SEPSA IN VAZOAKTIVNA ZDRAVILA

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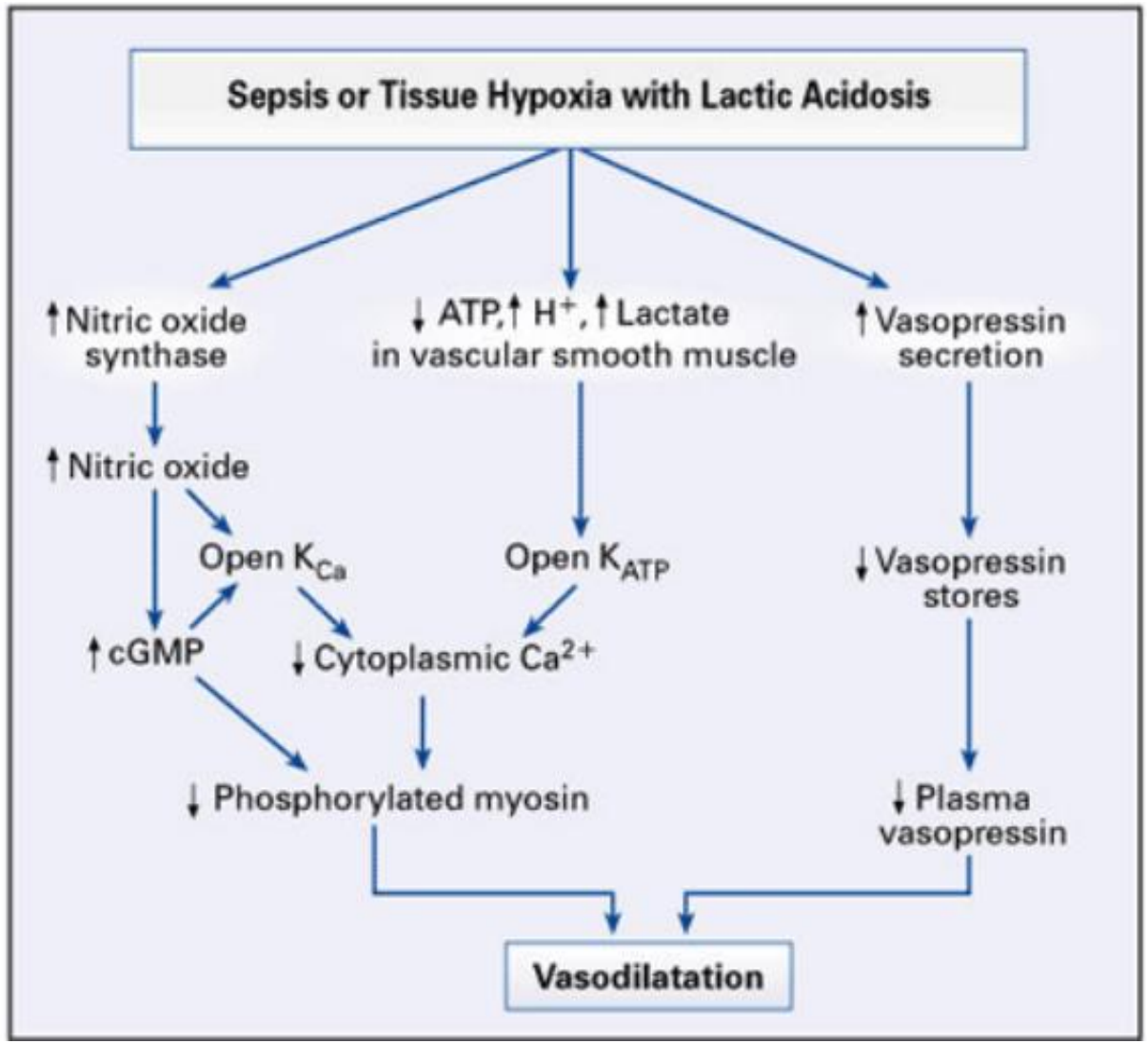
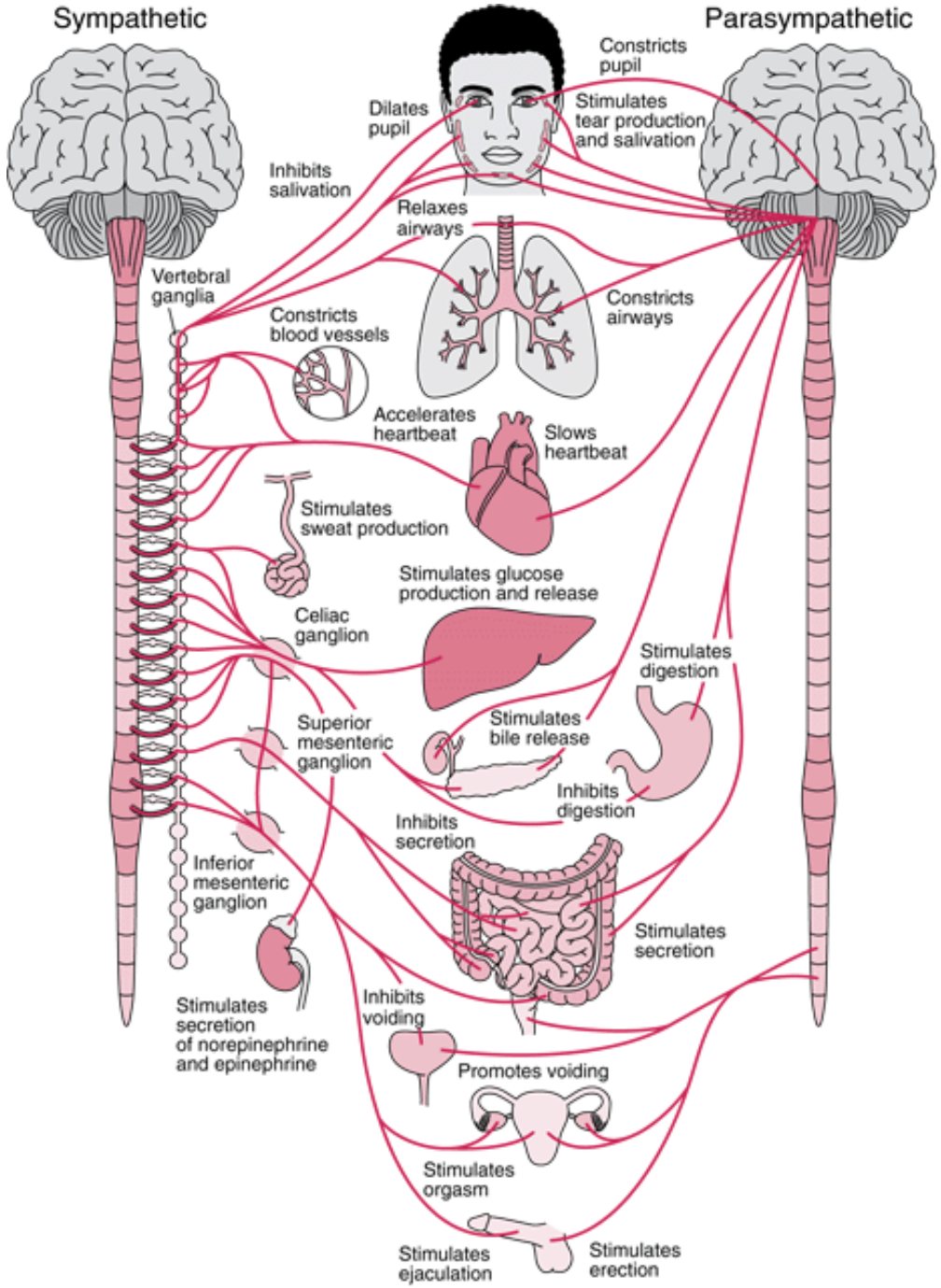
SEPSA-DEFINICIJA

- Življenje ogrožajoče stanje, ki prizadene več organov ali organskih sistemov, kot neprimeren odgovor imunskega sistema na okužbo
- Septični šok kot „podvrsta“ sepse z višjo umrljivostjo in poškodbami na celičnem nivoju
- Pregled smernic „*Surviving Sepsis Campaign 2021*“
- Viri citirani v smernicah, zato posebej niso navedeni
- *Kdaj vazoaktivna zdravila?* Ko s tekočinskim zdravljenjem ne vzpostavimo ustreznega krvnega obtoka, ki bi zagotavljal ustrezno oskrbo tkiv s kisikom in hranili
- 30 ml/kg balansiranega kristaloida?


Sepsis or Tissue Hypoxia with Lactic Acidosis
↑ Nitric oxide synthase
↓ ATP, ↑ H+, ↑ Lactate in vascular smooth muscle
↑ Vasopressin secretion
↑ Nitric oxide
Open KCa
Open KATP
↓ Vasopressin stores
↑ cGMP
↓ Cytoplasmic Ca2+
↓ Phosphorylated myosin
↓ Plasma vasopressin
Vasodilatation


Sympathetic
Parasympathetic
Constricts pupil
Dilates pupil
Stimulates tear production and salivation
Inhibits salivation
Relaxes airways
Vertebral ganglia
Constricts airways
Constricts blood vessels
Accelerates heartbeat
Slows heartbeat
Stimulates sweat production
Stimulates glucose production and release
Celiac ganglion
Stimulates digestion
Stimulates bile release
Superior mesenteric ganglion
Inhibits digestion
Inhibits secretion
Inferior mesenteric ganglion
Stimulates secretion
Stimulates secretion of norepinephrine and epinephrine
Inhibits voiding
Promotes voiding
Stimulates orgasm
Stimulates ejaculation
Stimulates erection

DELOVANJE NA RECEPTORJE

Table 1 Relative Receptor Potency[3]					
Agent	**Alpha-1**	**Beta-1**	**Beta-2**	**Dopamine**	**Vasopressin-1**
Dobutamine	+	+++++	+++	0	0
Dopamine	+++	++++	++	+++++	0
Epinephrine	+++++	++++	+++	0	0
Milrinone	0	0	0	0	0
Norepinephrine	+++++	+++	++	0	0
Phenylephrine	+++++	0	0	0	0
Vasopressin	0	0	0	0	+++++
0 = no significant receptor affinity; + through +++++ = minimal to maximal receptor affinity					

SMERNICE

HEMODYNAMIC MANAGEMENT		
32. For adults with sepsis or septic shock, we recommend using crystalloids as first-line fluid for resuscitation.	***Strong,*** *moderate-quality evidence*	
33. For adults with sepsis or septic shock, we suggest using balanced crystalloids instead of normal saline for resuscitation.	***Weak,*** *low quality of evidence*	**CHANGED from *weak recommendation***, *low quality of evidence.* "We suggest using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock"
34. For adults with sepsis or septic shock, we suggest using albumin in patients who received large volumes of crystalloids.	***Weak,*** *moderate-quality evidence*	
35. For adults with sepsis or septic shock, we recommend against using starches for resuscitation.	***Strong,*** *high-quality evidence*	

36. For adults with sepsis and septic shock, we suggest against using gelatin for resuscitation.	***Weak,*** *moderate-quality evidence*	**UPGRADE from *weak recommendation***, *low quality of evidence* "We suggest using crystalloids over gelatins when resuscitating patients with sepsis or septic shock."
37. For adults with septic shock, we recommend using norepinephrine as the first-line agent over other vasopressors.	***Strong*** Dopamine. *High-quality evidence* Vasopressin. *Moderate-quality evidence* Epinephrine. *Low quality of evidence* Selepressin. *Low quality of evidence* Angiotensin II. *Very low-quality evidence*	
38. For adults with septic shock on norepinephrine with inadequate mean arterial pressure levels, we suggest adding vasopressin instead of escalating the dose of norepinephrine.	***Weak,*** *moderate quality evidence*	
39. For adults with septic shock and inadequate mean arterial pressure levels despite norepinephrine and vasopressin, we suggest adding epinephrine.	***Weak,*** *low quality of evidence*	
40. For adults with septic shock, we suggest against using terlipressin.	***Weak,*** *low quality of evidence*	
41. For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, we suggest either adding dobutamine to norepinephrine or using epinephrine alone.	***Weak,*** *low quality of evidence*	

42. For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, we suggest against using levosimendan.	***Weak,*** *low quality of evidence*	***NEW***
43. For adults with septic shock, we suggest invasive monitoring of arterial blood pressure over noninvasive monitoring, as soon as practical and if resources are available.	***Weak,*** *very low quality of evidence*	
44. For adults with septic shock, we suggest starting vasopressors peripherally to restore mean arterial pressure rather than delaying initiation until a central venous access is secured.	***Weak,*** *very low quality of evidence*	***NEW***
45. There is insufficient evidence to make a recommendation on the use of restrictive versus liberal fluid strategies in the first 24 hr of resuscitation in patients with sepsis and septic shock who still have signs of hypoperfusion and volume depletion after the initial resuscitation.	***No recommendation***	**NEW** "We suggest using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock" ***Weak recommendation***, *low quality of evidence* "We suggest using crystalloids over gelatins when resuscitating patients with sepsis or septic shock." ***Weak recommendation***, *low quality of evidence*

VAZOAKTIVNA ZDRAVILA

36. For adults with sepsis and septic shock, we suggest against using gelatin for resuscitation.	***Weak,*** *moderate-quality evidence*	**UPGRADE from *weak recommendation*,** *low quality of evidence* "We suggest using crystalloids over gelatins when resuscitating patients with sepsis or septic shock."
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39. For adults with septic shock and inadequate mean arterial pressure levels despite norepinephrine and vasopressin, we suggest adding epinephrine.	***Weak,*** *low quality of evidence*	
40. For adults with septic shock, we suggest against using terlipressin.	***Weak,*** *low quality of evidence*	
41. For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, we suggest either adding dobutamine to norepinephrine or using epinephrine alone.	***Weak,*** *low quality of evidence*	

TEORIJA

- Noradrenalin; α-1 in ß-1adrenergični agonist, ki povzroči vazokonstrikcijo in povišan SAT z minimalnim učinkom na srčno frekvenco
- Dopamin; odvisno od doze deluje na dopaminske-1, α-1 in ß-1 adrenergične receptorje. Ob nižjih odmerkih povzroči vazodilatacijo v ledvičnem, splanhničnem, cerebralnem in koronarnem žilju, ob višanju odmerka pa pride do vazokonstrikcije in povišanja sistemskega upora (α receptorji)
- Noradrenalin > dopamin, povzroča manj aritmij, nižja umrljivost (Avni, 2015)
- Adrenalin; deluje predvsem na ß-1 (pogojeno z odmerkom), ß-2 ter α-1 receptor.

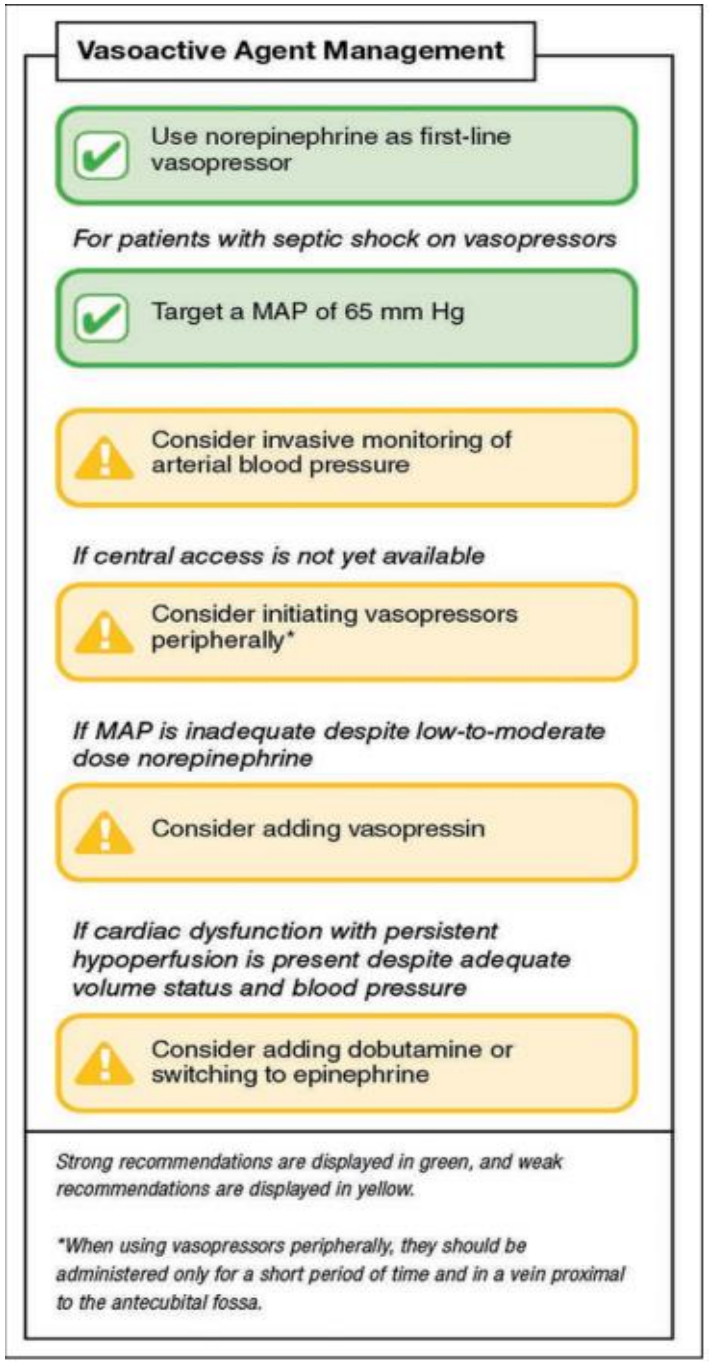
Nizek odmerek: poviša MV, zmanjša sistemski upor žilja in spremenljiv učinek na srednji tlak

Visok odmerek: poviša uporovnost žilja in MV

- Poviša tvorbo laktata preko ß-2 receptorjev v mišicah

- Vazopresin; endogeni peptidni hormon, ki se tvori v hipotalamusu in shranjuje v posteriornem delu hipofize; deluje na V1 receptorje gladkih mišic
- sprva so koncentracije zvišane, nato pa se koncentracija zniža (24-48 ur po začetku šokovnega stanja), bolnik ima „relativno pomanjkanje vazopresina“
- odmerek do 0,03 enote/min, vse kar je višje pomeni več ishemije (koronarno, splanhnično žilje, žilje prstov)
- VANISH študija (vazpresin vs. noradrenalin; brez razlike v 28 dnevni umrljivosti, manj pogoste hemodialize)
- VAST študija (noradrenalin, noradrenalin plus vazopresin; brez izboljšanja 28-dnevne umrljivosti v kombinacijski skupini, VENDAR podskupina, ki je imela manj hud šok (< 15 mcg/min noradrenalin) in je prejemala vazopresin je imela nižjo umrljivost)
- „catecholamin-sparing effect of vasopressin“

- skupina 10 RCT; vazopresin + noradrenalin zmanjša umrljivost v primerjavi z noradrenalinom, ne vpliva na nadomestno ledvično zdravljenje
- kdaj dodati vazopresin?; ko teče noradrenalina 0,25-0,5 mcg/kg/min
- kako zdraviti, če potrebuješ velike odmerke vazopresorja? Nobody knows!
- adrenalin kot tretja linija zdravil, vendar ista prijemališča, ki so nasičena ob uporabi noradrenalina, vazopresin je takrat bolj smiselna alternativa
- adrenalin morda bolj smiseln samo v refraktarnem septičnem šoku ob miokardni disfunkciji
- končno priporočilo: noradrenalin kot prva izbira pred dobutaminom, vazopresinom, adrenalinom, selepresinom ali angiotenzinom II


Vasoactive Agent Management
Use norepinephrine as first-line vasopressor
For patients with septic shock on vasopressors
Target a MAP of 65 mm Hg
Consider invasive monitoring of arterial blood pressure
If central access is not yet available
Consider initiating vasopressors peripherally*
If MAP is inadequate despite low-to-moderate dose norepinephrine
Consider adding vasopressin
If cardiac dysfunction with persistent hypoperfusion is present despite adequate volume status and blood pressure
Consider adding dobutamine or switching to epinephrine
Strong recommendations are displayed in green, and weak recommendations are displayed in yellow.
*When using vasopressors peripherally, they should be administered only for a short period of time and in a vein proximal to the antecubital fossa.

Manj uporabljena zdravila za vzdrževanje krvnega pritiska in njih mesto v zdravljenju:

1. Selepresin: zelo selektiven V1 agonist, deluje na žilno gladko mišičje, ne deluje preko V1b in V2 receptrojev kot vazopresin, zanimiv nekateholaminski vazopresor

Raziskovan v dveh študijah; trije različni odmerki (1,25/2,5/3,75 ng/kg/min) za primeren MAP- odmerek 2,5 ng/kg/min učinkovit za MAP>60 mmHg pri 50% bolnikov v 12h in 70% po 24 urah (v primerjavi z noradrenalinom).

V drugi študiji so dodali še 5 ng/kg/min, s katero so dokazali, da je „less is more“- brez razlik v ciljih raziskave

Nato pa še meta analiza, kjer pa selepresin ni bil nič boljši v primerjavi z noradrenalinom

2. Angiotenzin II; deluje preko renin-angiotenzinskega sistema

Dve študiji; manjša z dvema skupinama je dokazala klinično učinkovitost brez hudih stranskih učinkov, potem pa večja RCT s 344 bolniki z diagnozo vazodilatatornega šoka → brez razlik v smrtnosti v primerjavi z noradrenalinom

3. Terlipresin; prozdravilo, endotelijske peptidaze ga pretvorijo v lizin vazopresin, s "slow release" učinkom in razpolovnim časom 6 ur. Bolj specifičen za V1 receptor, 9 študij, spet brez razlik v umrljivosti, vendar več mezenterialnih ishemij v skupini (3 primeri)

POVZETEK ZA KLINIČNO PRAKSO

1. Poznavanje etiologije in fiziologije šoka
2. Poskusiti s tekočinskim zdravljenjem
3. VENDAR ne čakati predolgo z uvedbo terapije
4. Daš tisto, kar imaš na voljo
5. Smotrno zaporedje; noradrenalin → vazopresin → adrenalin?
   ↳ kortikosteroid


That's all Folks!

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