- In vitro human hepatocytes
- Bicarb decreases intracellular pH in concert with increase in pCO_2 in ECF

2 physio RCTs - bicarb v saline

Cooper 1990

- 14 ICU patients with lactic acidosis
- Received 2 mmol/kg bicarb over 15 minutes, or equiv volume saline
- Arterial pH rose after bicarb (as did pCO₂)
- Each increased PCWP and CO equally
- Neither changed MAP

Mathieu 1991

- 10 ICU patients with lactic acidosis
- 1 mmol/kg bicarb as bolus, or equiv volume saline
- Arterial pH rose after bicarb, but tissue oxygenation didn't change
- No impact of either bicarb or NaCl on hemodynamics

Bicarb Clinical Trials

- Fang 2008: RCT 5 mL/kg of NS versus hypertonic saline v bicarb. 94 patient with severe sepsis. MAP and CO improved faster in bicarb gtt, but no differences in mortality. These patients all had mean normal pH at study entry
- Jung 2011 : prospective multicenter obs - pH < 7.20, bicarb (5-55%) depended on center, not mechanism of acidemia. no association between bicarb and mortality
- Chen 2013: prospective RCT – septic shock and lactic acidosis (pH < 7.15 at study entry), n = 65. bicarb improved CI, O2 delivery, and SVO2 and resulted in lower mortality – Chinese language only, not translated

Bicarb Clinical Trials

- Kim 2013: single center retrospective study 2011-2012 (Korea)
- Lactate >3.3 with AGMA. 102 patients. split into groups depending on whether they received $>20\text{mEq NaHCO}_3$. Mean pH was 7.3 (?). 67% of patients (69) received bicarb. Bivariate analysis bicarb associated with mortality ($p=0.006$). Those receiving bicarb had lower pH (mean 7.24), higher SOI scores, vent. Bicarb stayed significant in MV model.

