**Introduction**

Hemodynamic monitoring and management are critical in caring for critically ill patients. Hemodynamic parameters such as blood pressure, cardiac output, and systemic vascular resistance guide diagnosis and treatment of shock states and influence outcomes. While historically performed intermittently, advancements in technology have enabled continuous or semi-continuous monitoring.

As experts in pharmacology and pharmacokinetics, pharmacists play an important role in helping optimize hemodynamic management. This involves assisting with appropriate vasopressor selection, dosing, titration, and monitoring of effects. Pharmacists can also help recognize and address adverse drug events related to vasoactive medications.

Key aspects that will be covered in this subtopic include:

* Interpretation of hemodynamic data from monitoring devices and markers of perfusion
* Strategies to improve tissue perfusion and oxygenation
* Pharmacologic management with vasopressors, inotropes, and vasodilators
* Use of hemodynamic data to guide resuscitation in shock states
* Challenges and controversies related to hemodynamic monitoring and management

The goal is to provide a practical overview of concepts for pharmacists to understand and apply at the point of care when caring for critically ill patients requiring hemodynamic support.

**Clinical Presentation**

Hemodynamic monitoring is a critical tool in caring for patients at risk of cardiovascular instability or shock. It allows for early recognition of inadequate tissue perfusion and tailored interventions to restore perfusion before end-organ dysfunction occurs.

Who Requires Hemodynamic Monitoring

* Elderly patients, who have impaired cardiovascular reserve
* Patients with chronic conditions affecting the heart, lungs, kidneys or vascular system
* Critically ill patients, especially those requiring vasoactive medications or mechanical ventilation
* Patients undergoing major surgery under general anesthesia

Recognizing Hemodynamic Instability

* Vital signs:
  + Hypotension (systolic BP <90 mmHg, MAP <65 mmHg)
  + Tachycardia (HR >120 bpm)
* Reduced urine output (<0.5 mL/kg/hr)
* Mental status changes: confusion, lethargy
* Weakness, dizziness, syncope
* Cool, pale, clammy skin
* Delayed capillary refill

Causes of Hemodynamic Instability

* Sepsis and septic shock
* Cardiogenic shock (MI, decompensated heart failure)
* Hypovolemic shock (hemorrhage, dehydration)
* Anaphylactic shock
* Adverse medication effects

The Pharmacist's Role

* Assist with appropriate selection of vasoactive medications
* Recommend dosing and titration strategies
* Monitor efficacy and safety of therapies
* Recognize and manage adverse drug events

In summary, hemodynamic monitoring allows for early recognition of shock states and guided management to restore adequate tissue perfusion. As medication experts, pharmacists play a key role in the interprofessional team caring for critically ill patients requiring hemodynamic support.

**Foundations of Hemodynamic Monitoring**

**A. Basic Hemodynamic Parameters**

Understanding the core hemodynamic parameters and their physiological significance is crucial for interpreting monitoring data and assessing cardiovascular status.

Blood Pressure

* Systolic pressure reflects peak pressure during ventricular contraction
* Diastolic pressure represents lowest pressure during ventricular relaxation
* Mean arterial pressure (MAP) approximates average arterial pressure over one cardiac cycle and correlates directly with organ perfusion

Heart Rate

* Heart rate drives cardiac output as one determinant of stroke volume
* Tachycardia occurs to compensate for reduced stroke volume in shock states

Stroke Volume

* The blood volume ejected from the ventricle with each contraction
* Affected by preload, afterload, contractility, heart rate

Cardiac Output

* The volume of blood pumped by the ventricle per minute (HR x SV)
* Represents systemic blood flow and oxygen delivery to tissues

Systemic Vascular Resistance

* Resistance to blood flow through the systemic vasculature
* Affected by vessel diameter, blood viscosity, vessel length

Central Venous Pressure

* Right atrial pressure which correlates with right ventricular preload
* Reflects intravascular volume status

B. Normal Reference Ranges

While patient-specific factors affect hemodynamic parameters, general reference ranges are:

* MAP: 70-105 mmHg
* Cardiac Output: 4-8 L/min
* Systemic Vascular Resistance: 800-1200 dynes/sec/cm5
* Central Venous Pressure: 6-12 mmHg

C. Physiological Significance

The physiological significance of each parameter can guide clinical decision making:

* Blood Pressure reflects tissue perfusion adequacy
* Heart Rate compensates for reduced stroke volume in shock states
* Stroke Volume represents cardiac contractility and volume responsiveness
* Cardiac Output indicates overall systemic blood flow and oxygen delivery
* Systemic Vascular Resistance impacts cardiac afterload
* Central Venous Pressure estimates volume status and preload

D. Frank-Starling Relationship

The Frank-Starling relationship describes the intrinsic relationship between ventricular preload and stroke volume. As preload increases, ventricular stretch and contractile strength increase up to an optimal point. This intrinsic property allows the heart to respond to changes in venous return.

E. Determinants of Stroke Volume and Cardiac Output

* Preload: End-diastolic ventricular volume (influenced by CVP)
* Afterload: Arterial pressure against which the ventricle must eject (influenced by SVR)
* Contractility: Inotropic state of the myocardium
* Heart rate: The frequency of ventricular contractions

F. Clinical Relevance

Thoroughly understanding these fundamental parameters provides the basis for selecting appropriate monitoring modalities, interpreting data, diagnosing shock states, and guiding hemodynamic resuscitation efforts.

**Advanced Hemodynamic Monitoring**

While non-invasive monitoring provides valuable intermittent data, direct and continuous cardiovascular measurements are often needed to effectively manage critically ill patients.

A. Arterial Catheter

Involves percutaneous cannulation of a peripheral artery, most commonly the radial. The catheter is connected to a pressure transducer to provide the following:

* Continuous, accurate blood pressure monitoring
* Analysis of arterial blood gases
* High-fidelity waveform analysis
* Permits minimally invasive cardiac output monitoring when paired with dedicated software

Key advantages over non-invasive methods include:

* Precision - arterial waveform has a much higher degree of accuracy than non-invasive cuff measurements
* Continuous data - provides real-time blood pressure trends versus intermittent non-invasive readings
* Waveform analysis - assesses abnormal pressure wave reflections and derived parameters

Risks include limb ischemia, thrombosis, bleeding, and infection. An Allen's test should be performed prior to cannulation to confirm dual radial artery supply. Ultrasound guidance improves safety.

B. Central Venous Catheter

Permits the following measurements via a multi-lumen catheter placed in a central vein (internal jugular, subclavian, femoral):

* Central venous pressure monitoring
* Administration of fluids, medication, nutrition
* Obtaining venous blood samples
* Monitoring central venous oxygen saturation

Key advantages:

* Enables CVP monitoring as an estimate of volume status and right heart preload
* Allows infusion of irritant or high-osmolar solutions well-tolerated in large central veins
* Permits sampling of venous blood gas tensions

Risks include pneumothorax, vascular injury, thrombosis, and infection. Ultrasound guidance is recommended to improve safety.

C. Pulmonary Artery Catheter

Involves inserting a specialized catheter to measure key parameters:

* Pulmonary artery pressures
* Right atrial pressure
* Cardiac output using thermodilution
* Mixed venous oxygen saturation

This comprehensive hemodynamic profile enables detailed cardiovascular assessment.

Catheter setup:

* Pressure transducers for continuous monitoring of RA, PA, and pulmonary capillary wedge (PCWP) pressures
* Thermistor at catheter tip connects to computer for thermodilution cardiac output measurements
* Fiberoptic connector permits continuous SvO2 monitoring

Key advantages:

* Comprehensive dynamic cardiovascular data
* Cardiac output monitoring avoids need for indirect surrogate calculations
* Mixed venous oxygen saturation reflects global tissue oxygen extraction

Risks include arrhythmias, valvular or vascular injury, thrombosis, infection, and pulmonary artery rupture. Expertise is needed for insertion and data interpretation.

D. Miniaturized Pulmonary Artery Catheter

Provides measurements similar to traditional pulmonary artery catheters but utilizes a smaller diameter catheter inserted via the internal jugular vein.

Key advantages compared to traditional pulmonary artery catheters:

* Lower risk of complications
* Better tolerated by patients
* Can remain in place for longer durations
* Eliminates catheter balloon inflation which can irritate and damage vessel lining or cardiac structures

E. PiCCO Monitoring System

PiCCO utilizes a specialized arterial catheter connected to a monitor providing continuous data:

* Cardiac output monitoring via transpulmonary thermodilution
* Global end-diastolic volume as a marker of cardiac preload
* Extravascular lung water to assess pulmonary edema
* Stroke volume variation to predict fluid responsiveness

This minimally invasive approach provides comprehensive volumetric, hemodynamic, and respiratory data. Key advantages over pulmonary artery monitoring include avoiding catheter-related complications. However, the proprietary system has a high upfront cost.

F. Echocardiography

Transthoracic or transesophageal echocardiography provides non-invasive, dynamic structural and functional cardiovascular assessment.

Parameters assessed:

* Cardiac chamber size, hypertrophy, wall motion abnormalities
* Valvular structure and function
* Ventricular systolic function
* Pericardial effusions, cardiac tamponade
* Intravascular volume status
* Cardiac output assessment

Advantages include direct visualization, quantitative data, portability, and versatility. Limitations include reliance on operator experience and intermittent sampling.

G. Near-Infrared Spectroscopy

Non-invasive technology utilizing infrared light to measure tissue oxygen saturation (StO2). Can be used to monitor thenar eminence StO2 as an indicator of peripheral perfusion.

While not a direct substitute for central measurements, may provide insight on microcirculatory flow in peripheral vascular beds. Portable for continuous, point-of-care monitoring.

H. Limitations of Advanced Monitoring

* Invasive modalities have associated risks
* Require expertise for appropriate use and data interpretation
* Provide intermittent versus continuous data depending on modality
* No single parameter gives full picture so composite assessment essential
* Do not replace clinical judgement and integration of all available data

**Dynamic Predictors of Fluid Responsiveness**

Static parameters like CVP are poor predictors of whether a patient will respond to fluid bolus with an increase in stroke volume or cardiac output. Dynamic indices that account for cardiopulmonary interactions tend to better predict volume responsiveness.

A. Stroke Volume Variation

* Cyclical variation in stroke volume during the respiratory cycle
* Calculated using the difference between maximum and minimum stroke volumes divided by their mean
* Value >10% suggests fluid responsiveness in mechanically ventilated patients
* As preload dependence decreases, SVV declines as well

B. Pulse Pressure Variation

* Cyclical variation in pulse pressure during the respiratory cycle
* Calculated using difference between maximal and minimal pulse pressure divided by their mean
* Value >13% suggests fluid responsiveness if no arrhythmias present
* Similar principle to SVV - greatest changes occur when preload responsive

C. Passive Leg Raise

* Measures change in stroke volume or cardiac output with leg elevation to 45 degrees
* Augments venous return and assesses position on Frank-Starling curve
* Increase >10% suggests fluid responsiveness

D. Inferior Vena Cava Distensibility

* Assessed via ultrasound evaluating IVC diameter changes during respiration
* Diameter variation >15% with sniff suggests fluid responsiveness

E. Limitations of Dynamic Predictors

* Require controlled mechanical ventilation with adequate tidal volume
* Least reliable in spontaneously breathing patients
* Need rapid fluid administration capability if test is positive
* Do not provide definitive indication for giving fluids - clinical context essential

**Fluid Resuscitation Endpoints**

The optimal endpoints for fluid resuscitation are controversial given lack of concrete supporting evidence. Experts have proposed considering parameters such as:

* Mean arterial pressure ≥ 65 mmHg
* Urine output ≥ 0.5 ml/kg/hr
* Normalization of heart rate
* Lactate < 2 mmol/L in sepsis
* CVP 8-12 mmHg
* ScvO2 >70% or SvO2 >65%

However, the appropriateness of any single parameter is debated. Trends are likely more useful than absolute thresholds. The overall clinical context guides whether endpoints reflect adequate resuscitation. No definitive recommendations exist on duration of initial fluid resuscitation.

**Pharmacotherapy in Shock**

Once shock is recognized, pharmacologic therapies are instituted alongside fluid resuscitation to improve tissue perfusion by optimizing cardiovascular function.

A. Vasopressors

Vasopressors are the mainstay of managing distributive shock when fluids fail to restore blood pressure and organ perfusion. They work by:

* Stimulating alpha-1 receptors to induce vasoconstriction
* Increasing systemic vascular resistance and mean arterial pressure

1. Norepinephrine

* Stimulates alpha-1 and beta-1 receptors but alpha effects predominate
* First-line vasopressor of choice in most guidelines
* Dosing: Start at 0.01-0.03 mcg/kg/min, titrate to MAP target (~65 mmHg)
* Can decrease cardiac output at higher doses by increasing afterload

1. Vasopressin

* Causes vasoconstriction by stimulating V1 receptors on vascular smooth muscle
* Often used as adjunctive agent in septic shock refractory to norepinephrine
* Dosing: 0.01 - 0.04 units/min is common target dose range

1. Dopamine

* Dose-dependent effects:
  + Low dose (0.5-4 mcg/kg/min): Vasodilation from D1 receptor activation
  + Medium dose (4-10 mcg/kg/min): Beta-1 effects increase contractility
  + High dose (>10 mcg/kg/min): Alpha stimulation raises SVR
* Not considered first-line agent due to arrhythmogenic potential
* Dosing: 2-20 mcg/kg/min titrated to clinical response

1. Epinephrine

* Has alpha and beta effects based on dose
* Predominant beta effects at lower doses improving contractility
* Potent vasoconstriction from alpha effects at higher doses
* Second-line agent for septic shock refractory to norepinephrine
* Dosing: Start at 0.05-0.1 mcg/kg/min, titrate up to ~2 mcg/kg/min

1. Phenylephrine

* Selective alpha-1 agonist with potent vasoconstriction
* Used for neurogenic/anesthesia-induced hypotension unresponsive to fluids
* Reflex bradycardia can occur, careful titration needed
* Dosing: 50-180 mcg/min infusion, 50-200 mcg IV push doses

Special Considerations for Vasopressors:

* Titrate to minimum dose necessary to maintain perfusion targets
* Monitor for cardiac ischemia and limb ischemia
* Avoid extravasation which can cause severe tissue necrosis
* Do not rely solely on blood pressure - assess end-organ perfusion

B. Inotropes

Inotropes improve myocardial contractility and cardiac output in cardiogenic shock or heart failure exacerbations characterized by:

* Reduced cardiac output with adequate filling pressures
* Elevated systemic vascular resistance

They work by:

* Increasing intracellular cAMP or calcium levels
* Enhancing myocardial contractile force

1. Dobutamine

* Direct-acting beta-1 receptor agonist
* Increases inotropy with minimal effects on heart rate or blood pressure
* Dosing: 2-20 mcg/kg/min titrated to clinical response

1. Milrinone

* Inhibits phosphodiesterase III preventing cAMP breakdown
* Improves contractility with vasodilatory effects from cAMP buildup
* Dosing: 25-75 mcg/kg load, then 0.375-0.75 mcg/kg/min infusion

1. Levosimendan

* Calcium sensitizer that improves contractility without increasing intracellular calcium
* Also causes vasodilation through ATP-sensitive potassium channels
* Dosing: 12-24 mcg/kg load, then 0.05-0.2 mcg/kg/min infusion
* Not available in the USA

Special Considerations for Inotropes:

* Weigh benefits versus risks of increased myocardial oxygen demand
* Monitor for hypotension, arrhythmias
* Avoid reliance on blood pressure changes to gauge efficacy
* Assess cardiac output and clinical endpoints of efficacy

C. Combination Therapy

* Pairing a vasopressor and inotrope is useful for shock states with both distributive and cardiogenic components
* This includes septic cardiomyopathy where systolic function is impaired
* Typical combinations are norepinephrine with dobutamine or milrinone
* Allows independent titration of agents to MAP versus cardiac output targets

D. Considerations in Cardiogenic Shock

* Avoid vasopressors if possible given detrimental increases in afterload
* Norepinephrine only if needed for profound hypotension despite inotropes
* Milrinone and dobutamine preferred for augmenting contractility
* Judicious fluids for hypovolemia but avoid volume overload
* Concomitant diuretic therapy to optimize volume status
* Target MAP ~65 mmHg or higher if chronic hypertension

VII. Conclusion

Advanced hemodynamic monitoring provides vital data to recognize and classify shock states, guide resuscitation efforts, and optimize cardiovascular performance. However, an understanding of normal physiology along with the limitations of monitoring tools is essential to effectively interpret data. Likewise, expertise in cardiovascular pharmacotherapy enables clinicians to strategically employ fluids, vasoactive medications, and inotropes to improve tissue perfusion in various shock states. Ultimately, hemodynamic management requires an integrated approach using clinical judgement to synthesize all available data points and tailor therapy to the individual patient.

## Key Guidelines and Evidence

* The Surviving Sepsis Campaign provides evidence-based guidelines on the management of sepsis and septic shock. Key recommendations related to hemodynamic monitoring and management include:
  + Dynamic parameters like passive leg raise should be used to predict fluid responsiveness when available (weak recommendation, low quality evidence)
  + Norepinephrine is recommended as the first-line vasopressor (strong recommendation, high quality evidence)
  + Epinephrine may be added to norepinephrine for refractory hypotension (weak recommendation, moderate quality evidence)
  + Dobutamine is suggested in patients with persistent cardiogenic shock (weak recommendation, low quality evidence)
* The ALBIOS trial found no difference in 90-day mortality between resuscitation with albumin and crystalloids in patients with severe sepsis. However, the albumin group required less renal replacement therapy.1
* The CLASSIC trial found no difference in 28-day mortality between hydroxyethyl starch solutions and Ringer's lactate for fluid resuscitation in patients with sepsis. However, the starch group had higher rates of renal failure requiring dialysis.2
* A meta-analysis demonstrated a relationship between central venous oxygen saturation (ScvO2) and mortality in patients with sepsis. Achieving a ScvO2 >70% was associated with decreased mortality.3

## Clinical Scenarios

A 45-year old female is admitted to the medical ICU for severe sepsis from pneumonia. Despite adequate initial fluid resuscitation, she remains hypotensive requiring escalating doses of norepinephrine to maintain her blood pressure. You are asked to evaluate whether advanced hemodynamic monitoring may be beneficial.

* What advanced hemodynamic monitoring technique would provide the most useful data to guide further resuscitation efforts in this patient?

Pulmonary artery catheterization permits continuous monitoring of key parameters such as cardiac output, mixed venous oxygen saturation, and pulmonary pressures. This data would help determine if cardiac dysfunction is contributing and guide further fluid, inotrope, or vasopressor management.

A 55-year old male with a history of hypertension and diabetes is admitted to the surgical ICU following emergent bowel resection for mesenteric ischemia. His blood pressure is well-controlled on his home medications. On post-operative day 3, he becomes acutely hypotensive and tachycardic. His surgical site is clean and he has good urine output.

* What is the likely cause of this patient's hypotension based on the clinical scenario?

This presents as distributive shock likely from systemic inflammation in the post-operative period. Sepsis from an alternate source such as the surgical site, lungs, or urinary tract is less likely given the clinical stability in the prior days. Fluid resuscitation and empirical antibiotics are indicated.

## Tips for Board Exam Questions

* Know the normal reference ranges for key hemodynamic parameters including cardiac output, systemic and pulmonary pressures, and target oxygen saturation values.
* Recognize distributive, cardiogenic, obstructive and hypovolemic shock based on clinical presentation and hemodynamic findings.
* Understand the mechanisms of action, indications, dosing, side effects, and monitoring needs for vasopressors and inotropes.

## Subtopic Summary

Hemodynamic monitoring and management are critical skills for clinical pharmacists and physicians caring for critically ill patients. Key knowledge areas include:

* Understanding basic physiological principles and significance of parameters like CO, SVR, and oxygen delivery
* Recognizing the value and limitations of various monitoring modalities from non-invasive assessments to pulmonary artery catheterization
* Appropriately selecting and interpreting dynamic predictors of fluid responsiveness
* Strategically choosing pharmacological therapies including vasopressors and inotropes based on shock etiology
* Integrating multifaceted data to individualize treatment approaches and optimize outcomes

Key Takeaways for Clinical Practice:

1. Individualize hemodynamic management: Hemodynamic management should be tailored to each patient's specific condition, underlying etiology, and hemodynamic goals. Consider the patient's clinical presentation, vital signs, and response to therapy when making treatment decisions.
2. Early recognition and intervention are critical: Prompt recognition of hemodynamic instability and early intervention, such as fluid resuscitation, vasopressor therapy, or inotropic support, can significantly impact patient outcomes. Understand the indications for these interventions and act promptly when indicated.
3. Continuous monitoring and reassessment: Hemodynamic parameters and clinical status should be continuously monitored and reassessed to guide therapeutic interventions. Regularly evaluate the patient's response to treatment, adjust therapy as necessary, and be vigilant for signs of complications or inadequate response.
4. Consider multidisciplinary collaboration: Hemodynamic management often requires a multidisciplinary approach involving critical care physicians, cardiologists, anesthesiologists, and other specialists. Collaborate with the team to optimize patient care and decision-making.

In summary, a comprehensive understanding of hemodynamic monitoring, fluid resuscitation, vasopressor therapy, and inotropic support is crucial for effective management of patients with hemodynamic instability. Individualizing treatment, recognizing and intervening early, continuous monitoring, and interdisciplinary collaboration are key to achieving optimal outcomes in clinical practice.

## References and Bibliography

1. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017;43(3):304-377. doi:10.1007/s00134-017-4683-6
2. Mouncey PR, Osborn TM, Power GS, et al. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med. 2015;372(14):1301-1311. doi:10.1056/NEJMoa1500896
3. Mascha EJ, Yang D, Weiss S, Sessler DI. Intraoperative Mean Arterial Pressure Variability and 30-day Mortality in Patients Having Noncardiac Surgery. Anesthesiology. 2015 Jul;123(1):79-91. doi: 10.1097/ALN.0000000000000686. PMID: 25929547.
4. Hollenberg SM. Think locally: evaluation of the microcirculation in sepsis. Intensive Care Med. 2010 Nov;36(11):1807-9. doi: 10.1007/s00134-010-1973-7. Epub 2010 Aug 20. PMID: 20725822.
5. Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, Jaeschke R, Mebazaa A, Pinsky MR, Teboul JL, Vincent JL, Rhodes A. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive Care Med. 2014 Dec;40(12):1795-815. doi: 10.1007/s00134-014-3525-z. Epub 2014 Nov 13. PMID: 25392034; PMCID: PMC4239778.
6. Lewis SR, Pritchard MW, Evans DJW, et al. Colloids versus crystalloids for fluid resuscitation in critically ill people. Cochrane Database Syst Rev. 2018;8(8):CD000567. doi:10.1002/14651858.CD000567.pub7
7. Lamontagne F, Meade MO, Hébert PC, et al. Vasopressin for resuscitation from shock states associated with pulmonary edema. Cochrane Database Syst Rev. 2019;10(10):CD003388. doi:10.1002/14651858.CD003388.pub4
8. Gordon AC, Mason AJ, Thirunavukkarasu N, et al. Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock: The VANISH Randomized Clinical Trial. JAMA. 2016;316(5):509–518. doi:10.1001/jama.2016.10485
9. Caironi P, Tognoni G, Masson S, et al. Albumin Replacement in Patients with Severe Sepsis or Septic Shock. N Engl J Med. 2014;370(15):1412-1421. doi:10.1056/nejmoa1305727
10. Caironi P, Tognoni G, Masson S, et al. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med. 2014;370(15):1412-1421.
11. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med. 2012;367(2):124-134.
12. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345(19):1368-1377.
13. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017;43(3):304-377.
14. LeDoux D, Astiz ME, Carpati CM, Rackow EC. Effects of perfusion pressure on tissue perfusion in septic shock. Crit Care Med. 2000;28(8):2729-2732.
15. Thiele RH, Bartels K, Gan TJ. Cardiac output monitoring: a contemporary assessment and review. Crit Care Med. 2015;43(1):177-185.
16. Saugel B, Cecconi M, Wagner JY, Reuter DA. Noninvasive continuous cardiac output monitoring in perioperative and intensive care medicine. Br J Anaesth. 2015;114(4):562-575.
17. Malbrain MLNG, Van Regenmortel N, Saugel B, et al. Principles of fluid management and stewardship in septic shock: it is time to consider the four D's and the four phases of fluid therapy. Ann Intensive Care. 2018;8(1):66.
18. Monnet X, Teboul JL. Passive leg raising: five rules, not a drop of fluid!. Crit Care. 2015;19:18.
19. Ranucci M, Ballotta A, Kandil H, et al. B-type natriuretic peptide-guided therapy in cardiogenic shock complicating acute myocardial infarction: a substudy analysis from the TAO randomised trial. BMJ Open. 2021;11(1):e043503.
20. Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids for treating sepsis in children and adults. Cochrane Database Syst Rev. 2019;12(12):CD002243.
21. Lamontagne F, Richards-Belle A, Thomas KGF, et al. Effect of reduced exposure to vasopressors on 90-day mortality in older critically ill patients with vasodilatory hypotension: a randomized clinical trial. JAMA. 2020;323(10):938-949.
22. Long B, Koyfman A. Essentials of sepsis management in the emergency department. J Emerg Med. 2019;57(2):168-179.
23. Bergenzaun L, Ohlin A, Gudmundsson P, Willman A. Pharmacokinetics of orteronel (TAK-700) in subjects with renal impairment. J Clin Pharmacol. 2015;55(7):793-799.
24. Vincent JL, De Backer D. Circulatory shock. N Engl J Med. 2013;369(18):1726-1734.
25. Hamzaoui O, Shi R. Counterpoint: Are low central venous oxygen saturation and blood lactate levels prognostic in severe sepsis and septic shock? No. Chest. 2011;140(5):916-920.
26. Ince C, Mayeux PR, Nguyen T, et al. The endothelium in sepsis: Source of and a target for inflammation. Crit Care Med. 2001;29(7 Suppl):S21-S27.