Vasoactive Agents and Dexmedetomidine

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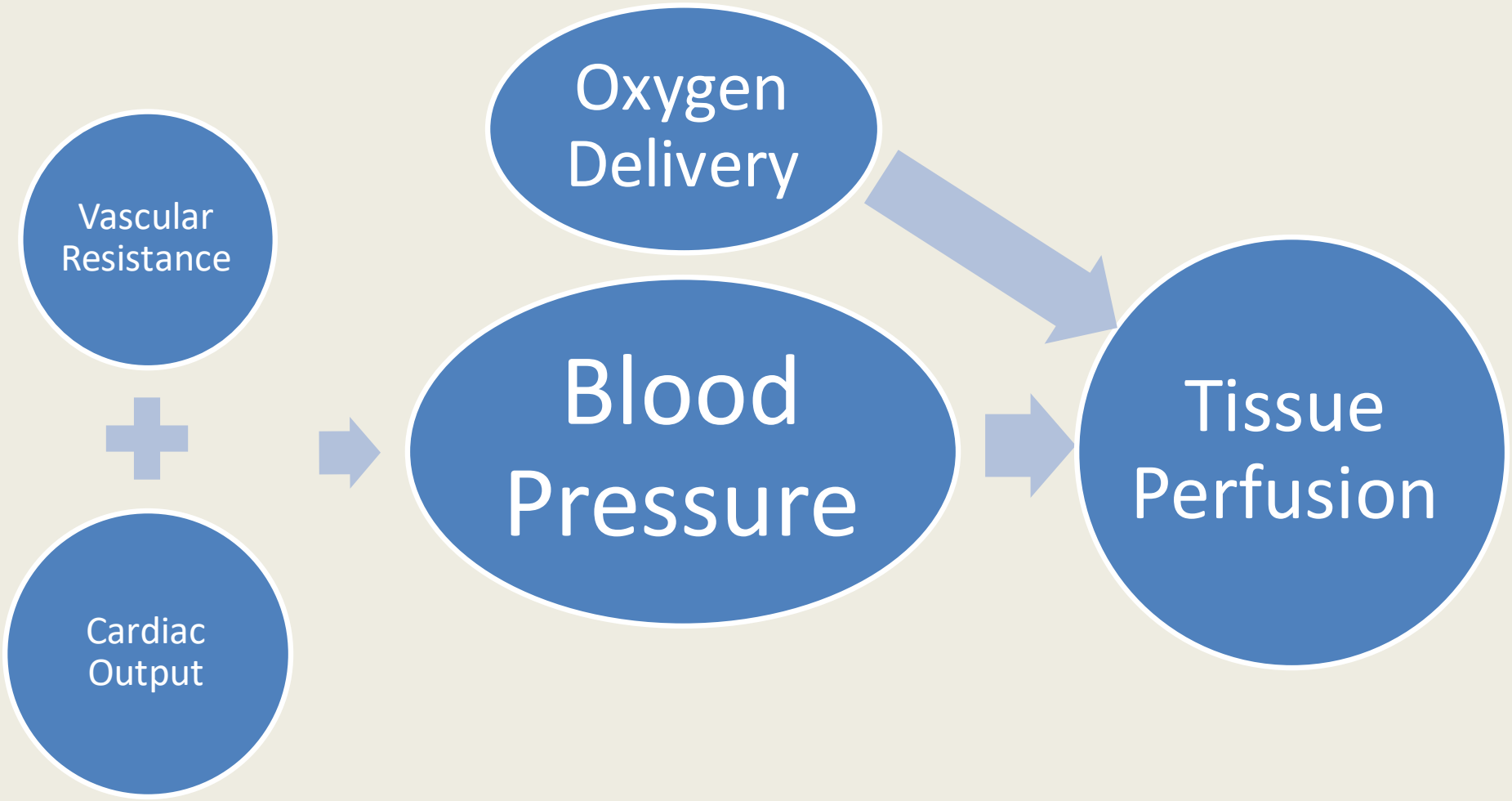
Objectives

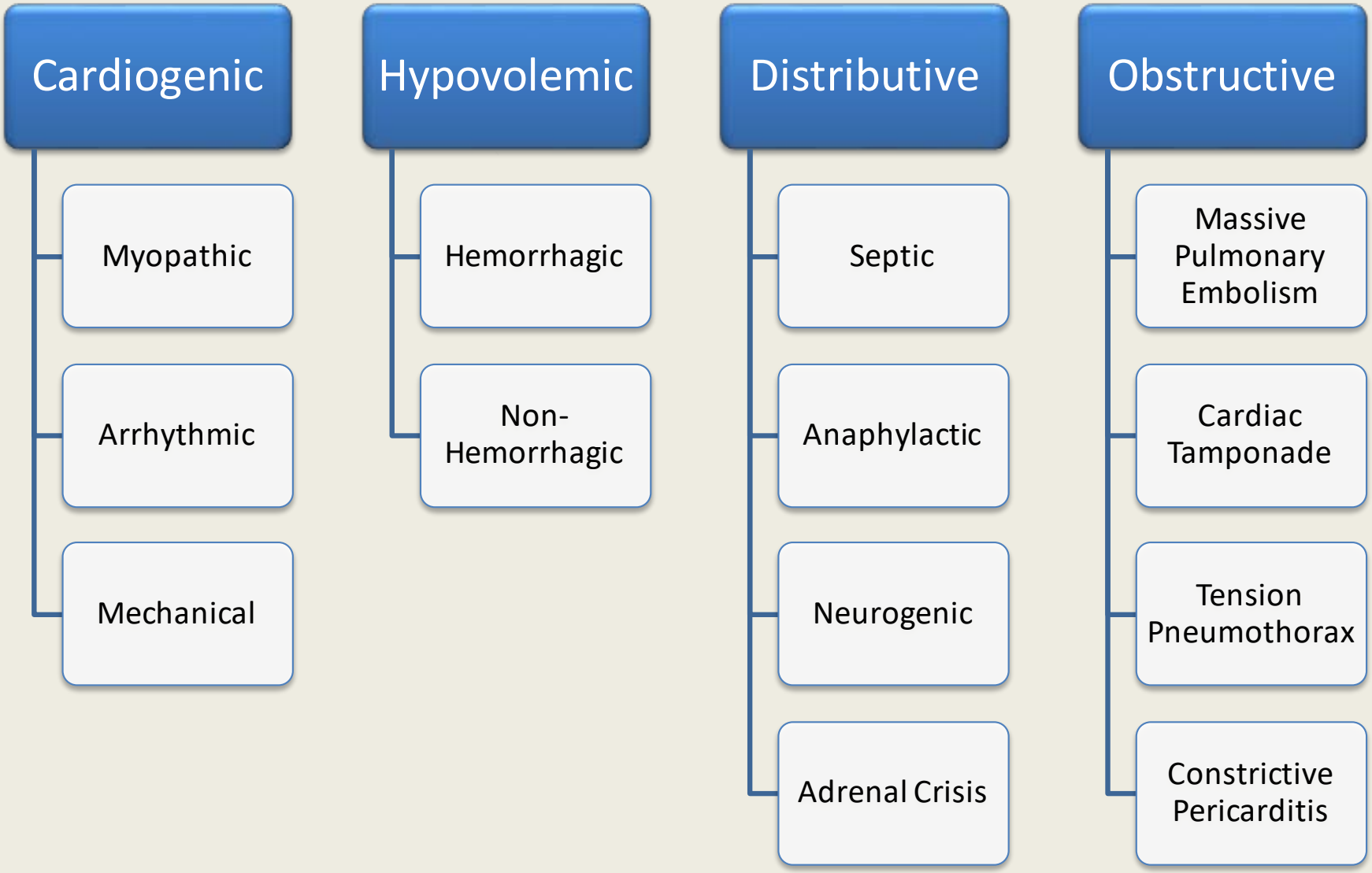
- Differentiate between the various shock states and the role of vasoactive medications in the management of shock
- State the indication, mechanism, dosing, administration and monitoring of vasoactive agents
- Describe broadly the goals of pain, sedation and delirium management in the intensive care unit
- Explain the indication, mechanism, dosing, administration, monitoring and role of dexmedetomidine in the intensive care unit setting

What is Shock?



Jentzer J. *J Cardiovasc Pharmacol Ther*. 2015

Types of Shock

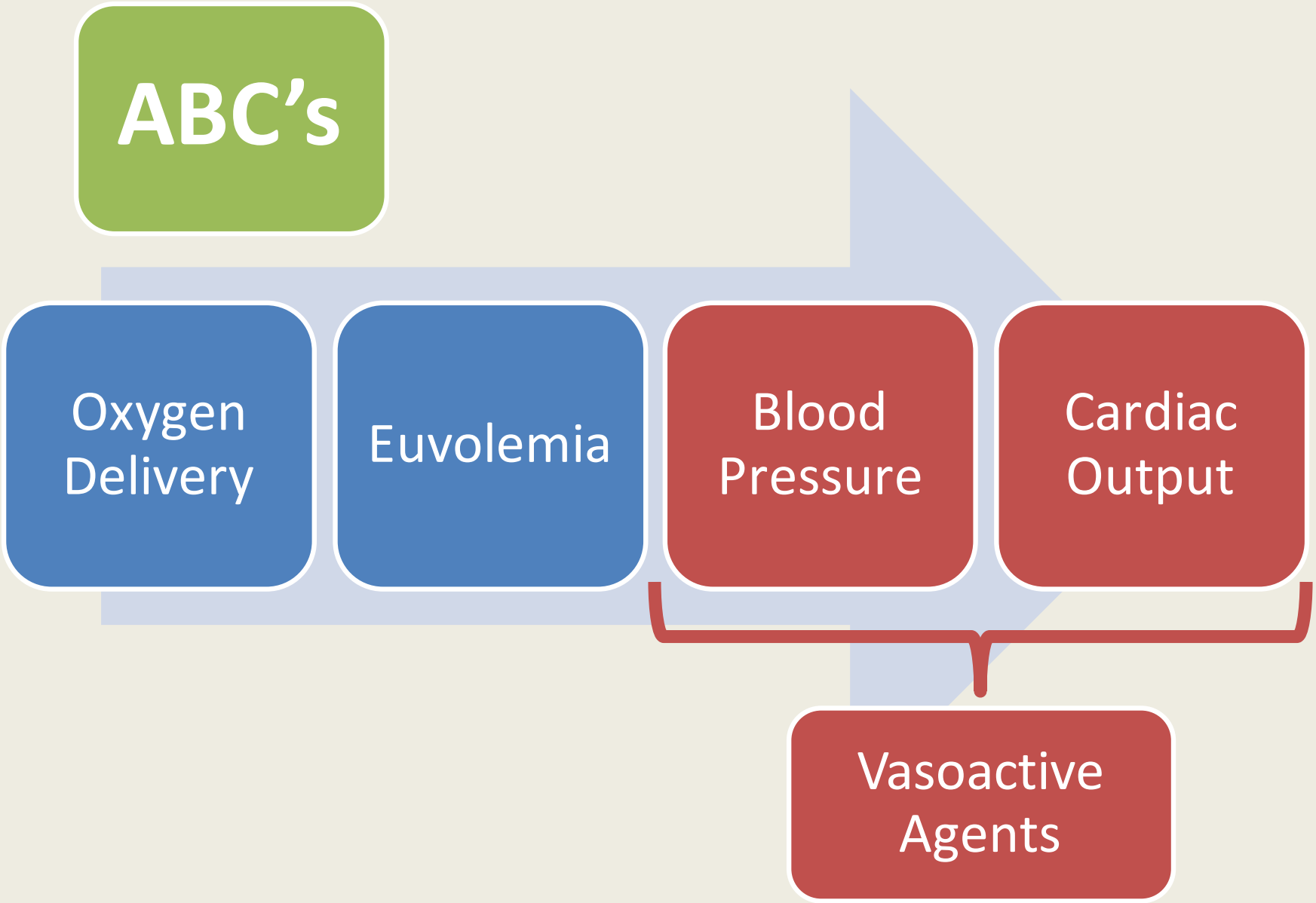


Goals of Shock Resuscitation

- Restoration of tissue perfusion
  - Normal mentation
  - Urine output >0.5 ml/kg/hr
  - Mean Arterial Pressure >65 mmHg
  - Normalized lactic acid

- Treat the cause

Shock Management



Vasoactive Medications

Adrenergic Receptors

- Alpha-1 receptor
  - Constrict arterioles
  - Divert blood TO brain and central arteries
  - Divert blood FROM mesentery, skin, kidneys, peripheral veins

- Beta receptors
  - Beta 1: Increase heart rate (chronotropy) and cardiac contractility (inotropy)
  - Beta 2: Oppose alpha-1 receptors, increase glucose and lactate production

Jentzer J. *J Cardiovasc Pharmacol Ther*. 2015

Other Receptors

- Dopamine Receptor
  - Dilate mesenteric and renal arterioles
  - Increase urine output
- Vasopressin 1a Receptor
  - Constricts blood vessels
- Nitric Oxide Agents
  - Relieves tension on vascular smooth muscle
  - Leads to vasodilation

Jentzer J. *J Cardiovasc Pharmacol Ther*. 2015
Nitroglycerin. Micromedex. 2018.
Nitroprusside. Micromedex. 2018.

Types of Vasoactive Medications

Inoconstrictors

- Constrict vasculature
- Increase heart rate and contractility
- **Norepinephrine, Epinephrine, Dopamine**

Vasoconstrictors

- Constrict vasculature
- No effect on heart
- **Phenylephrine, Vasopressin**

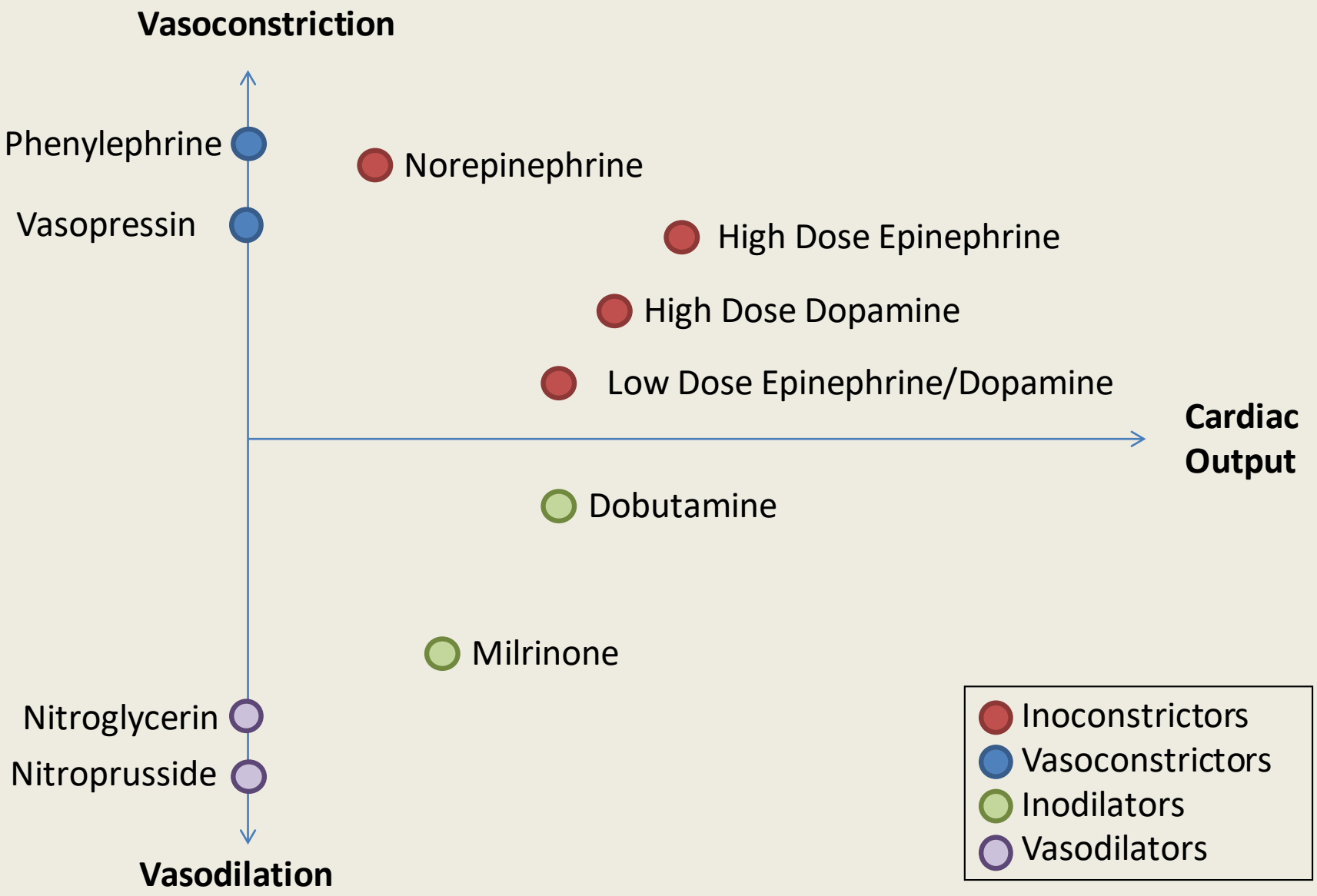
Inodilators

- Dilate vasculature
- Increase heart rate and contractility
- **Dobutamine, Milrinone**

Vasodilator

- Dilate vasculature
- No effect on heart
- **Nitroprusside, Nitroglycerin**

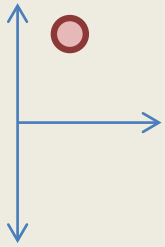
Jentzer J. *J Cardiovasc Pharmacol Ther*. 2015



Jentzer J. *J Cardiovasc Pharmacol Ther*. 2015

Inoconstrictor

Norepinephrine



Alpha 1 (↑BP)	Beta 1 (↑HR)	Beta 2 (↓BP)
+++	+	Minimal

- Norepinephrine gives its own fluid bolus

Medication	Initial Dose	Typical Dose Range	Titration Increment	Weaning Increment
Norepinephrine	2-4 mcg/min	2-20 mcg/min	1-2 mcg/min	1-2 mcg/min

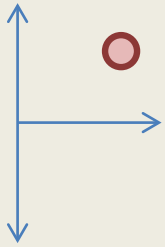
- No max dose

- First line for most types of shock

Jentzer J. *J Cardiovasc Pharmacol Ther*. 2015
Monnet X. *Crit Care Med*. 2011

Inoconstrictor

Epinephrine



Alpha 1 (↑BP)	Beta 1 (↑HR)	Beta 2 (↓BP)
+++	+++	+

- Epinephrine increases lactic acid and glucose

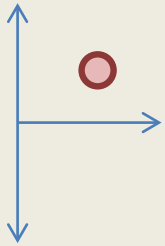
Medication	Initial Dose	Typical Dose Range	Titration Increment	Weaning Increment
Epinephrine	1 mcg/min	1-20 mcg/min	1 mcg/min	1 mcg/min

- No max dose
- 2nd or 3rd line for most types of shock
- First line for anaphylactic shock

Jentzer J. *J Cardiovasc Pharmacol Ther*. 2015.
Levy B. *Shock*. 2008.
Myburgh JA. *Inten Care Med*. 2008.

Inoconstrictor

Dopamine



Dopamine Receptor	Beta 1 (↑HR)	Beta 2 (↓BP)	Alpha 1 (↑BP)
1-5 mcg/kg/min	6-10 mcg/kg/min		>10 mcg/kg/min

- "Renal Dose" dopamine makes monitoring more difficult

Medication	Initial Dose	Typical Dose Range	Titration Increment	Weaning Increment
Dopamine	2-10 mcg/kg/min 5-10 mcg/kg/min (Inotropic) >10 mcg/kg/min (Vasoconstriction)	2-20 mcg/kg/min	2-5 mcg/kg/min	1 mcg/kg/min

- Rarely "First Line"

Jentzer J. *J Cardiovasc Pharmacol Ther*. 2015

Why Not Dopamine?
Mortality

Trial	Dopamine Mortality	Norepinephrine Mortality	P-Value
SOAP I (1058 patients)	42.9%	35.7%	0.021
SOAP II (1679 patients)	50.2%	45.9%	0.07 (Trend)

SOAP II Trial

Cardiogenic Shock

Higher mortality with Dopamine (p=0.03)

2012 Meta-Analysis

Higher mortality with Dopamine vs Norepinephrine

(RR 1.12, CI 1.01-1.20; p = 0.035)

De Backer D. *NEJM*. 2010.
De Backer D. *Crit Care Med*. 2012.
Sakr Y. *Crit Care Med*. 2006.

Why Not Dopamine? Arrhythmias

Trial	Dopamine Arrhythmias	Norepinephrine Arrhythmias	P-Value
SOAP II (1679 patients)	24.1%	12.4%	<0.001
Patel and Colleagues (252 patients)	38%	11.8%	<0.001

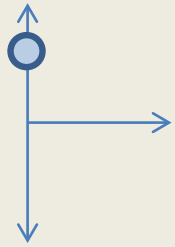
Renal Effects

Variable	Relative Risk (Confidence Interval)
Urine Output (1654 patients)	1.24 (1.14-1.35)
Renal Replacement Therapy (1216 patients)	0.93 (0.76-1.15)

De Backer D. *NEJM*. 2010.
Patel G. *Shock*. 2010.
Friedrich JO. *Ann Intern Med*. 2005.

Vasoconstrictor

Vasopressin



Alpha 1 (↑BP)	Beta 1 (↑HR)	Beta 2 (↓BP)	Vasopressin Receptor
-	-	-	+++

0.01 units/min Vasopressin

=

5 mcg/min Norepinephrine

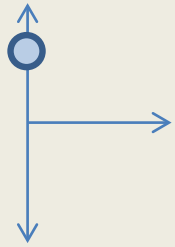
Medication	Initial Dose	Typical Dose Range	Titration Increment	Weaning Increment
Vasopressin	0.01-0.04 units/min	0.01-0.04 units/min	Not generally titrated	Not generally weaned

- Typically added to augment effects of other vasoactive agents

Jentzer J. *J Cardiovasc Pharmacol Ther*. 2015

Vasoconstrictor

Phenylephrine



Alpha 1 (↑BP)	Beta 1 (↑HR)	Beta 2 (↓BP)
+++	-	-

- May cause reflex tachycardia

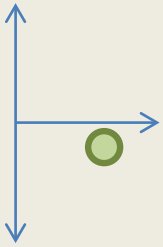
Medication	Initial Dose	Typical Dose Range	Titration Increment	Weaning Increment
Phenylephrine	40-200 mcg/min	20-300 mcg/min	20-40 mcg/min	20-40 mcg/min

- Longer half-life
- Niche: Tachyarrhythmia due to other vasoactive agents

Jentzer J. *J Cardiovasc Pharmacol Ther*. 2015

Inodilator

Dobutamine



Alpha 1 (↑BP)	Beta 1 (↑HR)	Beta 2 (↓BP)
No effect (0-10 mcg/kg/min) ++ (>10-15 mcg/kg/min)	+++	++

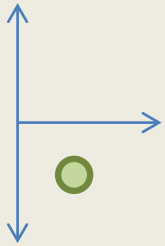
- Increases cardiac contractility
- Variable effect on blood pressure

Medication	Initial Dose	Typical Dose Range	Titration Increment	Weaning Increment
Dobutamine	2.5 mcg/kg/min	2.5-10 mcg/kg/min	2.5 mcg/kg/min	2.5 mcg/kg/min

- Rarely first line (Should be normo-hypertensive)
- Combined with norepinephrine in cardiogenic/mixed shock

Jentzer J. *J Cardiovasc Pharmacol Ther*. 2015

Milrinone



Inodilator

Inhibits Phosphodiesterase

Mimics

Beta 1 (↑HR)	Beta 2 (↓BP)	Alpha 1 (↑BP)
+++	++	-

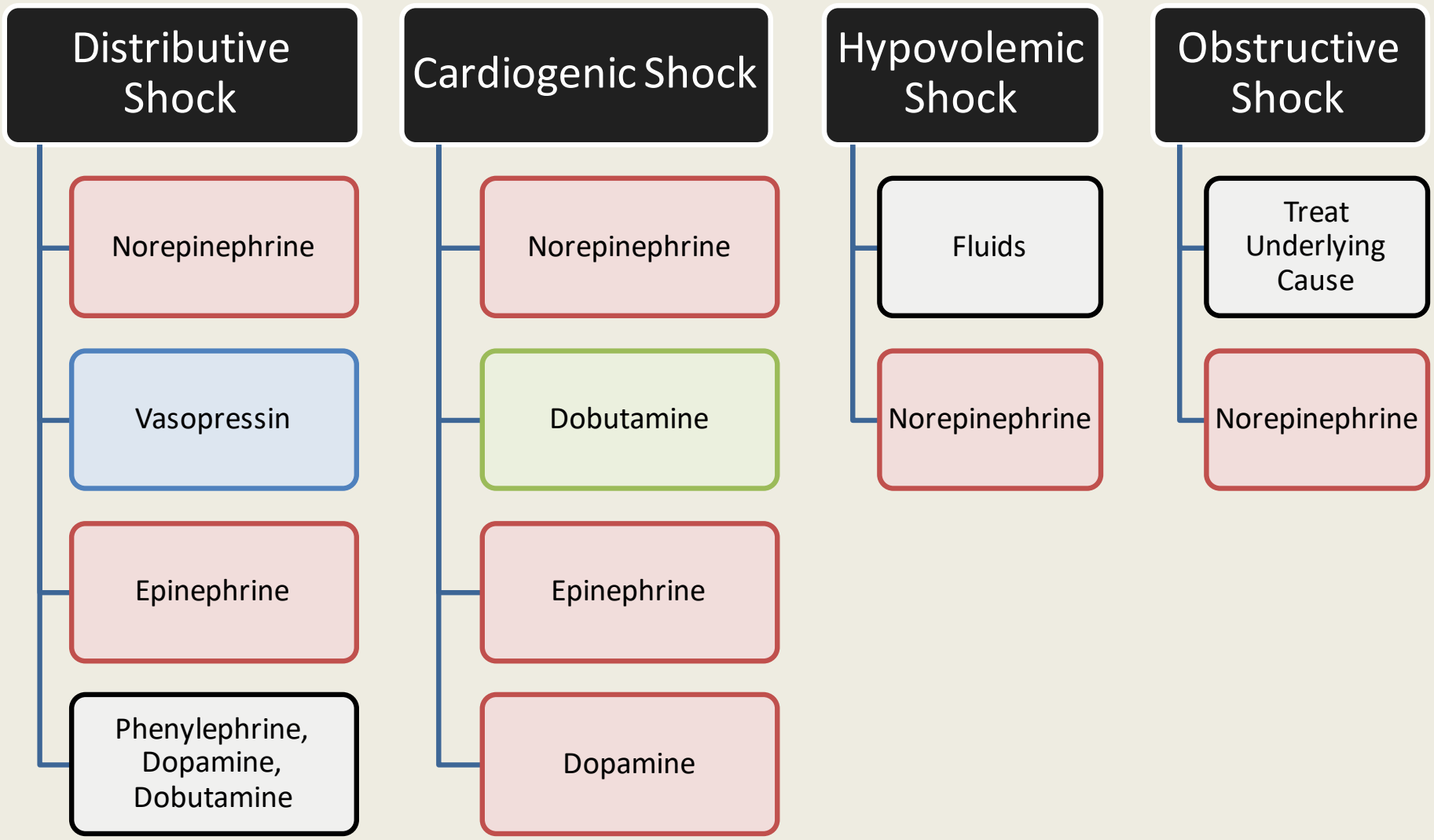
- Increases cardiac contractility
- Pulmonary and systemic vasodilation

Medication	Initial Dose	Typical Dose Range	Titration Increment	Weaning Increment
Milrinone	0.25 mcg/kg/min	0.25-0.75 mcg/kg/min	Dose increases per CO/CI	Not generally weaned

- Long half-life limits use
- Bridge therapy for end-stage heart failure

Jentzer J. *J Cardiovasc Pharmacol Ther*. 2015

Order of Vasoactive Agents



Jentzer J. *J Cardiovasc Pharmacol Ther*. 2015

Monitoring

Tachycardia
Arrhythmia
Hypertension

Vasoconstriction

- Skin
- Mesentery
- Kidneys
- Heart

Extravasation

- Peripheral Administration

Jentzer J. *J Cardiovasc Pharmacol Ther*. 2015

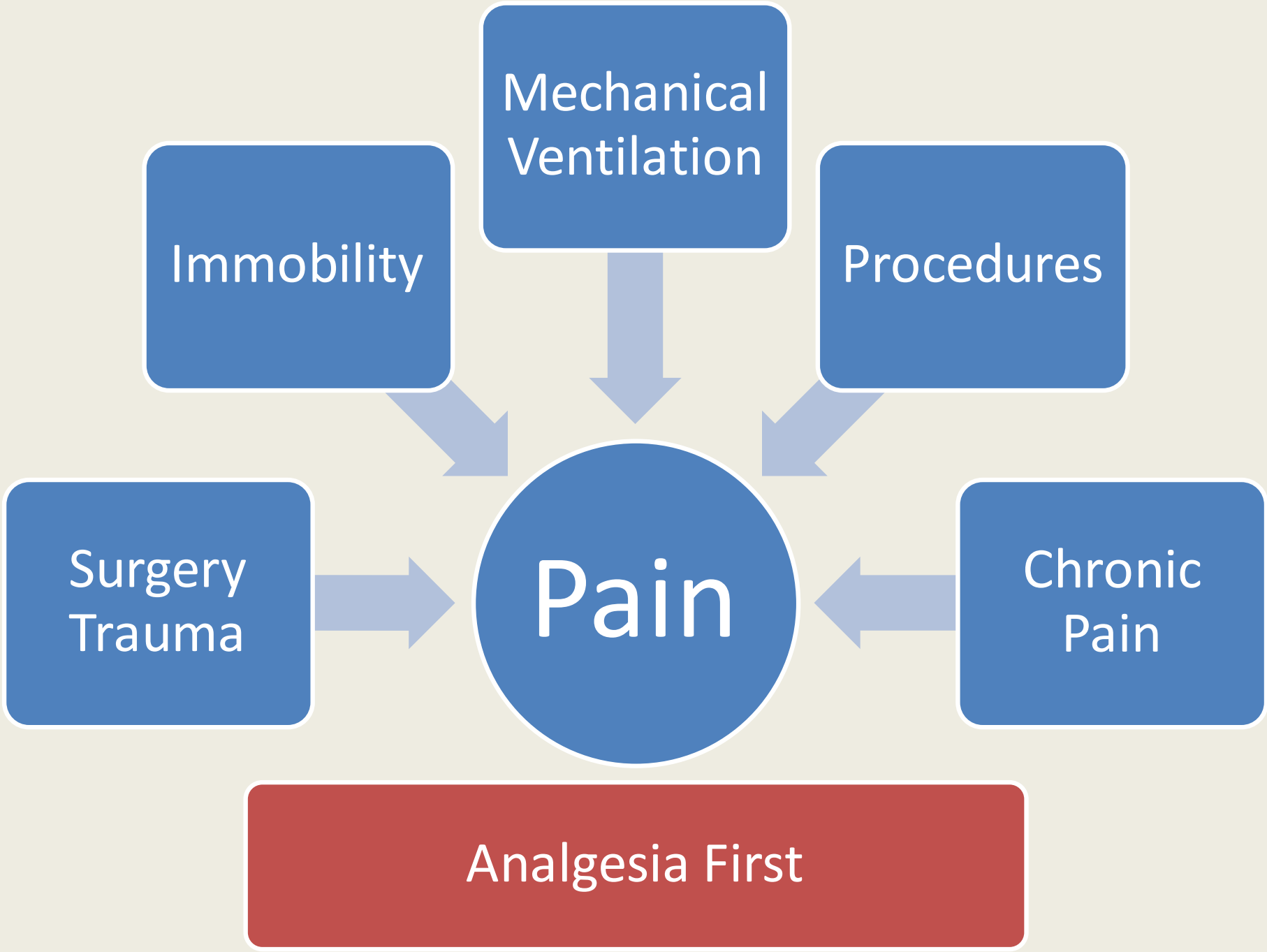
Angiotensin II

- New vasoactive agent available March, 2018
- ATHOS-3 Study. Compared to placebo:
  - Increased blood pressure
  - No difference in mortality
  - Increased thrombotic events
- My Opinion: Not enough evidence to justify use

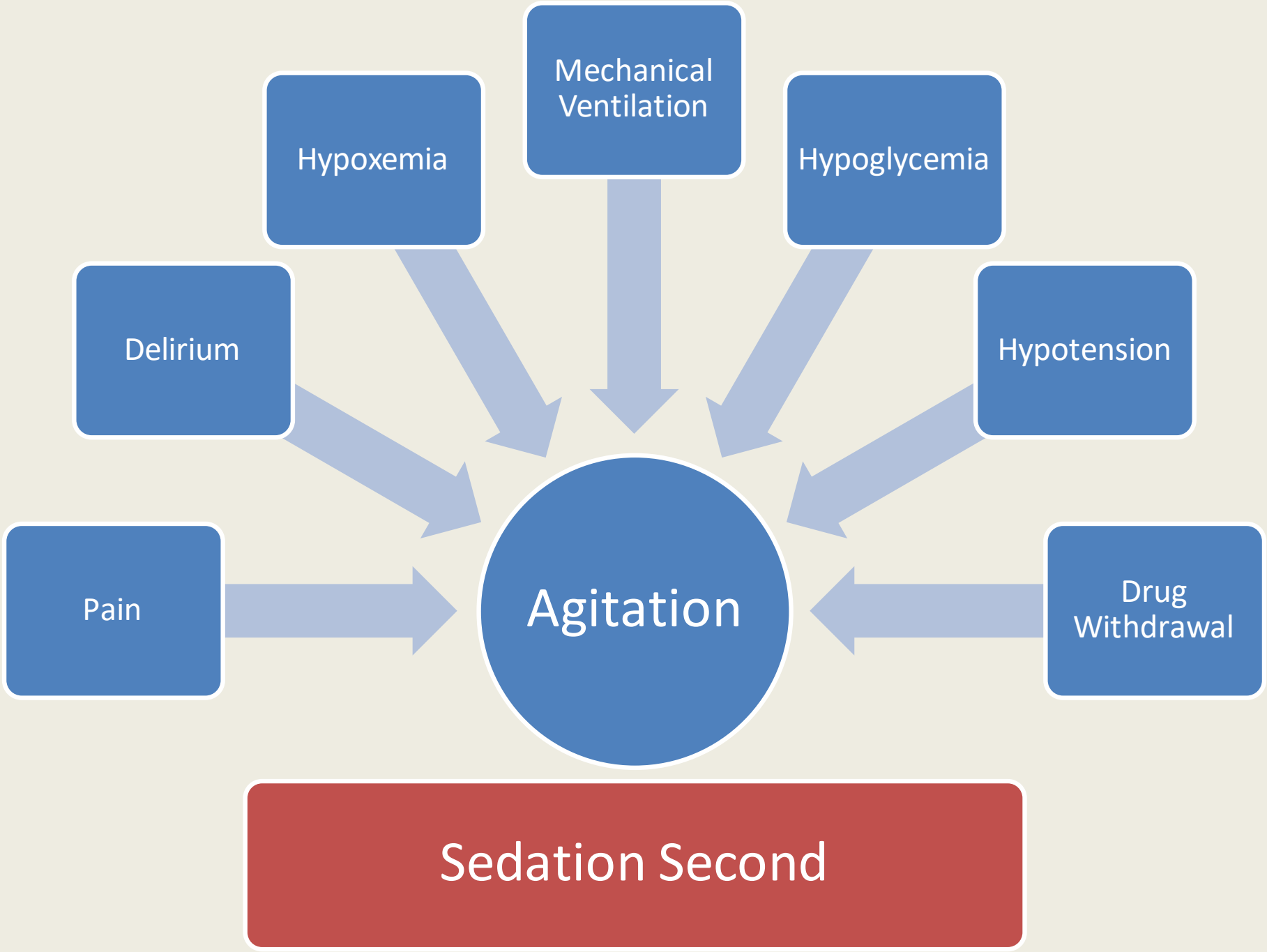
Khanna A. *NEJM*. 2017.
Giapreza [Package Insert]. La Jolla Pharmaceutical Company. 2017.

Sedation for Mechanical Ventilation

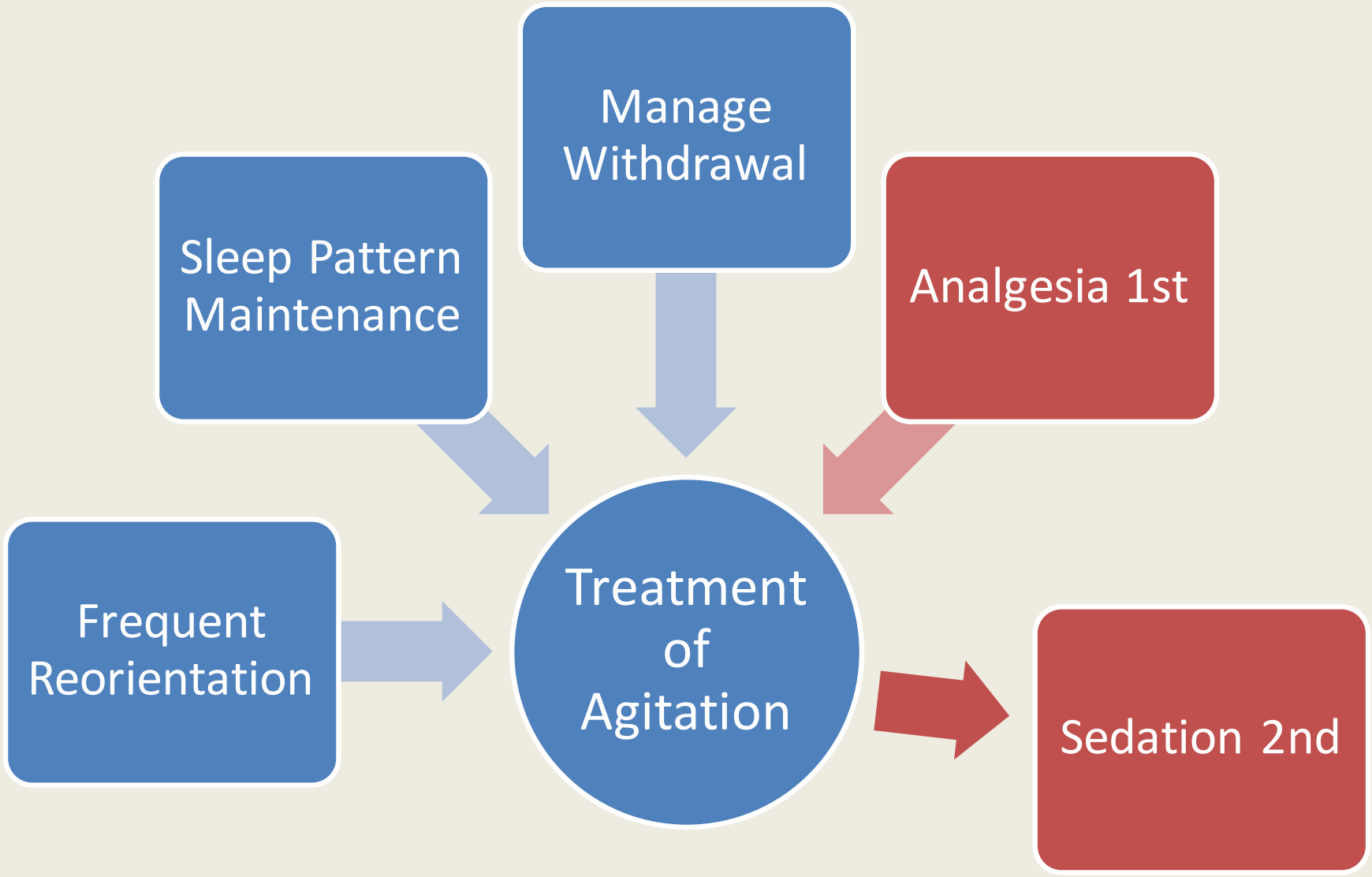
Emphasis on Dexmedetomidine



Barr J. *Crit Care Med*. 2013.

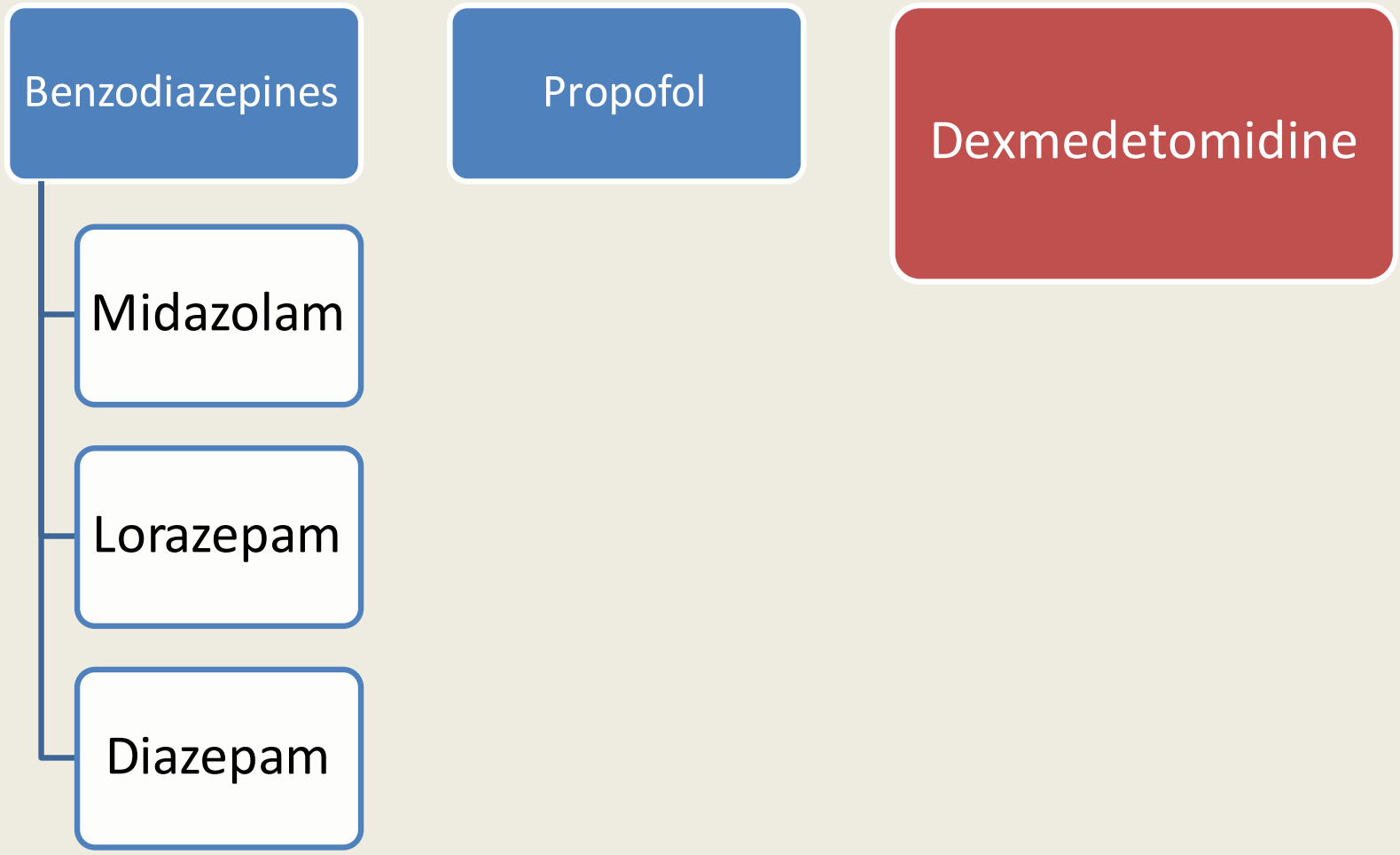


Barr J. *Crit Care Med*. 2013.



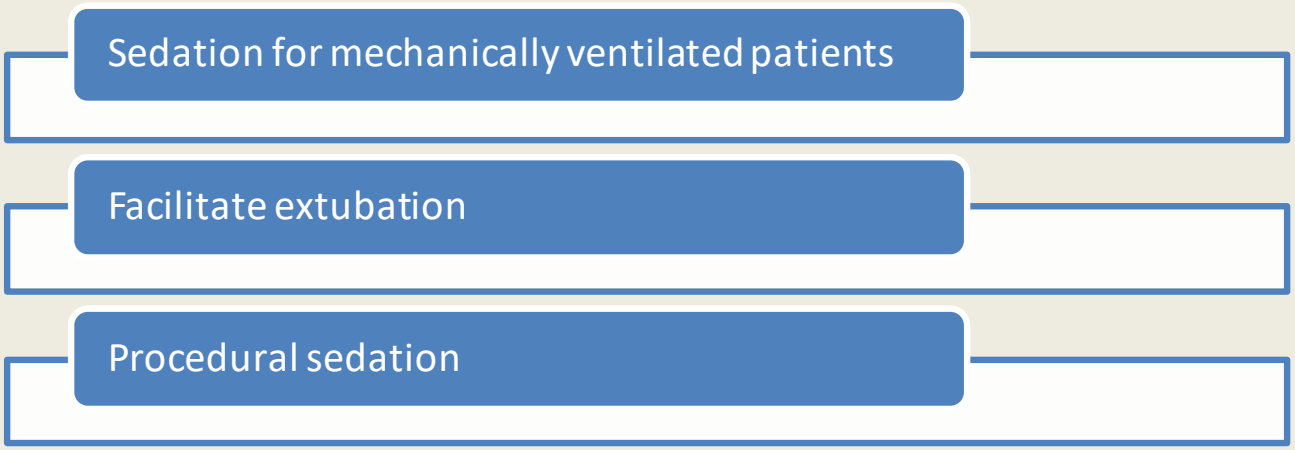
Barr J. *Crit Care Med*. 2013.

Sedatives


Benzodiazepines
Midazolam
Lorazepam
Diazepam
Propofol
Dexmedetomidine

Dexmedetomidine

- Sedative indicated for:



- Alpha-2 adrenergic agonist in central nervous system which produces sedation
  - Minimal risk for respiratory depression
  - May also produce hypotension/bradycardia
  - No anti-seizure activity

Dexmedetomidine Dosing

- Continuous infusion of 0.2-1.5 mcg/kg/hr
  - Typically initiated at 0.2-0.8 mcg/kg/hr
  - Increase/decrease by 0.1-0.2 mcg/kg/hr every 30 minutes
  - Max dose of 1.5 mcg/kg/hr
- Bolus doses generally not recommended
  - High risk of bradycardia and hypotension
  - 0.5-1 mcg/kg over 10 minutes
- Dexmedetomidine does not need to be discontinued prior to extubation

Barr J. *Crit Care Med*. 2013.

AVERA MCKENNAN
ICU INTUBATION
ORDER SET

3 DOSING SCHEMES

Dexmedetomidine Inj (Precedex Inj) 400 MCG
in
Sodium Chloride 0.9% (Ns 100ml) 100 ML
IV titrate TITRATE - Protocol

BOTTLE COMMENT:
Begin if RASS not at goal with analgesia-based program.
Low Dose - For age > 65 years, HR < 70, hypotension, liver dysfunction.
Conc: 4 mcg/ml
Begin at 0.2 to 0.3 mcg/kg/hr; titrate by 0.1 mcg/kg/hr (if RASS +1 to +2) or 0.2 mcg/kg/hr (if RASS > +2) every 25 to 30 minutes to goal RASS. Maximum
...

Edit

PROTOCOL:
Condition Dose/Route Instructions
Starting Rate 0.2 mcg/kg/hr

Titrate to: 1.5 mcg/kg/hr

Dexmedetomidine Inj (Precedex Inj) 400 MCG
in
Sodium Chloride 0.9% (Ns 100ml) 100 ML
IV titrate TITRATE - Protocol

BOTTLE COMMENT:
Begin if RASS not at goal with analgesia-based program.
Moderate Dose - For age 45 to 65 years, HR 70 to 90, normotensive.
Conc: 4 mcg/ml
Begin at 0.4 to 0.6 mcg/kg/hr; titrate by 0.1 mcg/kg/hr (if RASS +1 to +2) or 0.2 mcg/kg/hr (if RASS > +2) every 25 to 30 minutes to goal RASS. Maximum
...

Edit

PROTOCOL:
Condition Dose/Route Instructions
Starting Rate 0.4 mcg/kg/hr

Titrate to: 1.5 mcg/kg/hr

Dexmedetomidine Inj (Precedex Inj) 400 MCG
in
Sodium Chloride 0.9% (Ns 100ml) 100 ML
IV titrate TITRATE - Protocol

BOTTLE COMMENT:
Begin if RASS not at goal with analgesia-based program.
High Dose - For age < 45 years, HR > 90, hypertensive, substance withdrawl.
Conc: 4 mcg/ml
Begin at 0.7 to 0.8 mcg/kg/hr; titrate by 0.1 mcg/kg/hr (if RASS +1 to +2) or 0.2 mcg/kg/hr (if RASS > +2) every 25 to 30 minutes to goal RASS. Maximum
...

Edit

PROTOCOL:
Condition Dose/Route Instructions
Starting Rate 0.7 mcg/kg/hr

Titrate to: 1.5 mcg/kg/hr

Monitoring

- Continuous cardiac monitor
- RASS Sedation Scale (Typical goal of 0 to -1)
- Hypotension
- Bradycardia
- Withdrawal symptoms if on for several days
  - Nausea, vomiting, agitation, tachycardia, hypertension

Practical Uses for Dexmedetomidine

Light Sedation for Mechanical Ventilation

Facilitate Extubation

Adjunct for Severe Alcohol Withdrawal

- MUST be used with Benzodiazepines!!

Sedative with Potential for Lower Risk of Delirium

Further Readings

Vasoactive Medications

1. Jentzer JC, Coons JC, Link CB and Schmidhofer M. Pharmacotherapy update on the use of vasopressors and inotropes in the intensive care unit. *J of Cardiovasc Pharmacol and Ther*. 2015;20(3):249-60.
2. Vincent JL, De Backer D. Circulatory shock. *N Engl J Med.* 2013;369(18):1726-34.

Pain, Sedation, Delirium

1. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *CCM*. 2013;41(1):263-306.

Thank You!

References

Vasopressors

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References

Pain, Sedation, Delirium

1. **Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med*. 2013;41(1):263-306**.
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