HYPOTENSION

CHI Formulary Development Project

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Abbreviations

ABPM	Ambulatory Blood Pressure Monitoring
ACC	American College of Cardiology
AHA	American Heart Association
BID	Twice Daily
BP	Blood Pressure
CADTH	Canadian Agency for Drugs and Technologies in Health
CHI	Council of Health Insurance
CO	Cardiac Output
EMA	European Medicines Agency
ESC	European Society of Cardiology
FDA	Food and Drug Administration
HAS	Haute Autorité de Santé
HFrEF	Heart Failure and reduced Ejection Fraction
HRS	Heart Rhythm Society
HTA	Health Technology Assessment
IDF	Insurance Drug Formulary
IQWIG	Institute for Quality and Efficiency in Health Care
mmHg	Millimeter of Mercury
MAP	Mean Arterial Pressure
MRA	Mineralocorticoid Receptor Antagonist
NICE	National Institute for Health and Care Excellence
NOH	Neurogenic Orthostatic Hypotension
OH	Orthostatic Hypotension
PBAC	Pharmaceutical Benefits Advisory Committee
RRT	Renal Replacement Therapy
RCTs	Randomized control trials
SFDA	Saudi Food and Drug Authority
SVR	Systemic Vascular Resistance
TID	Three Times Daily

Executive Summary

Syncope, characterized by a temporary loss of consciousness and muscle strength, typically stems from a brief reduction in blood flow to the brain. Commonly referred to as fainting or passing out, this condition is often triggered by a sudden drop in blood pressure (BP). Under normal circumstances, the autonomic nervous system compensates by adjusting vascular tone, heart rate, and cardiac contractility. However, this compensatory response may sometimes be defective or insufficient, resulting in hypotension.

Hypotension is defined as a reduction in systemic blood pressure below generally accepted lower levels. While there isn't a universally agreed-upon standard for hypotensive values, readings below 90 mmHg/60 mmHg are commonly recognized as indicative of hypotension. Despite being a relatively benign condition, hypotension often goes unnoticed, primarily due to its typically asymptomatic nature. It becomes a concern when the pumping pressure is inadequate to properly perfuse vital organs with oxygenated blood, leading to symptoms that can significantly impact a patient's quality of life.

Hypotension can be classified into different types based on its underlying causes and clinical presentations[1]:

- Orthostatic hypotension (OH):
    - Neurogenic orthostatic hypotension results from inadequate vasoconstrictor mechanisms due to neurodegenerative disorders like multiple system atrophy, pure autonomic failure, Parkinson's disease, or autonomic peripheral neuropathies associated with conditions such as diabetes mellitus.
    - Non-neurogenic orthostatic hypotension (NOH) occurs due to factors other than neurological dysfunction such as dehydration.
- Medication-induced hypotension refers to a condition in which a patient's blood pressure drops significantly following the administration of certain drugs, such as anesthesia, diuretics, and vasodilators, especially in elderly patients.
- Cardiogenic hypotension, with low cardiac output as the predominant underlying mechanism, is caused by conditions affecting preload (e.g., volume loss, impaired venous return, venous pooling, left ventricular stiffness, pulmonary hypertension), afterload (hypertension), contractility (e.g., left ventricular dysfunction, amyloidosis), and chronotropy.
- Postprandial hypotension: a drop of BP occurs 1 to 2 hours after eating or drinking alcohol. The intestines require a large amount of blood for digestion.

It's most likely to affect older adults with high blood pressure or autonomic nervous system diseases.

- Neurally mediated hypotension occurs when BP drops after standing for a long period of time.
- Severe Hypotension is a significant and potentially life-threatening drop in blood pressure that can result from conditions such as septic shock such as sepsis-induced myocardial dysfunction significantly contributes to hemodynamic instability and is linked to unfavorable outcomes in septic shock patients.

In this report, all types of hypotension were discussed, with particular attention to OH and sepsis induced hypotension as distinctive and significant entities within that broader category, aiming to provide in-depth information about this specific condition while acknowledging the existence and importance of other types of hypotension.

In the management of OH, a systematic approach involves carefully removing medications that exacerbate OH while treating underlying conditions like hypertension, ischemia, and heart failure. The Food and Drug Administration (FDA) approved drugs for hypotension are midodrine and droxidopa. While midodrine can raise BP, droxidopa is often better tolerated and more likely to improve symptoms. Both medications may cause headaches and exacerbate supine hypertension, with midodrine potentially causing urinary retention and goosebumps. Fludrocortisone, intended to increase intravascular volume and minimally enhance vasoconstriction, may improve hypotension, but controlled trials are not entirely convincing. There is a risk of hypokalemia and peripheral edema, and fludrocortisone is contraindicated in heart and kidney failure. When combined with midodrine or droxidopa, fludrocortisone can be effective in managing hypotension. Pyridostigmine, an acetylcholinesterase inhibitor affecting nicotinic receptors and ganglionic neurotransmission, has shown efficacy in small, controlled trials for treating OH, particularly in increasing diastolic BP without worsening supine hypertension.

Concerning sepsis induced hypotension, inotropic therapy, particularly dobutamine and epinephrine/norepinephrine, is considered for patients with persistent hypoperfusion post-adequate fluid resuscitation or those with myocardial dysfunction showing low Cardiac Output (CO) and elevated cardiac filling pressures. While dobutamine demonstrates physiological benefits in terms of increasing CO, improving splanchnic perfusion, and addressing acidosis and hyperlactatemia, its effects can be unpredictable, potentially causing severe vasodilation and reduced Mean Arterial Pressure (MAP). The panel, considering network meta-analysis more robust than observational studies, suggests using inotropes selectively. There is no evidence favoring dobutamine over epinephrine, and both are deemed comparable in terms of desirable and undesirable consequences. A weak recommendation is

made for using either in patients with septic shock and cardiac dysfunction if hypoperfusion persists despite adequate fluid status and MAP. Discontinuation is advised in the absence of improvement or if adverse events occur. Further high-quality RCTs are deemed necessary to better understand the role of inotropes in sepsis.

Hypotension ranks as the second most prevalent cause of syncope (15% of syncope cases). It is frequently observed (30%) in older individuals (> 70years) and those with neurodegenerative diseases, diabetes, or hypertension. Unfortunately, hypotension often goes unnoticed or is misdiagnosed, potentially serving as an underestimated contributor to heightened cardiovascular morbidity and overall mortality[2].

The prevalence of hypotension in Middle Eastern countries, including Saudi Arabia, has not been extensively studied in terms of the epidemiological figures and clinical patterns. To address this gap, a study in Saudi Arabia assessed cardiovascular responses to standing up before and after meals in healthy individuals and those with diabetes, in the elderly compared to young adults[3]. In addition, the Ministry of Health in Saudi Arabia emphasizes a comprehensive approach to both prevent and treat hypotension, aiming to manage this condition effectively and enhance overall cardiovascular health among the Saudi population[4].

This report compiles all clinical and economic evidence related to hypotension according to the relevant sources. The ultimate objective of issuing hypotension guidelines by the Council of Health Insurance (CHI) is to update the IDF (CHI Drug Formulary) with the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to hypotension patients in Saudi Arabia. The focus of the review was on Saudi, North American, European, and international guidelines issued within the last five years.

Several classes and drugs can be used for the management of hypotension and are summarized in the table below.

SFDA registered drugs

Table 1. SFDA-Registered Drugs for the Management of Hypotension

Drug	Indication	Dose	Level of evidence and HTA recommendation
Somatostatin Agonists			
Octreotide	In patients with syncope and refractory recurrent	0.2–1.6 mg/kg daily, subcutaneous.	IIb / C-LD No HTA recommendations.

	postprandial or NOH.		
Acetylcholinesterase Inhibitors			
Pyridostigmine	In patients with autonomic failure and NOH refractory to other treatments.	30 mg twice daily, may increase dose at intervals of 1 to 2 weeks to 30 to 60 mg up to 3 times daily.	IIb / C-LD NICE: Research is still in process.
Vasopressin and analogues			
Vasopressin	Adjunctive therapy if MAP is inadequate despites low to moderate dose norepinephrine in refractory septic shock.	IV: Initial: 0.03 units per minute. Usual dose: 0.01 to 0.04 units/minute.	Strong, moderate quality evidence. No HTA recommendations.
Adrenergic Agonists			
Norepinephrine (noradrenaline)	First line therapy in septic shock. Short term treatment of severe chronic heart failure in acute decompensation when standard therapy is insufficient.	Initial: 0.05 to 0.15 mcg/kg/minute. Usual dose range: 0.025 to 1 mcg/kg/minute.	Strong, high-quality evidence. HAS: Positive recommendation.
Epinephrine (adrenaline)	Alternative therapy in refractory Septic shock.	IV: Initial: 0.01 to 0.2 mcg/kg/minute. Usual dose range: 0.01 to 0.5 mcg/kg/minute.	Low quality evidence. No HTA recommendations.
Dobutamine	Inotropic support in patients with septic shock who fail to meet	IV: 2 to 5 mcg/kg/minute. Usual range: 2 to 10mcg/kg/min.	Weak recommendation.

	hemodynamic goals with norepinephrine. Acute decompensated heart failure (short-term use).		NICE, IQWIG and HAS: Positive recommendations.
Dopamine	Cardiogenic shock (alternative agent). Septic shock (adjunctive agent with norepinephrine).	IV: 0.5 to 20 mcg/kg/minute. IV: 2 to 5mcg/kg/minute (up to 20mcg/kg/minute).	Strong, high-quality evidence. NICE, IQWIG and HAS: Positive recommendations.
Ephedrine	In anesthesia induced hypotension.	IV: 5 to 10 mg	HAS: Positive recommendation.
Midodrine	Is effective in relieving symptoms associated with NOH.	Oral: 2.5 mg 2 or 3 times daily during daytime hours.	IIa / B-R NICE: Positive recommendations.

Non SFDA registered drugs

- **FLUDROCORTISONE**, a synthetic corticosteroid, is indicated for NOH associated with conditions like Parkinson's disease. It primarily works by promoting sodium retention and potassium excretion in the kidneys, expanding plasma volume, and increasing BP. The initial dose ranges from 0.05 to 0.1 mg once daily, with a maintenance dose of 0.05 to 0.2 mg/day in 1 or 2 divided doses. Common side effects include fluid retention, hypertension, and electrolyte imbalances. Monitoring, including BP assessments, regular blood tests, and fluid status checks, is crucial. However, the clinical benefit of fludrocortisone for NOH is limited, with modest improvements noted. Caution is advised due to potential side effects, and comparative data with other treatments like midodrine are lacking.
- **DROXIDOPA**, a prodrug converted into norepinephrine in the body, acts as both a neurotransmitter and hormone, constricting blood vessels to maintain BP. It addresses the deficiency in norepinephrine often found in NOH by

increasing norepinephrine levels in the synaptic clefts. This enhancement facilitates vasoconstriction, helping elevate BP, particularly during postural changes like standing up. The usual initial dose is 100 mg three times daily, with adjustments based on individual response. The maintenance dose ranges from 200 to 600 mg daily, divided into multiple doses. Common side effects include headache, dizziness, nausea, and hypertension.

It is important to emphasize that these treatment approaches serve as general recommendations. The appropriate treatment plan for each patient should be determined based on the specific type of OH, as well as their overall health status. To provide a concise overview, the report will feature in section 3 a synthesis of key recommendations, focusing on the relevant drugs that align with these guidelines.

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

1.1 KSA Guidelines

There are no specific guidelines for the treatment of OH in Saudi Arabia; therefore, we will present the results of a study conducted in both healthy and diabetic Saudi patients that aims to evaluate the cardiovascular system's response to physiological stimuli, particularly the act of standing up from a supine position before and after food intake.

Additionally, we will explore relevant information from the Ministry of Health of Saudi Arabia, or any guidance provided on their official page, shedding light on the management and recommendations for OH within the Saudi healthcare context.

1.1.1 Orthostatic Hypotension Before and After Meal Intake in Diabetic Patients and Healthy Elderly People (*J Family Community Med*, 2012)

A study was conducted in Saudi Arabia, aiming to evaluate the cardiovascular system's response to physiological stimuli, specifically the act of standing up from a supine position before and after meal intake in both diabetic patients and the healthy Saudi population. The research involved 75 healthy and 49 diabetic participants. Parameters like heart rate, BP, and electrocardiograms were measured in various conditions. The findings indicated no significant postural changes between diabetic and non-diabetic groups but revealed a highly significant drop in BP and an increase in resting heart rate in the elderly compared to young adults, regardless of diabetic status. This suggests a potential defect in arterial baroreceptor control of BP and parasympathetic control of heart rate in the elderly Saudi population[4].

1.1.2 Orthostatic Hypotension – Saudi Ministry of Health

Orthostatic and postprandial hypotension are physiological observations rather than diseases, and they can manifest with or without symptoms. While they can affect individuals of all ages, they are more commonly observed in the elderly compared to younger or middle-aged individuals. The criteria for diagnosis involve a decrease in systolic BP of at least 20 mmHg or a decrease in diastolic BP of at least 10 mmHg within three minutes of standing[3].

1. Causes

High BP (hypertension), diabetes, heart failure, atherosclerosis, certain medications, neurological diseases (e.g., Parkinson's disease), dehydration, vitamin B12 deficiency, anemia, alcohol consumption, and prolonged bed rest.

2. Symptoms

Symptoms may vary but can include dizziness upon standing, feeling on the verge of fainting, headache, blurred vision, pressure across the back of the shoulders or neck, nausea, feeling hot, and fatigue.

3. Diagnosis

OH is confirmed by measuring BP while sitting and standing. A physical exam and additional tests, such as blood tests, electrocardiograms, echocardiograms, and stress tests, may be performed to identify underlying conditions.

4. Treatment

The goal of treatment is to restore normal BP by addressing the underlying causes. Lifestyle changes include staying hydrated, avoiding prolonged standing, not crossing legs when sitting, limited bed rest, gradual movements, specific exercises to raise BP, and using compression stockings.

5. Prevention

Keeping the doctor informed about symptoms, gradually changing positions, gentle exercises before and after getting up, having a support object when standing, avoiding walking when dizzy, maintaining adequate hydration, avoiding hot showers, and using extra pillows for head elevation during sleep are recommended preventive measures.

1.2 European Guidelines

1.2.1 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Syncope (2018)

This guideline provides an overview of current recommendations for diagnosis and managing syncope, including complicated OH[5].

1.2.1.1 Education and Lifestyle Measures: Class I, Level C

- Educate patients about the nature of the condition, coupled with lifestyle advice.
- Even with a relatively small increase in BP (10–15 mmHg), understanding the condition and making lifestyle changes can significantly improve orthostatic symptoms.
- AMBP recordings can help identify abnormal diurnal patterns and nocturnal hypertension in treated patients.

1.2.1.2 Adequate Hydration and Salt Intake: Class I, Level C

- Emphasize the importance of expanding extracellular volume.
- In the absence of hypertension, advise patients to maintain sufficient salt and water intake, aiming for 2–3 liters of fluids per day and 10 grams of sodium chloride.
- Rapid ingestion of cool water has been reported as effective in combating orthostatic intolerance and postprandial hypotension.

1.2.1.3 Discontinuation/Reduction of Vasoactive Drugs: Class IIa, Level B.

- Evaluate the association of vasoactive drugs (antihypertensive agents, nitrates, diuretics, neuroleptic antidepressants, dopaminergic drugs, or phosphodiesterase-5 inhibitors) with OH and falls.
- Intensive antihypertensive therapy, defined as higher doses, increased number of drugs, or lowering BP to a target <140/90 mmHg, may increase the risk of OH.
- The total number of BP-lowering medications or the use of three or more antihypertensive drugs could be significant predictors of OH.
- Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers are less likely to be associated with OH compared to beta-blockers and thiazide diuretics.

- Principal strategy involves discontinuing the causative medication in drug-induced autonomic failure.

1.2.1.4 Non-pharmacological therapy

- Encourage leg crossing and squatting in patients experiencing warning symptoms and capable of performing these maneuvers. **Class IIa, Level C**
- Address gravitational venous pooling in older patients using abdominal binders or compression stockings. **Class IIa, Level B**
- Elevating the head of the bed (>10 degrees) during sleep prevents nocturnal polyuria, maintains favorable fluid distribution, and improves nocturnal hypertension. **Class IIa, Level C**

1.2.1.5 Pharmacological therapy

Midodrine: Class IIa, Level B

- Alpha-agonist midodrine is a valuable addition to first-line treatment in chronic autonomic failure.
- While not a cure, midodrine effectively increases BP in both supine and upright postures, alleviating OH symptoms.
- The quality of evidence is moderate, and further research may impact the estimation of benefit.

Fludrocortisone: Class IIa, Level C

- Mineralocorticoid fludrocortisone (0.1–0.3 mg once daily) stimulates renal sodium retention and fluid volume expansion.
- Observational studies and a double-blind trial suggest hemodynamic benefits and symptom reduction with higher BP.
- Quality of evidence is moderate, and further research may influence the estimated benefit.

Droxidopa

- Droxidopa, a centrally and peripherally acting alpha/beta-agonist, is FDA-approved for symptomatic neurogenic orthostatic hypotension (NOH).
- Recent short-term randomized controlled trials (four studies, 485 patients) investigated its efficacy in treating NOH.
- After 2 weeks of treatment, they observed a slight elevation in standing systolic BP and identified certain improvements in the quality of life for patients using droxidopa compared to a placebo. However, these benefits

diminished after 8 weeks, indicating that there is currently inadequate evidence to support the long-term efficacy of droxidopa.

Additional Therapies

Less frequently used treatments include desmopressin for nocturnal polyuria, octreotide for postprandial hypotension, erythropoietin for anemia, pyridostigmine, walking sticks, frequent small meals, and judicious exercise.

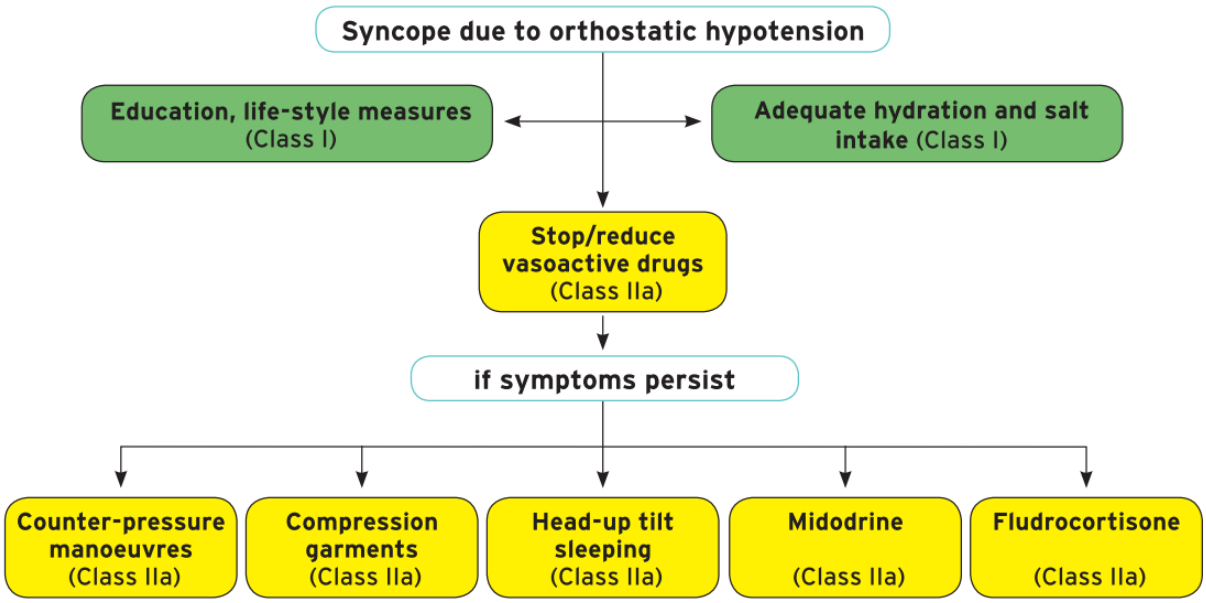

Figure 1. *Schematic Practical Guide for the Treatment of Orthostatic Hypotension. Retrieved from the ESC 2018 Guideline.*

1.2.2 European Society of Cardiology (ESC) Management of Low Blood Pressure in Ambulatory Heart Failure with Reduced Ejection Fraction Patients (2020)

Low BP is common in patients with heart failure and reduced ejection fraction (HFrEF). Low BP is prevalent in 10–15% of HF patients in clinical trials, but this proportion is higher in routine clinical practice. OH is notably common, exceeding 10%, especially in elderly subjects. Due to the absence of explicit management directives, this review by the ESC suggests an algorithm comprising a five-step process for handling hypotension in patients with HFrEF. It is crucial to reassess BP after each step before considering further adjustments. The subsequent steps will exclusively concentrate on stable patients with HFrEF[6].

Step I: Confirm low BP and assess its link with symptoms.

- Due to the prognostic significance of HFrEF drugs, establishing a link between symptoms (dizziness, fatigue, especially upon standing) and low BP is crucial.
- A decrease of 20 mmHg in systolic BP and/or 10 mmHg in diastolic BP within the first 3 minutes after standing up suggests BP-related symptoms.
- In the absence of OH, Ambulatory BP Monitoring (ABPM) can be considered to detect hypotensive episodes associated with symptoms reported during ABPM recordings.
- If SBP is ≥ 100 mmHg without postural symptoms, HFrEF medication should not be altered.
- If SBP is < 90 mmHg with clear postural symptoms, proceed to step II.
- Use of stockings is recommended for patients with postural hypotension.

Step II: Identify hypotensive factors unrelated to HFrEF and stop/reduce non-heart failure with reduced ejection fraction BP-lowering therapies.

- Explore non-drug-related causes of hypotension, such as diarrhea, fever, dehydration, etc.
- Correct the cause of hypotension and avoid long-term changes to chronic HF treatment. Transient discontinuation may be considered until the acute event resolves, with early re-introduction whenever possible.
- Decrease or stop BP-lowering treatments without evidence of morbidity-mortality reduction in HFrEF patients.
- Reduce or discontinue cardiovascular treatments not indicated in HFrEF, such as calcium channel blockers, centrally acting antihypertensive drugs, or alpha-blockers, irrespective of administration form.
- Identify and replace 'hidden' hypotensive drugs, such as alpha-blockers for prostate disease or intraocular beta-blockers for glaucoma, with an alternative drug class.

Step III: Adjust Diuretic Doses.

- If no congestive signs are present, cautiously decrease diuretics, considering potential replacement with a Mineralocorticoid Receptor Antagonist (MRA) in some cases.
- Assess salt intake, as low salt intake may contribute to low extracellular volume. Increase salt intake cautiously if needed.

- If diuretic adjustment is unsuccessful or impossible, discuss adjusting other HFrEF therapeutic classes.

Step IV: Adjust HFrEF Treatments According to Clinical Profile.

- Distribute medication doses throughout the day (e.g., half in the morning and half in the evening).
- Consider additional measures like increased physical activity or cardiovascular rehabilitation to counter hypotension.
- Heart Rate < 60 bpm:
    - Discontinue glycoside and/or If channel inhibitor as a first step.
    - Consider reducing beta-blocker dosage or, in severe cases, discontinuation as a second step.

Considerations for Re-introduction or Dose Escalation

Regardless of therapeutic class, if a drug has been decreased or discontinued during a hypotensive period, re-introduction or dose escalation should be considered, especially when a triggering hypotensive factor has been identified and resolved.

Consideration of Comorbidities in Treatment Modifications

- Comorbidities, such as complicated diabetes, anemia, and neurological conditions, should be considered when making treatment modifications.
- Features favoring low BP may arise from the presence of comorbidities, frailty, or cognitive issues, prompting a cautious approach in using high-dose HF medications.
- In this specific clinical context, decreasing HF medication, even without symptoms, can be considered due to the higher risk of adverse effects associated with low BP.

1.2.3 European Society of Cardiology (ESC) e-Journal of Cardiology Practice: Low Blood Pressure (2019)

This article published in the ESC e-journal of cardiology practice looks at different aspects of treating OH, from the prevention of fainting, initial non-pharmacological management, to patient awareness that pressure drops often occur at night. Among drugs, mineralocorticoids are considered as well as droxidopa which shows promising results[7].

Detection of Underlying Causes

Before specific treatment for low BP, identify and address potential causes like hemorrhaging or low cardiac output.

Patient Education on Self-Help Measures

- Teach patients preventive measures for fainting and syncope.
- Maneuvers include:
    - Repeated rising on heels to mobilize blood volume.
    - Isometric handgrips to stimulate vasoconstriction.
    - Sitting or lying down in a cooler room during pre/syncope.

Non-Pharmacological Treatments

- Tilt bed for a "head-up" position, especially effective at night.
- Drinking ice-cold water before bedtime may improve venous return.
- Compression stockings counteract venous pooling in limbs.
- Tilt training to enhance neuro-cardiogenic balance.
- Constitutional hypotension patients may benefit from increased salt intake.

Pharmacological Treatment

- Limited hard proof of drug efficacy.
- Fludrocortisone acetate can increase BP by improving sodium/potassium balance.
- Various drugs like ephedrine, caffeine, and midodrine used with varying success, often acting through constriction.
- Droxidopa, a precursor of noradrenaline, shows promising results but requires further exploration and long-term confirmation.
- Orthostatic changes linked to drugs for accompanying conditions may be resolved by stopping or reducing drug dosage.

1.3 North American Guidelines

1.3.1 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients with Syncope: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society (2017)

In 2017, the American College of Cardiology (ACC), the American Heart Association (AHA) and the Heart Rhythm Society (HRS) released a consolidated set of clinical guidelines for the diagnosis and treatment of patients with OH. Recommendations are synthesized in the following section[8].

Nonpharmacological interventions

Management of OH begins with nonpharmacologic interventions as part of a stepwise approach:

- Patient Education
- Diagnostic Testing and Patient Understanding: continuous noninvasive BP monitoring during diagnostic testing.
- Lifestyle Recommendations: encourage avoidance of prolonged inactivity, large meals, and alcoholic beverages, drinking 500 mL of water quickly before standing in the morning or before activities is feasible and supported by evidence, abdominal compression may be more effective than lower limb compression, sleeping with the head of the bed elevated may be considered in select cases with marked nighttime supine hypertension.

Pharmacological interventions

Table 2. Pharmacological Interventions for the Management of Hypotension

RECOMMENDATIONS	COR/LOE
Neurogenic Orthostatic Hypotension	
Acute water ingestion: consuming at least 240 mL of water can temporarily improve tolerance, likely through sympathetic activity. The peak effect occurs around 30 minutes post-ingestion, with additional benefits seen at ≥ 480 mL. The presence of glucose or salt may reduce this effect.	I / B-R
Physical counter-pressure maneuvers and compression garments can be beneficial in patients with NOH with syncope.	IIa / C-LD

Midodrine has proven to be effective in relieving symptoms associated with NOH. However, its use may be constrained by the occurrence of supine hypertension. Additionally, individuals using Midodrine may experience common side effects, including scalp tingling, piloerection, and urinary retention. Dose: 2.5–10 mg bid or tid.	IIa / B-R
Droxidopa effectively improves NOH symptoms in conditions like Parkinson's disease. Small studies suggest it may reduce falls. However, its use may be limited by factors such as supine hypertension, and side effects like headache, dizziness, and nausea, are possible. Dose: 100 to 600 mg tid.	IIa / B-R
Fludrocortisone boosts plasma volume, alleviating OH symptoms. Regular use may prevent OH, particularly in astronauts post-space flight, although supine hypertension can be a limitation. When supine hypertension is present, alternative medications are recommended before fludrocortisone. Common side effects encompass edema, hypokalemia, and headache, while more serious reactions like adrenal suppression and immunosuppression can occur with doses exceeding 0.3 mg daily. Dose: 0.05 to 0.3 mg daily.	IIa / C-LD
While data on salt and fluid supplementation for OH are limited, these treatments may enhance BP and alleviate OH symptoms. Salt supplementation, typically 6 to 9 g (100 to 150 mmol) per day, increases plasma volume, but its benefits are limited in individuals with already high salt intake. However, these interventions may not be beneficial for individuals with a history of hypertension, kidney disease, heart failure, or cardiac dysfunction, and the long-term effects, including benefits and risks, remain unknown.	IIb / C-LD
In patients with autonomic failure and NOH refractory to other treatments, pyridostigmine can improve orthostatic tolerance through increases in peripheral vascular resistance and BP. Side effects include nausea, vomiting, abdominal cramping, sweating, salivation, and urinary incontinence. Dose: 30 to 60 mg bid or tid.	IIb / C-LD
Octreotide may be beneficial in patients with syncope and refractory recurrent postprandial or NOH. Dose: 0.2–1.6 mg/kg daily, subcutaneous	IIb / C-LD
Non-Neurogenic Orthostatic Hypotension (dehydration and drugs)	

Fluid resuscitation via oral or intravenous bolus is recommended in patients with syncope due to acute dehydration. sodium supplementation improves plasma volume and improves orthostatic tolerance. This additional dietary sodium may be provided as sodium tablets or sodium already dissolved in beverage	I / C-LD
Reducing or withdrawing medications that may cause hypotension can be beneficial in selected patients with syncope.	IIa / B-NR

1.4 International Guidelines

1.4.1 Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock (2021)

The guidelines provide guidance for healthcare professionals caring for adult patients experiencing sepsis or septic shock within a hospital setting. It is essential to note that the recommendations herein are not a substitute for a clinician's decision-making abilities when confronted with a patient's unique clinical variables. The guidelines are summarized below[9].

Sepsis represents a critical malfunction of organs, resulting from an unregulated response by the host to an infection. It poses a significant global health challenge, affecting millions annually and causing mortality rates ranging from one in three to one in six cases. Timely recognition and proper management in the initial hours following sepsis onset significantly enhance outcomes. MAP is a crucial factor determining mean systemic filling pressure. It plays a major role in driving venous return and CO. Increasing MAP generally leads to elevated tissue blood flow, enhancing the supply side of tissue perfusion. Some tissues, like the brain and kidneys, can auto-regulate blood flow. MAP below approximately 60 mm Hg are associated with decreased organ perfusion. Organ perfusion tends to decrease linearly with decreasing MAP. The panel recommends targeting a MAP of 65 mm Hg in the initial resuscitation of septic shock patients requiring vasopressors.

- ✓ For adults with septic shock on vasopressors, we recommend an initial target MAP of 65 mm Hg over higher MAP targets. **Strong, moderate-quality evidence**
- ✓ We advise the prioritized use of norepinephrine as the first-line vasopressor for adults experiencing septic shock. In situations where norepinephrine is unavailable, epinephrine or dopamine can serve as alternatives, but we strongly advocate for initiatives aimed at enhancing the accessibility of norepinephrine. Caution is recommended, particularly for patients prone to arrhythmias, when opting for dopamine and epinephrine. **Strong, High-quality evidence**

- ✓ In our clinical practice, the introduction of vasopressin is typically considered when the norepinephrine dose falls within the range of 0.25–0.5 μg/kg/min. **Strong, Moderate-quality evidence.**
- ✓ In cases where adults with septic shock are on norepinephrine and exhibit insufficient MAP, our recommendation is to consider the addition of vasopressin instead of increasing the norepinephrine dose. **Weak, moderate quality evidence**
- ✓ For adults with septic shock and inadequate MAP levels despite norepinephrine and vasopressin, we suggest adding epinephrine. **Weak, low quality of evidence**
- ✓ For adults with septic shock, we suggest against using terlipressin. **Weak, low quality of evidence**
- ✓ For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial BP, we suggest either adding dobutamine to norepinephrine or using epinephrine alone. **Weak, low quality of evidence**
- ✓ For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial BP, we suggest against using levosimendan. **Weak, low quality of evidence**
- ✓ For adults with septic shock, we suggest invasive monitoring of arterial BP over noninvasive monitoring, as soon as practical and if resources are available. **Weak, very low quality of evidence**
- ✓ For adults with septic shock, we suggest starting vasopressors peripherally to restore MAP rather than delaying initiation until a central venous access is secured. In the context of septic shock management, the prompt initiation of vasopressors is crucial. Traditionally administered via central venous access, concerns about extravasation and local tissue complications have driven this practice. However, securing central access is time-consuming and may cause delays, especially in resource-limited settings. Comparisons between central and peripheral catheters for initial vasopressor infusion lack large, randomized trials. Studies suggest that peripheral administration is generally safe, with minimal extravasation-related complications. The time to initiate vasopressors may be shorter with peripheral access, potentially improving outcomes. The panel weakly recommends rapid peripheral vasopressor initiation, transitioning to central access if needed, considering resource limitations and expertise. Prospective studies are essential to further guide the safety and adequacy of peripheral lines in various settings. **Weak, very low quality of evidence**

Norepinephrine

- Norepinephrine acts strongly on α-1 and β-1 adrenergic receptors.
- It induces vasoconstriction and increases MAP with minimal impact on heart rate.
- It is a more potent vasoconstrictor compared to dopamine.
- A systematic review and meta-analysis of 11 Randomized Controlled Trials (RCTs) indicated that norepinephrine, in comparison to dopamine, resulted in lower mortality (RR, 0.89; 95% CI, 0.81–0.98) and a reduced risk of arrhythmias (RR, 0.48; 95% CI, 0.40–0.58).

Dopamine

- Dopamine acts dose-dependently on dopamine-1, α-1, and β-1 adrenergic receptors.
- Lower dosages cause vasodilation via dopamine-1 receptor activity in specific beds. Higher dosages lead to α-adrenergic receptor activity, resulting in vasoconstriction and increased Systemic Vascular Resistance (SVR).
- Dopamine's β-1 adrenergic receptor activity may cause dose-limiting arrhythmias.
- Despite potential use in patients with myocardial dysfunction, the higher risk of arrhythmias limits dopamine's application.

Epinephrine

- Epinephrine's action is also dose-dependent with potent β-1 adrenergic receptor activity and moderate β-2 and α-1 adrenergic receptor activity.
- At low doses, it primarily acts on β-1 adrenergic receptors, increasing CO and decreasing SVR with variable effects on MAP. At higher doses, epinephrine increases both SVR and CO.
- Potential adverse effects include arrhythmias and impaired splanchnic circulation.
- Epinephrine may stimulate aerobic lactate production via skeletal muscle β-2 adrenergic receptors, complicating the use of serum lactate as a resuscitation guide.
- A randomized blinded study comparing epinephrine with norepinephrine in shock patients showed no difference in 90-day mortality (HR, 0.88; 95% CI, 0.63–1.25) and vasopressor-free days.

Vasopressin

- Endogenous peptide hormone produced in the hypothalamus and released by the posterior pituitary gland.
- Mechanism involves binding to V1 receptors, leading to increased arterial BP.
- Elevated in early septic shock but decreases in most patients within 24-48 hours, termed "relative vasopressin deficiency."
- Administered at a fixed dose (0.03 units/min) for septic shock treatment.
- Higher doses are associated with cardiac, digital, and splanchnic ischemia.

VANISH Trial on Vasopressin vs. Norepinephrine

- No significant difference in 28-day mortality between vasopressin and norepinephrine groups.
- Vasopressin use reduced the risk of Renal Replacement Therapy (RRT) but had no impact on kidney injury.

VASST Trial on Norepinephrine vs. Norepinephrine + Vasopressin

- No improvement in 28-day mortality with the addition of vasopressin.
- Subgroup analysis suggested improved survival in less severe shock with vasopressin.
- Both trials demonstrated a catecholamine-sparing effect of vasopressin, potentially reducing adrenergic burden.

Combination Therapy with Vasopressin and Norepinephrine

- Meta-analysis of 10 RCTs showed reduced mortality with vasopressin plus norepinephrine compared to norepinephrine alone.
- No significant reduction in the need for RRT, digital ischemia, or arrhythmias.
- Starting vasopressin when norepinephrine dose is in the range of 0.25-0.5 µg/kg/min is suggested.

Selepressin

- A highly selective V1 agonist studied in septic shock trials.
- Phase IIb/III trial showed no clinical superiority over norepinephrine, leading to a weak recommendation against its use.
- Not currently commercially available.

Angiotensin II

- A synthetic hormone studied in clinical trials for vasodilatory shock.
- Meta-analysis found no significant difference in mortality compared to norepinephrine.
- Very low-quality evidence considered an adjunctive vasopressor therapy.

Terlipressin

- Prodrug converted to lysine vasopressin with a slow-release effect.
- Meta-analysis showed no difference in mortality but an increase in adverse events.
- Considered a weak recommendation against its use in septic shock due to higher undesirable consequences.

Table 3 provides a summary of different inotropic drugs used in the management of septic shock.

Table 3. Inotropic Drugs Used in Septic Shock

Vasopressor	Mechanism of Action	Vasoconstrictive Effects	Comparative Characteristics
Norepinephrine	Strong action on α-1 and β-1 adrenergic receptors.	• Induces potent vasoconstriction, increases MAP. • Minimal Impact on heart rate.	• More potent vasoconstrictor compared to dopamine. • Lower mortality and reduced risk of arrhythmias compared to dopamine. • First-line recommendation in septic shock.
Dopamine	Dose-dependent effects on dopamine-1, α-1, and β-1 receptors.	• Vasodilation at lower doses, vasoconstriction at higher doses. • Dose-limiting arrhythmias.	No clear superiority over norepinephrine.

Epinephrine	Dose-dependent actions with potent β-1 and moderate β-2 and α-1 activity.	• Increases both SVR and CO. • Potential for arrhythmias, impaired splanchnic circulation.	• Potential use in refractory septic shock with myocardial dysfunction. • No significant difference in mortality compared to norepinephrine.
Vasopressin	Binds to V1 receptors, increases arterial BP.	Associated with cardiac, digital, and splanchnic ischemia.	• Reduced risk of RRT in comparison to norepinephrine. • Combination therapy with norepinephrine reduces mortality in septic shock.
Selepressin	Highly selective V1 agonist.	-	• No clinical superiority over norepinephrine, not commercially available. • Limited evidence, weak recommendation against use.
Angiotensin II	Vasoconstrictor effects through stimulation of the renin-angiotensin system.	-	• Increase in MAP achieved, similar mortality to norepinephrine. • Limited evidence, potential role as adjunctive therapy.
Terlipressin	Prodrug converted to lysine	-	• No significant difference in

	vasopressin with a slow-release effect.		mortality, higher adverse events. • Limited evidence, weak recommendation against use.

1.5 Systematic Reviews & Meta-Analyses

Table 4. Systematic Reviews and Meta-Analyses for the Management of Hypotension

Author (Year)	Title	Primary Objective	Outcomes	Results
Gibbon and Frith (2021)[10]	**The effects of caffeine in adults with neurogenic orthostatic hypotension: a systematic review**	To systematically review the evidence base for the effectiveness and safety of caffeine for the treatment of neurogenic orthostatic hypotension in adults.	Studies were considered if the outcomes measured included any of the following: symptoms, diagnostic vital sign changes (e.g., orthostatic BP drop), change in resting BP or adverse effects/events.	Participants had neurogenic orthostatic hypotension, with a mean standing systolic blood pressure of 86 mmHg. Two studies evaluated caffeine alone. Three studies administered caffeine in combination with ergotamine. Caffeine dose ranged from 100 to 300 mg. Nature and timing of outcomes measured varied between studies, with measurements being recorded from 30 to 480 min after intervention. Caffeine/ergotamine improved symptoms in one study and reduced orthostatic blood pressure drop in two studies. Caffeine/ergotamine increased seated blood pressure in three studies, whilst the results for caffeine alone were inconsistent. No serious adverse events were reported. All studies demonstrated high risk of bias. Caffeine should only be considered as a treatment for adults with neurogenic orthostatic hypotension when evidence-based treatments have been exhausted.

Section 2.0 Drug Therapy

2.1 Somatostatin agonists

2.1.1 Octreotide

Information on Octreotide is detailed in the table below[11].

Table 5. Octreotide Drug Information

SCIENTIFIC NAME OCTREOTIDE	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	I95
Drug Class	SOMATOSTATIN ANALOG
Drug Sub-class	SOMATOSTATIN ANALOG
ATC Code	H01CB02
Pharmacological Class (ASHP)	SOMATOSTATIN AGONISTS
DRUG INFORMATION	
Dosage Form	Powder and solvent for suspension or solution for injection.
Route of Administration	Injectable form, subcutaneous
Dose	0.2–1.6 mg/kg daily, subcutaneous
Maximum Daily Dose	N/A
Adjustment	**Altered kidney function:** Oral, parenteral: No initial or maintenance dosage adjustments are likely necessary for any degree of kidney dysfunction, although clearance is reduced, and dosage modifications may be necessary in patients with end-stage kidney disease receiving dialysis. Hemodialysis, intermittent (thrice weekly):

	SUBQ, IV: There are no specific dosage adjustments recommended by the manufacturer; however, clearance is reduced by ~50%. Consider initiation at the low end of the normal range; titrate based on tolerability and response. IM (depot): Initial: 10 mg intragluteally every 4 weeks; may titrate based on tolerability and response. Oral: Initial: 20 mg once daily; titrate if needed every 2 to 4 weeks based on tolerability and clinical response in 20 mg/day increments up to 80 mg/day. Refer to indication-specific adult dosing section for more specific titration recommendations. <u>Peritoneal dialysis:</u> SUBQ, IV: No dosage adjustment provided by manufacturer; clearance is reduced by ~50%. Consider initiation at the low end of the normal range and titrate based on efficacy and tolerability. IM (depot): Initial: 10 mg intragluteally every 4 weeks; titrate based on tolerability and response. Oral: Initial: 20 mg once daily; titrate if needed every 2 to 4 weeks based on tolerability and clinical response in 20 mg/day increments up to 80 mg/day. Refer to indication-specific adult dosing section for more specific titration recommendations. <u>CRRT</u>: Drug clearance is dependent on the effluent flow rate, filter type, and method of renal replacement. Recommendations are based on high-flux dialyzers and effluent flow rates of 20 to 25 mL/kg/hour (or ~1,500 to 3,000 mL/hour) and minimal residual kidney

	function unless otherwise noted. Close monitoring of response and adverse reactions (eg, glucose dysregulation) due to drug accumulation is important. Oral, parenteral: There are no data available on removal by CRRT (has not been studied); however, some removal is expected based on physicochemical characteristics. No initial or maintenance dosage adjustments are likely necessary.
Prescribing edits	N/A
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	N/A
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	<u>Most serious:</u> • Cholelithiasis and related complications • Glucose dysregulation • Necrotizing enterocolitis <u>Most common:</u> • Cardiovascular: Hypertension (≤13%), sinus bradycardia (19% to 25%) • Dermatologic: Alopecia (1% to 13%), diaphoresis (21%) • Endocrine & metabolic: Hyperglycemia (2% to 27%), hypothyroidism (1% to 12%) • Gastrointestinal: Abdominal distress (≤61%), abdominal pain (≤44%), biliary tract disease (52% to 63%; length of therapy dependent; including acute

	cholecystitis [1%], cholelithiasis (5% to 38%), constipation (≤21%), diarrhea (≤61%), flatulence (≤38%), gallbladder sludge (24%), nausea (≤61%), upper abdominal pain (8% to 11%), vomiting (≤21%) • Hematologic & oncologic: Anemia (≤15%) • Immunologic: Antibody development (25%; to octreotide; no efficacy change) • Local: Pain at injection site (2% to 50%) • Nervous system: Dizziness (5% to 12%), fatigue (1% to 11%), headache (6% to 33%) • Neuromuscular & skeletal: Arthralgia (1% to 26%), asthenia (1% to 22%)
Drug Interactions	Risk X: • Macimorelin • Fexinidazole
Special Population	Older adult: Dosage adjustment may be necessary; significant increases in elimination half-life have been observed in older adults.
Contraindications	Hypersensitivity to octreotide or any component of the formulation.
Monitoring Requirements	• Acromegaly (measure serum growth hormone (GH)). • Carcinoid: 5-HIAA, plasma serotonin and plasma substance P. • Thyroid function (baseline and periodic); vitamin B_{12} level; blood glucose, glycemic control and antidiabetic regimen, zinc level (patients with excessive GI fluid loss maintained on TPN); biliary tract abnormality monitoring if clinically indicated; routine gallbladder

	ultrasound is not considered necessary. • Cardiac monitoring (patients receiving IV).
Precautions	<u>Concerns related to adverse effects:</u> • Abnormal Schillings test: Chronic treatment has been associated with abnormal Schillings test; monitor vitamin B12 levels. • Cardiovascular events: Complete atrioventricular block has been reported in patients receiving IV therapy during surgical procedures; most causes occurred with continuous IV infusion at higher than recommended doses. Safety of continuous IV infusion has not been established in patients receiving octreotide for approved indications. • Hypothyroidism: Suppresses secretion of TSH; monitor for hypothyroidism. <u>Disease-related concerns:</u> • Cardiovascular disease: Use with caution in patients with heart failure or concomitant medications that alter heart rate or rhythm; bradycardia, conduction abnormalities, and arrhythmia have been observed in acromegalic and carcinoid syndrome patients. • Excessive GI fluid loss. • Hepatic and renal impairment. • Neuroendocrine tumors: Prophylactic cholecystectomy is recommended in patients with GI or pancreatic neuroendocrine tumors undergoing abdominal surgery if octreotide treatment is planned.
Black Box Warning	N/A

REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from the HTA bodies, including the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), the Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Health Care, and the Pharmaceutical Benefits Advisory Committee (PBAC) didn't yield any guidance for octreotide in OH. This is probably because treatment paradigms haven't much changed in the last decade, with no new drugs introduced in the management landscape.

CONCLUSION STATEMENT – OCTREOTIDE

Octreotide is a synthetic analog of somatostatin, a hormone that inhibits the release of various other hormones in the body. In the context of OH, the pressor effect of octreotide is sufficiently potent to prevent OH in some patients with autonomic neuropathy. It may be beneficial in patients with syncope and refractory recurrent postprandial or NOH.

Octreotide is typically administered in the form of subcutaneous injections, and the dosage may vary depending on the severity of symptoms and individual patient response, usually between 0.2 to 1.6 mg/kg daily. Common side effects include gastrointestinal disturbances, such as nausea and diarrhea, as well as potential alterations in glucose metabolism. Despite these side effects, octreotide remains a valuable therapeutic option for managing OH. There are no recommendations issued by the HTA bodies for octreotide.

2.2 Adrenergic Agonists

2.2.1 Midodrine

Information on Midodrine is detailed in the table below[12].

Table 6. Midodrine Drug Information

SCIENTIFIC NAME MIDODRINE	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes

PMDA	N/A
Indication (ICD-10)	I95
Drug Class	Alpha-1 Adrenergic Agonist
Drug Sub-class	Selective alpha-1 receptor agonist
ATC Code	C01CA17
Pharmacological Class (ASHP)	Alpha-1 Adrenergic Agonist
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral use
Dose (Adult) [DDD]*	**Oral: Initial:** 2.5 mg 2 or 3 times daily during daytime hours (eg, every 3 to 4 hours) when patient is upright; titrate as needed based on response and tolerability. Avoid administering <4 hours before bedtime to minimize risk of supine hypertension.
Maximum Daily Dose Adults	30 mg/day
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics	N/A
Adjustment	**Altered kidney function:** eGFR < 30 mL/minute/1.73m^2: Initiate with a low dose (eg, 2.5 mg 1 to 3 times daily); increase to indication-specific dose as needed based on tolerability and response. **Hemodialysis, intermittent (thrice weekly):** Dialyzable (extent undetermined): Initiate with a low dose (eg, 2.5 mg 1 to 2 times daily); increase to indication-specific dose as needed based on tolerability and response.
Prescribing edits	CU, ST
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): Can be given either as monotherapy or in combination with fludrocortisone.	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	

QL (Quantity Limit): N/A	
ST (Step Therapy): Fludrocortisone is the primary pharmacological treatment for OH, while midodrine was considered a secondary option, either alone or in combination with fludrocortisone.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**>10%:** -Dermatologic: Piloerection, pruritus -Genitourinary: Dysuria (including urinary frequency, urinary retention, urinary urgency) -Nervous system: Paresthesia **1% to 10%:** -Cardiovascular: Supine hypertension -Dermatologic: Skin rash -Nervous system: Chills, pain (including abdominal pain)
Drug Interactions	**Category X**: -Iobenguane Radiopharmaceutical Products: Alpha1-Agonists may diminish the therapeutic effect of Iobenguane Radiopharmaceutical Products. Do not administer these drugs until at least 7 days after each iobenguane dose. -Lisuride
Special Population	N/A
Pregnancy	Adverse events were observed in animal reproduction studies. Information related to the use of midodrine in pregnancy is limited.
Lactation	It is not known if midodrine is excreted in breast milk. The manufacturer recommends that caution be exercised when administering midodrine to nursing women.
Contraindications	Severe organic heart disease; acute renal disease; urinary retention; pheochromocytoma; thyrotoxicosis;

	supine hypertension; poorly controlled hypertension.
Monitoring Requirements	BP while supine, sitting, and standing upon awakening; signs or symptoms of bradycardia; renal and hepatic function.
Precautions	**Disease-related concerns:** • Diabetes • Hepatic impairment: Midodrine is a prodrug metabolized to an active metabolite (desglymidodrine). • Renal impairment: Desglymidodrine, the active metabolite, is primarily renally excreted; assess renal function prior to initial dose; initiate with a reduced dose • Visual problems: Use with caution in patients with visual problems, especially if receiving fludrocortisone.
Black Box Warning	**Appropriate Use:** Because midodrine can cause marked elevation of supine BP, it should be used in patients whose lives are considerably impaired despite standard clinical care.
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of hypotension treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Midodrine.**

Table 7. Midodrine HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Midodrine	NICE[13]	**06 October 2015** • Midodrine is indicated for adults with OH due to autonomic dysfunction; its use for other types of OH is considered off-label. This approval is applicable when other potential causes have been ruled out, and alternative treatments have proven insufficient. • Limited evidence suggested that midodrine had a positive impact on certain symptoms of OH, such as syncope (fainting) and low energy levels. However, less favorable results were observed for other symptoms like light-headedness and dizziness. • The European Federation of Neurological Societies currently designates fludrocortisone as the primary pharmacological treatment for OH, while midodrine was considered a secondary option, either alone or in combination with fludrocortisone. • No studies assessing the cost-effectiveness of midodrine in treating OH were found.
	CADTH	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT – MIDODRINE

Midodrine hydrochloride, an α1-agonist, increases effective circulating blood volume and renal perfusion by increasing systemic and splanchnic BP. Midodrine is indicated for adults with OH due to autonomic dysfunction. This approval is applicable when other potential causes have been ruled out, and alternative treatments have proven insufficient. The usual dose is 2.5 mg 2 or 3 times daily. It can be gradually increased based on supine and standing BP measurements, up to a maintenance dose of 10 mg three times daily. However, careful evaluation of treatment response, weighing expected benefits and risks, is crucial, and if uncontrolled supine hypertension persists, discontinuation of midodrine is necessary. Adverse events seen commonly included piloerection (goose

bumps), itching, and tingling of the scalp, urinary retention, and supine hypertension. Midodrine's use is backed by NICE, although no studies assessing the cost-effectiveness of midodrine in treating OH were identified.

2.2.2 Dopamine

Information on Dopamine is detailed in the table below.

Table 8. Dopamine Drug Information

SCIENTIFIC NAME DOPAMINE[14]	
SFDA Classification	Prescription
SFDA	Yes
US FDA	N/A
EMA	N/A
MHRA	N/A
PMDA	N/A
Indication (ICD-10)	I95
Drug Class	Vasopressor
Drug Sub-class	Adrenergic Agonist Agent
ATC Code	C01CA04
Pharmacological Class (ASHP)	Vasopressor
DRUG INFORMATION	
Dosage Form	Concentrate for solution for infusion
Route of Administration	IV use
Dose (Adult) [DDD]	**Hypotension or shock:** **Cardiogenic shock (alternative agent):** **Note:** Typically, not the preferred initial agent in cardiogenic shock; consider other inotropic and/or vasopressor options. **Continuous infusion: IV:** Usual dosage range: 0.5 to 20 mcg/kg/minute; titrate based on clinical end point (eg, end-organ perfusion). **Septic shock and other vasodilatory shock states (alternative agent):** **Note: Not** recommended for septic shock *except* as an alternative to

	norepinephrine in patients with bradycardia who have a low risk of tachyarrhythmias. **Continuous infusion: IV:** Initial: 2 to 5 mcg/kg/minute; titrate to goal MAP up to a dose of 20 mcg/kg/minute. **Post–cardiac arrest shock (alternative agent):** **Note:** Typically, not the preferred initial agent in post–cardiac arrest shock due to risk of tachyarrhythmias; consider other inotropic and/or vasopressor options. **Continuous infusion: IV:** Usual dosage range: 5 to 20 mcg/kg/minute; titrate based on clinical end points (eg, MAP, end-organ perfusion). **Inotropic support:** **Note:** May consider in patients with severe systolic dysfunction with decreased end-organ perfusion. **Continuous infusion: IV:** 5 to 15 mcg/kg/minute; doses at lower end of this range are preferred as inotropic actions predominate at lower doses and vasoconstrictive actions predominate at higher doses.
Maximum Daily Dose Adults	N/A
Dose (pediatrics)	**Hemodynamic support:** **Infants, Children, and Adolescents:** **Continuous IV or intraosseous infusion:** 2 to 20 mcg/kg/minute; titrate gradually by 5 to 10 mcg/kg/minute increments until optimal response is obtained.
Maximum Daily Dose Pediatrics	N/A
Adjustment	N/A
Prescribing edits	CU
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	Norepinephrine

G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	N/A
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Cardiovascular:** Angina pectoris, atrial fibrillation, bradycardia, cardiac conduction disorder, ectopic beats, hypertension, hypotension, palpitations, tachycardia, vasoconstriction, ventricular arrhythmia. **Dermatologic:** Peripheral gangrene (with prolonged or high dose, can occur with low doses with concomitant occlusive vascular disease), piloerection **Gastrointestinal:** Nausea, vomiting **Nervous system:** Anxiety, headache **Respiratory:** Dyspnea
Drug Interactions	**Category X:** • Ergot Derivatives • Lisuride
Special Population	N/A
Pregnancy	Do not refrain from administering essential medications for critically ill pregnant patients due to worries about potential fetal teratogenicity. The medications employed for treating cardiac arrest in pregnant individuals align with those used in non-pregnant patients. While the use of dopamine may be contemplated in the post-resuscitation phase, it is crucial to weigh the potential impact of vasoactive medications on the fetus.
Lactation	It is not known if dopamine is present in breast milk.

Contraindications	Pheochromocytoma
Monitoring Requirements	BP; heart rate; ECG; hemodynamic parameters as appropriate (eg, CVP, RAP, CI, PCWP, SVR, $ScvO_2$ or SvO_2); end-organ perfusion (eg, urine output, mental status); infusion site for blanching/extravasation; intravascular volume status.
Precautions	***Concerns related to adverse effects:*** • **Arrhythmias:** May cause increases in heart rate, increasing the risk of tachycardia and other tachyarrhythmias including ventricular arrhythmias. • **Extravasation:** Vesicant; ensure proper needle or catheter placement prior to and during infusion. Avoid extravasation; infuse into a large vein if possible. Avoid infusion into leg veins. Watch IV site closely. If extravasation occurs, infiltrate the area with diluted phentolamine (5 to 10 mg in 10 mL of saline) with a fine hypodermic needle. Phentolamine should be administered as soon as possible after extravasation is noted to prevent sloughing/necrosis. ***Disease-related concerns:*** • **Cardiovascular disease:** Use with caution in patients with cardiovascular disease, cardiac arrhythmias and/or occlusive vascular disease. • **Active myocardial ischemia/post-myocardial infarction:** Use with caution in patients with active myocardial ischemia or recent myocardial infarction; may increase myocardial oxygen consumption. · **Electrolyte imbalance**: Correct electrolyte disturbances, especially hypokalemia or hypomagnesemia, prior

	to use and throughout therapy to minimize the risk of arrhythmias. • **Shock:** The use of dopamine in adult patients with shock (majority of patients had septic shock) demonstrated a higher incidence of adverse events (eg, tachyarrhythmias. Higher 28-day mortality was also seen in patients with septic shock with the use of dopamine as compared to norepinephrine. ***Dosage form specific issues:*** • **Sodium metabisulfite:** Product may contain sodium metabisulfite.
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Hypotension treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Dopamine.**

Table 9. Dopamine HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Dopamine	NICE[15]	**November 2021** Avoid the routine administration of inotropes or vasopressors in individuals experiencing acute heart failure and hypoperfusion syndrome. Contemplate the use of inotropes or vasopressors for those with acute heart failure and potentially reversible cardiogenic shock. Ensure that these treatments are administered in a cardiac care unit, high dependency unit, or a suitable setting capable of providing at least level 2 care (

		Level 2 care is for people needing more detailed observation or intervention, including support for a single failing organ system or postoperative care and for those stepping down from higher levels of care).
	CADTH	N/A
	HAS[16]	**April 2016** Indicated for short-term treatment of severe chronic heart failure in acute decompensation when standard therapy is insufficient and when the use of an inotropic agent is deemed appropriate. In situations where the patient is in a state of shock or severe hypoperfusion, it is recommended to use positive inotropes. The use of dopamine is restricted to patients experiencing persistent hypoperfusion.
	IQWIG[17]	**August 2014** The use of inotropic drugs for long-term treatment is only recommended as a palliative measure in end-stage heart failure patients who do not respond to standard medications. Additionally, they are recommended for short-term use in handling acute situations. The guideline advises against intravenous inotropic drug administration, except in cases of increased left ventricular filling pressure or severely affected cardiac index. Continuous or close monitoring of BP is also recommended for patients receiving inotropic drugs.
	PBAC	N/A

CONCLUSION STATEMENT- Dopamine

Dopamine is indicated in the management of cardiogenic shock, it serves as an alternative agent, supporting cardiac function by enhancing the force of heart muscle contractions. Additionally, in septic shock cases, dopamine functions as an adjunctive agent alongside norepinephrine. Administered intravenously, the dosage ranges from 0.5 to 20 mcg/kg/minute in cardiogenic shock and 2 to 5 mcg/kg/minute (with potential escalation to 20 mcg/kg/minute) in septic shock scenarios. It should be administered with caution due to its potential side effects. It has the capacity to increase heart rate, elevating the risk of tachycardia and other

tachyarrhythmias, including ventricular arrhythmias. The use of dopamine is supported by NICE, IQWIG, and HAS.

2.2.3 Dobutamine

Information on Dobutamine is detailed in the table below.

Table 10. Dobutamine Drug Information

SCIENTIFIC NAME DOBUTAMINE[18]	
SFDA Classification	Prescription
SFDA	Yes
US FDA	N/A
EMA	N/A
MHRA	N/A
PMDA	N/A
Indication (ICD-10)	I95
Drug Class	Vasopressor
Drug Sub-class	Adrenergic Agonist Agent
ATC Code	C01CA07
Pharmacological Class (ASHP)	Vasopressor
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	IV use
Dose (Adult) [DDD]	**Acute decompensated heart failure: Note:** May consider for short-term use in patients with low cardiac index and hypotension or end-organ hypoperfusion. **Continuous infusion: IV:** Initial: 2 to 5 mcg/kg/minute; titrate based on clinical end point (eg, systemic perfusion or end-organ perfusion); usual dosage range: 2 to 10 mcg/kg/minute. **Inotropic support (off-label use): Note:** In patients with shock (eg, sepsis) who fail to meet hemodynamic goals with vasopressor therapy (eg, norepinephrine), dobutamine may be

	added to vasopressor therapy if there is continued hypoperfusion despite volume resuscitation. **Continuous infusion: IV:** Initial: 2 to 5 mcg/kg/minute; titrate based on clinical end point (eg, BP, end-organ perfusion); usual dosage range: 2 to 10 mcg/kg/minute; however, doses as low as 0.5 mcg/kg/min have been used in less severe cardiac decompensation.
Maximum Daily Dose Adults	20 mcg/kg/minute
Dose (pediatrics)	**Hemodynamic support: Infants, Children, and Adolescents: Continuous IV or intraosseous infusion: Initial:** 0.5 to 1 mcg/kg/minute; titrate gradually every few minutes until desired response achieved; usual range: 2 to 20 mcg/kg/minute.
Maximum Daily Dose Pediatrics	20 mcg/kg/minute
Adjustment	N/A
Prescribing edits*	ST
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	Inotropic drugs like dobutamine are usually reserved for patients who do not show a response to conventional treatments.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**1% to 10%:** **Cardiovascular:** Angina pectoris, chest pain, increased heart rate, increased

	systolic blood pressure, palpitations, premature ventricular contractions **Gastrointestinal:** Nausea **Nervous system:** Headache **Respiratory:** Dyspnea
Drug Interactions	-Beta-Blockers: May diminish the therapeutic effect of Dobutamine. ***Risk C: Monitor therapy.*** -Calcium Salts: May diminish the therapeutic effect of Dobuamine. ***Risk C: Monitor therapy***. -Cannabinoid-Containing Products: May enhance the tachycardic effect of Sympathomimetics. ***Risk C: Monitor therapy.*** -COMT Inhibitors: May increase the serum concentration of COMT Substrates. ***Risk C: Monitor therapy.***
Special Population	Older adults: Use with caution in older adults; start at lower end of the dosage range.
Pregnancy	In cases of cardiac arrest during pregnancy, the same medications used in non-pregnant females should be administered. Concerns about fetal teratogenicity should not lead to the withholding of appropriate medications. While dobutamine use in the post-resuscitation phase may be considered, it is crucial to weigh the potential effects of inotropic support on the fetus.
Lactation	It is not known if dobutamine is present in breast milk.
Contraindications	-Pheochromocytoma -Hypersensitivity to dobutamine or sulfites (some contain sodium metabisulfate), or any component of the formulation -Hypertrophic cardiomyopathy with outflow tract obstruction (formerly

	known as idiopathic hypertrophic subaortic stenosis).
Monitoring Requirements	BP; heart rate; ECG; hemodynamic parameters as appropriate (eg, CVP, RAP, MAP, CI, PCWP, SVR, $ScvO_2$ or SvO_2); intravascular volume status; kidney function; urine output.
Precautions	***Concerns related to adverse effects:*** • **Arrhythmias:** Ventricular arrhythmias, including nonsustained ventricular tachycardia and supraventricular arrhythmias, have been reported. Observe closely for arrhythmias in patients with decompensated heart failure; sudden cardiac death has been observed. • **Heart failure complications:** An increased risk of hospitalization and death has been observed with prolonged use in New York Heart Association Class III/IV heart failure patients. • **Tachycardia:** May cause dose-related increases in heart rate**.** • **Ventricular ectopy:** May exacerbate ventricular ectopy (dose related). ***Disease-related concerns:*** •**Aortic stenosis:** Ineffective therapeutically in the presence of mechanical obstruction such as severe aortic stenosis. • **Electrolyte imbalance:** Correct electrolyte disturbances, especially hypokalemia or hypomagnesemia, prior to use and throughout therapy to minimize the risk of arrhythmias. • **Hypovolemia:** If needed, correct hypovolemia first to optimize hemodynamics.

	• **Active myocardial ischemia/myocardial infarction (post):** Use with caution in patients with active myocardial ischemia or recent myocardial infarction; can increase myocardial oxygen demand. ***Concurrent drug therapy issues:*** • **Monoamine oxidase inhibitors:** Use with extreme caution in patients taking monoamine oxidase inhibitors; prolong hypertension may result from concurrent use. ***Dosage form specific issues:*** • **Sodium sulfite:** Product may contain sodium sulfite
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Hypotension treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Dobutamine.**

Table 11. Dobutamine HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Dobutamine	NICE[15]	**November 2021** Avoid the routine administration of inotropes or vasopressors in individuals experiencing acute heart failure and hypoperfusion syndrome. Contemplate the use of inotropes or vasopressors for those with acute heart failure and potentially reversible cardiogenic shock.

		Ensure that these treatments are administered in a cardiac care unit, high dependency unit, or a suitable setting capable of providing at least level 2 care (Level 2 care is for people needing more detailed observation or intervention, including support for a single failing organ system or postoperative care and for those stepping down from higher levels of care).
	CADTH	N/A
	HAS[16]	**April 2016** Indicated for short-term treatment of severe chronic heart failure in acute decompensation when standard therapy is insufficient and when the use of an inotropic agent is deemed appropriate. In situations where the patient is in a state of shock or severe hypoperfusion, it is recommended to use positive inotropes. Inotropic drugs like dobutamine are usually reserved for patients who do not show a response to conventional treatments. These medications aim to enhance short-term hemodynamic parameters, specifically CO and BP.
	IQWIG[17]	**August 2014** The use of inotropic drugs for long-term treatment is only recommended as a palliative measure in end-stage heart failure patients who do not respond to standard medications. Additionally, they are recommended for short-term use in handling acute situations. The guideline advises against intravenous inotropic drug administration, except in cases of increased left ventricular filling pressure or severely affected cardiac index. Continuous or close monitoring of BP is also recommended for patients receiving inotropic drugs.
	PBAC	N/A

CONCLUSION STATEMENT- Dobutamine

Dobutamine is indicated as a support measure for patients in septic shock who do not achieve hemodynamic goals with norepinephrine alone. Additionally, dobutamine finds application in the short-term management of acute decompensated heart failure. Administered intravenously at a dosage ranging from 2 to 5 mcg/kg/minute, with a usual range of 2 to 10 mcg/kg/minute, its use is supported by NICE, IQWIG, and HAS recommendations. Some individuals may experience cardiovascular effects, including angina pectoris, chest pain, an elevated heart rate, increased systolic BP, palpitations, and premature ventricular contractions. These side effects highlight the importance of cautious administration and vigilant monitoring when using dobutamine, as healthcare professionals strive to strike a balance between therapeutic benefits and potential cardiovascular risks in each patient.

2.2.4 Ephedrine Hydrochloride

Information on Ephedrine is detailed in the table below[19].

Table 12. Ephedrine Drug Information

SCIENTIFIC NAME EPHEDRINE	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	I95
Drug Class	CARDIAC STIMULANTS EXCL. CARDIAC GLYCOSIDES
Drug Sub-class	ADRENERGIC AND DOPAMINERGIC AGENTS
ATC Code	C01CA26
Pharmacological Class (ASHP)	Adrenergic agents
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	**Anesthesia induced hypotension:**

	5 to 10 mg, repeat as needed to maintain BP
Maximum Daily Dose Adults	Maximum total cumulative dose: 50 mg.
Dose (pediatrics)	0.1 to 0.3 mg/kg/dose;
Maximum Daily Dose Pediatrics	50mg daily
Adjustment	There are no dosage adjustments.
Prescribing edits	**N/A**
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	N/A
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	• Gastrointestinal: nausea, vomiting • Nervous system: dizziness • Bradycardia, hypertension, irregular pulse, palpitations, tachycardia, ventricular ectopy. • Tachyphylaxis
Drug Interactions	Risk X: • Ergo derivatives • Kratom • Inhalational Anesthetics • Lisuride • Monoamine oxidase inhibitors
Special Population	Use with caution in elderly
Pregnancy	Metabolic acidosis has been reported in neonates following maternal use of ephedrine. Serious postpartum hypertension and possibly stroke may occur if ephedrine is administered with oxytocic medications.
Lactation	Ephedrine is present in breast milk. According to the manufacturer, the

	decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother.
Contraindications	N/A
Monitoring Requirements	Blood pressure, pulse; monitor patients with renal impairment for adverse reactions.
Precautions	**Concerns related to adverse effects:** May cause hypertension if used prophylactically for hypotension. **Disease-related concerns:** Use with caution in patients with renal impairment; increased elimination half-life may occur.
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of anesthesia induced hypotension treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Ephedrine.**

Table 13. Ephedrine HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Ephedrine	NICE	N/A
	CADTH	N/A
	HAS[20]	According to the recommendations of the French Anaesthesia and Intensive Care Society (SFAR), the two vasopressors used as a first-line treatment are ephedrine and noradrenaline, due to their combined α and β actions which allow for the correction of arterial

		hypotension with the maintenance of cardiac output despite the increase in arterial resistance.
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Ephedrine

Ephedrine is a medication that belongs to the sympathomimetic class of drugs. The FDA-approved primary use for ephedrine is in addressing clinically significant hypotension during the perioperative period. In fact, general anesthesia induction and maintenance during operative procedures often lead to vasodilation and hypotension, necessitating the use of vasopressors. Ephedrine is frequently chosen to address hypotension induced by spinal or epidural anesthesia, especially in obstetrics where sympathectomy during spinal anesthetics results in hypotension in 80% of patients. The usual dose: IV: Initial: 5 to 10 mg, repeat as needed to maintain BP (maximum total cumulative dose: 50 mg). Ephedrine may produce palpitations, headache, dizziness, nausea, vomiting, restlessness, and anxiety in the conscious patient. Ephedrine is also arrhythmogenic, and clinicians should be cautious when administering patients predisposed to arrhythmias or taking other arrhythmogenic medications, particularly digitalis. Another common effect of ephedrine is an alteration in the time until the onset and duration of action of other drugs. This effect is most notable during induction when giving ephedrine to a hypotensive patient before rocuronium[21,22–25]. HAS approves the use of ephedrine in anesthesia induced hypotension.

2.2.5 Norepinephrine

Information on Norepinephrine is detailed in the table below[19].

Table 14. Norepinephrine Drug Information

SCIENTIFIC NAME NOREPINEPHRINE	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	I95

Drug Class	CARDIAC STIMULANTS EXCL. CARDIAC GLYCOSIDES
Drug Sub-class	ADRENERGIC AND DOPAMINERGIC AGENTS
ATC Code	C01CA03
Pharmacological Class (ASHP)	Adrenergic agents
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	**Septic shock and other vasodilatory shock states** IV: Initial: 0.05 to 0.15 mcg/kg/minute; titrate to goal mean arterial pressure (MAP). Usual dose range: 0.025 to 1 mcg/kg/minute. Non-weight-based dosing: IV: Initial: 5 to 15 mcg/minute; titrate to goal MAP; usual dose range: 2 to 80 mcg/minute;
Maximum Daily Dose Adults	Maximum dose range for refractory shock: 1 to 3.3 mcg/kg/minute.
Dose (pediatrics)	0.05 to 0.1 mcg/kg/minute; titrate to desired effect.
Maximum Daily Dose Pediatrics	Usual maximum dose: 2 mcg/kg/minute
Adjustment	There are no dosage adjustments.
Prescribing edits	**N/A**
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	N/A
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions	• Gastrointestinal: nausea, vomiting

(most common and most serious)	• Bradycardia, hypertension, irregular pulse, palpitations, tachycardia, ventricular ectopy. • Anxiety • Dyspnea
Drug Interactions	Risk X: • Ergo derivatives • Kratom • Lisuride
Special Population	N/A
Pregnancy	Norepinephrine is an endogenous catecholamine and crosses the placenta. Medications used for the treatment of cardiac arrest in pregnancy are the same as in the non-pregnant woman. Appropriate medications should not be withheld due to concerns of fetal teratogenicity.
Lactation	It is not known if norepinephrine is present in breast milk. The manufacturer recommends that caution be exercised when administering norepinephrine to breastfeeding women.
Contraindications	N/A
Monitoring Requirements	Blood pressure, pulse; intravascular volume.
Precautions	**Concerns related to adverse effects:** Extravasation. **Disease-related concerns:** Hypovolemia and hypoxia.
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of septic shock treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency

in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Norepinephrine.**

Table 15. Norepinephrine HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Norepinephrine	NICE	N/A
	CADTH	N/A
	HAS[20]	According to the recommendations of the French Anaesthesia and Intensive Care Society (SFAR), the two vasopressors used as a first-line treatment are ephedrine and noradrenaline, due to their combined α and β actions which allow for the correction of arterial hypotension with the maintenance of cardiac output despite the increase in arterial resistance. Approval of reimbursement for noradrenaline tartrate, solution for injection/infusion for the restoration and maintenance of peri-operative blood pressure following hypotension induced by spinal anesthesia or general anesthesia in adults.
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT – NOREPINEPHRINE

Norepinephrine, a critical neurotransmitter and hormone, acts as a potent vasoconstrictor by stimulating alpha-adrenergic receptors in the peripheral vasculature. Norepinephrine is used as a first-line therapy in the management of septic shock-induced hypotension. The typical initial dose of norepinephrine for managing refractory septic shock ranges from 0.05 to 0.15 mcg/kg/minute, with the usual dose falling within the range of 0.025 to 1 mcg/kg/minute. In addition, it is used in short-term treatment of severe chronic heart failure in acute decompensation when standard therapy is insufficient. While norepinephrine is generally effective in elevating blood pressure, its use is not without potential side effects. Common adverse effects include increased heart rate, hypertension, and reduced blood flow to peripheral tissues. Careful monitoring and titration are essential to balance its hemodynamic benefits with potential side effects in the peri-operative setting. HAS approves the use of ephedrine in anesthesia induced hypotension.

2.2.6 Epinephrine

Information on Epinephrine is detailed in the table below[26].

Table 16. Epinephrine Drug Information

SCIENTIFIC NAME EPINEPHRINE	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	I95
Drug Class	CARDIAC STIMULANTS EXCL. CARDIAC GLYCOSIDES
Drug Sub-class	ADRENERGIC AND DOPAMINERGIC AGENTS
ATC Code	C01CA24
Pharmacological Class (ASHP)	Adrenergic agents
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	**Septic shock and other vasodilatory shock states (adjunctive agent):** IV: Initial: 0.01 to 0.2 mcg/kg/minute; titrate to goal MAP or end-organ perfusion; usual dose range: 0.01 to 0.5 mcg/kg/minute. Non-weight-based dosing: IV: Initial: 1 to 15 mcg/minute; titrate to goal MAP or end-organ perfusion; usual dose range: 1 to 40 mcg/minute; maximum dose range for refractory shock: 40 to 160 mcg/minute.
Maximum Daily Dose Adults	Maximum dose range for refractory shock: 0.5 to 2 mcg/kg/minute

Dose (pediatrics)	0.1 to 1 mcg/kg/minute; rates >0.3 mcg/kg/minute associated with vasopressor activity
Maximum Daily Dose Pediatrics	N/A
Adjustment	There are no dosage adjustments.
Prescribing edits	**CU**
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	Considered as adjunctive use when goal MAP not achieved with initial vasopressor or need for inotropic therapy.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	N/A
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	• Gastrointestinal: nausea, vomiting • Bradycardia, hypertension, irregular pulse, palpitations, tachycardia, ventricular ectopy, angina pectoris, chest pain. • Anxiety • Dyspnea
Drug Interactions	Risk X: • Ergo derivatives • Kratom • Lisuride • Bromperidol • Isoproterenol • blonanserin
Special Population	Older patients and pediatrics
Pregnancy	Epinephrine crosses the placenta. Epinephrine is recommended for the treatment of anaphylaxis in pregnant

	women. Specific dosing is not available; use with caution and monitor hemodynamic response.
Lactation	It is not known if epinephrine is present in breast milk. Epinephrine is generally considered compatible in breastfeeding and is recommended for the treatment of anaphylaxis in breastfeeding women.
Contraindications	N/A
Monitoring Requirements	Blood pressure, pulse; intravascular volume, monitor site of infusion for blanching/extravasation.
Precautions	**Concerns related to adverse effects:** Extravasation and cardiac effects **Disease-related concerns:** Hypovolemia and hypoxia, arrythmia, use with caution in patients with pheochromocytoma and thyroid disease.
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from the HTA bodies, including the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), the Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Health Care, and the Pharmaceutical Benefits Advisory Committee (PBAC) didn't yield any guidance for epinephrine in septic shock management. This is probably because treatment paradigms haven't much changed in the last decade, with no new drugs introduced in the management landscape.

CONCLUSION STATEMENT – EPINEPHRINE

Epinephrine, a critical neurotransmitter and hormone, acts as a potent vasoconstrictor by stimulating alpha-adrenergic receptors in the peripheral vasculature. In cases of hypotension and septic shock, epinephrine is employed to enhance cardiac output and restore blood pressure. Epinephrine is considered for adjunctive use when the target pressure is not achieved with the initial vasopressor or when inotropic therapy is required. The initial dose typically ranges from 0.05 to 0.2 mcg/kg/minute, with adjustments based on the patient's response. The

maintenance dose is often titrated to achieve the desired blood pressure, usually falling between 0.02 to 0.5 mcg/kg/minute. While epinephrine proves effective in stabilizing hemodynamics, it is not without potential side effects. Common adverse reactions include increased heart rate, palpitations, and elevated blood pressure. Careful monitoring is essential to manage potential complications and ensure optimal therapeutic outcomes. There are no recommendations issued by the HTA bodies for epinephrine.

2.4 Parasympathomimetic Agents

2.4.1 Pyridostigmine

Information on Pyridostigmine is detailed in the table below[27].

Table 17. Pyridostigmine Drug Information

SCIENTIFIC NAME PYRIDOSTIGMINE	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes (off-label)
EMA	Yes (off-label)
MHRA	N/A
PMDA	N/A
Indication (ICD-10)	I95
Drug Class	Cholinesterase Inhibitors
Drug Sub-class	Reversible Acetylcholinesterase Inhibitors
ATC Code	N07AA02
Pharmacological Class (ASHP)	Parasympathomimetic (Cholinergic) Agents
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral use
Dose (Adult) [DDD]*	**Postural orthostatic tachycardia syndrome (off-label use): Immediate release: Oral: Initial:** 30 mg twice daily, may increase dose at intervals of 1 to 2 weeks to 30 to 60 mg up to 3 times daily.

Maximum Daily Dose Adults	180 mg/day
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics	N/A
Adjustment	There are no dosage adjustments.
Prescribing edits	N/A
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	• Gastrointestinal: Increased peristalsis, vomiting • Nervous system: Asthenia • Neuromuscular & skeletal: Fasciculations • Ophthalmic: Miosis
Drug Interactions	• **Ceritinib:** Management: If this combination cannot be avoided, monitor patients for evidence of symptomatic bradycardia, and closely monitor BP and heart rate during therapy. ***Risk D: Consider therapy modification.*** • **Fexinidazole:** Bradycardia-Causing Agents may enhance the arrhythmogenic effect of Fexinidazole***. Risk X: Avoid combination.*** • **Fingolimod:** Management: Consult with the prescriber of any bradycardia-causing agent to see if the agent could be switched to an agent that does not cause bradycardia prior to initiating

	fingolimod. If combined, perform continuous ECG monitoring after the first fingolimod dose. ***Risk D: Consider therapy modification.***
Special Population	**Bromide sensitivity:** Use with caution in patients with bromide sensitivity.
Pregnancy	Pyridostigmine can traverse the placenta. Additionally, the transfer of maternal antibodies via the placenta can lead to transient neonatal myasthenia gravis in newborns. Medications should be administered if there is a clear indication, considering the overall health and prognosis of the mother.
Lactation	Pyridostigmine has been identified in breast milk. Monitoring breastfed infants for fatigue related to transient neonatal myasthenia gravis is advised. However, current guidelines state that breastfeeding is deemed acceptable in women taking pyridostigmine.
Contraindications	• Hypersensitivity to pyridostigmine, anticholinesterase agents, or any component of the formulation • Mechanical intestinal or urinary obstruction
Monitoring Requirements	ECG, BP, and heart rate especially when administered IV; cholinergic reactions (eg, nausea, vomiting, diarrhea, increased salivation) especially when administered IV.
Precautions	**Concerns related to adverse effects:** • Cholinergic effects: Symptoms of excess cholinergic activity may occur (eg, salivation, sweating, urinary incontinence). Overdosage may result in cholinergic crisis (eg, muscle weakness), which must be distinguished from myasthenic crisis,

	discontinue immediately in the presence of cholinergic crisis. • Hypersensitivity reactions: May occur, have atropine and epinephrine ready to treat hypersensitivity reactions. **Disease-related concerns:** • Cardiovascular disease: Use with caution in patients with bradycardia or other cardiac arrhythmias. • Glaucoma: Use with caution, additive effect with antiglaucoma drugs may cause or exacerbate problems with night vision. • Renal impairment: Use with caution in patients with renal impairment, initial lower doses may be needed. • Respiratory disease: Use with extreme caution in patients with asthma, bronchospastic disease, or chronic obstructive pulmonary disease.
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from the HTA bodies, including the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), the Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Health Care, and the Pharmaceutical Benefits Advisory Committee (PBAC) didn't yield any guidance for pyridostigmine in hypotension. This is probably because treatment paradigms haven't much changed in the last decade, with no new drugs introduced in the management landscape.

CONCLUSION STATEMENT- Pyridostigmine

Pyridostigmine works by inhibiting the acetylcholinesterase enzyme from breaking down the neurotransmitter acetylcholine, and thereby increases the bioavailability of acetylcholine and enhances the transmission of nerve impulses at neuromuscular junctions. It is indicated for postural orthostatic tachycardia syndrome (off-label use). The usual dose is 30 mg twice daily and we may increase

dose at intervals of 1 to 2 weeks to 30 to 60 mg up to 3 times daily. When administered intravenously, close monitoring of ECG, BP, and heart rate is crucial, with particular attention to potential cholinergic reactions such as nausea, vomiting, diarrhea, and increased salivation. Use with caution in patients with bromide sensitivity. There are no recommendations issued by the HTA bodies for octreotide.

2.5 Vasopressin and analogues

2.5.1 Vasopressin

Information on Vasopressin is detailed in the table below[28].

Table 18. Vasopressin Drug Information

SCIENTIFIC NAME VASOPRESSIN	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	I95
Drug Class	POSTERIOR PITUITARY LOBE HORMONES
Drug Sub-class	VASOPRESSIN AND ANALOGUES
ATC Code	H01BA01
Pharmacological Class (ASHP)	Vasopressin agonists
DRUG INFORMATION	
Dosage Form	Injectable solution
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	**Septic shock and other vasodilatory shock states (adjunctive agent):** Continuous infusion: IV: 0.03 units/minute added to norepinephrine as a fixed dose (not titrated); usual dosage range: 0.01 to 0.04 units/minute;
Maximum Daily Dose Adults	Doses >0.04 units/minute should be reserved for salvage therapy due to potential risk of ischemic complications

Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics	N/A
Adjustment	There are no dosage adjustments.
Prescribing edits	**CU**
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	Considered as adjunctive use when goal mean arterial pressure is not achieved with initial catecholamine vasopressor (eg, norepinephrine) or to decrease catecholamine vasopressor dosage requirements.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	N/A
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	• Gastrointestinal: Mesenteric ischemia • Skin lesion • Cardiovascular: Atrial fibrillation, bradycardia, ischemic heart disease, limb ischemia (distal), low cardiac output, right heart failure, shock
Drug Interactions	**Risk X:** Fexinidazole
Special Population	N/A
Pregnancy	Vasopressin may produce tonic uterine contractions. Due to pregnancy-induced physiologic changes, vasopressin clearance may be increased in the second and third trimesters; dose adjustment may be needed. Clearance returns to normal within 2 weeks postpartum.
Lactation	It is not known if vasopressin is present in breast milk.

Contraindications	Hypersensitivity to vasopressin or any component of the formulation; hypersensitivity to chlorobutanol.
Monitoring Requirements	Serum and urine sodium, urine-specific gravity, urine and serum osmolality; urine output, fluid input and output, BP, heart rate, digital/extremity infusion site for blanching/extravasation.
Precautions	**Concerns related to adverse effects:** • Diabetes insipidus: Reversible diabetes insipidus may occur following discontinuation of vasopressin therapy. • Extravasation: vesicant; ensure proper needle or catheter placement prior to and during infusion. **Disease-related concerns:** • Cardiovascular disease: Use with caution in patients with bradycardia or other cardiac arrhythmias. • Renal impairment: Use with caution in patients with renal impairment, initial lower doses may be needed. • Migraine
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from the HTA bodies, including the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), the Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Health Care, and the Pharmaceutical Benefits Advisory Committee (PBAC) didn't yield any guidance for vasopressin in septic shock management. This is probably because treatment paradigms haven't much changed in the last decade, with no new drugs introduced in the management landscape.

CONCLUSION STATEMENT- Vasopressin

Vasopressin, a key player in maintaining vascular tone and fluid balance, operates by stimulating V1a receptors on vascular smooth muscle. In the context of hypotension and septic shock, vasopressin serves as a valuable vasopressor, inducing vasoconstriction and elevating blood pressure. It is often considered as an adjunctive therapy when the goal mean arterial pressure is not achieved with initial catecholamine vasopressor (eg, norepinephrine) or to decrease catecholamine vasopressor dosage requirements. The typical dose of vasopressin ranges from 0.01 to 0.04 units/minute. Adjustments are made based on the patient's response. While vasopressin is generally well-tolerated, side effects such as hyponatremia and decreased cardiac output may occur. Close monitoring is imperative to address any adverse reactions promptly and ensure optimal therapeutic outcomes. Notably, there are no specific recommendations issued by health technology assessment (HTA) bodies for vasopressin.

2.6 Other Drugs

This section details drugs that are approved by the U.S. Food and Drug Administration (FDA) and/or the European Medicines Agency (EMA) and are recommended to be used for the management of hypotension; however, they are not currently registered by the Saudi Food and Drug Authority (SFDA).

2.6.1 Fludrocortisone [29,30]

Fludrocortisone is a synthetic corticosteroid that primarily acts by promoting sodium retention and potassium excretion in the kidneys, expanding plasma volume, and increasing BP. Fludrocortisone is indicated for NOH associated with disorders such as Parkinson's disease. This medication plays a vital role in regulating BP, contributing to its widespread use in clinical practice. The initial dose varies but is typically in the range of 0.05 to 0.1 mg once daily. The maintenance dose should be between 0.05 to 0.2 mg/day administered in 1 or 2 divided doses. No specific dosage adjustments for patients with renal or hepatic impairment are recommended; however, it is advisable to use the medication with caution.

Common side effects include fluid retention, hypertension, and electrolyte imbalances. Monitoring individuals on fludrocortisone is crucial for ensuring efficacy and safety. Regular BP assessments, especially in different positions, gauge the medication's impact. Periodic blood tests monitor electrolyte levels, preventing imbalances. Fluid status assessments, including monitoring for edema and weight changes, detect potential fluid retention. Prompt reporting of unusual symptoms allows for timely adjustments. Regular follow-ups and patient education on adherence optimize overall management, emphasizing safety in treating OH.

HAS assessment of fludrocortisone for NOH suggests a limited clinical benefit, lacking proven added value in treating this condition. While fludrocortisone is authorized for use in cases of NOH when non-medicinal measures prove ineffective, the available data indicate only a modest improvement in BP upon standing. Notably, there is a lack of comparative data to establish the efficacy and safety of fludrocortisone compared to midodrine, another treatment option. The approval for non-hospital pharmacy reimbursement and hospital treatment is granted, but caution is advised due to the known safety profile, including side effects such as swelling of the ankles, hypertension, nausea, headaches, vertigo, and dizziness.

2.6.2 Droxidopa [1,31]

Droxidopa is a prodrug converted into norepinephrine in the body, acting as both a neurotransmitter and hormone that constricts blood vessels to maintain BP. Individuals with NOH often have a deficiency in norepinephrine. Droxidopa addresses this deficiency by increasing norepinephrine levels in the synaptic clefts—the small gaps between nerve endings and target cells. This enhancement of norepinephrine facilitates vasoconstriction, aiding in the elevation of BP, particularly in response to changes in body position, such as standing up.

The usual initial dose of droxidopa is often 100 mg three times daily, and adjustments may be made based on individual patient response. The maintenance dose is typically in the range of 200 to 600 mg daily, divided into multiple doses.

Common side effects include headache, dizziness, nausea, and hypertension. Given these potential side effects, it is crucial to monitor BP regularly during treatment. Additionally, caution should be exercised in patients with certain cardiovascular conditions. Regular monitoring of BP, especially in the initial stages of treatment, is essential to assess the medication's effectiveness and manage potential side effects. Healthcare providers may adjust the dosage based on the patient's response to achieve optimal BP control while minimizing adverse effects.

Pregnancy Category C is assigned to droxidopa. The potential benefits of using droxidopa during pregnancy should be carefully weighed against the potential risks. Similarly, the transfer of droxidopa into breast milk and its effects on nursing infants are not well-established. Therefore, it is advisable for breastfeeding women to discuss the risks and benefits with their healthcare providers before using droxidopa.

Section 3.0 Key Recommendations

The key recommendations are listed below along with their respective levels of evidence:

Nonpharmacological therapy

- **Patient Education:** Provide patients with comprehensive information about the nature of their condition, accompanied by lifestyle recommendations. **Class I, Level C**
- **Volume Expansion Emphasis:** Stress the importance of expanding extracellular volume for effective management. **Class I, Level C**
- **Salt and Water Intake Recommendations:** In the absence of hypertension, advise patients to maintain adequate salt and water intake, aiming for 2–3 liters of fluids per day and 10 grams of sodium chloride. **Class I, Level C**
- **Effectiveness of Cool Water Ingestion:** Highlight reports suggesting that the rapid ingestion of cool water can effectively counteract orthostatic intolerance and postprandial hypotension. **Class I, Level C**
- **Encouraging PCM** like leg crossing and squatting in patients experiencing warning symptoms and capable of performing these maneuvers. **Class IIa, Level C**
- **Addressing gravitational venous pooling** in older patients using abdominal binders or compression stockings. **Class IIa, Level B**
- **Elevating the head of the bed** (>10 degrees) during sleep prevents nocturnal polyuria, maintains favorable fluid distribution, and improves nocturnal hypertension. **Class IIa, Level C**

Pharmacological therapy

- **Midodrine** has demonstrated efficacy in alleviating symptoms related to NOH. Nevertheless, its utilization might be limited due to the occurrence of supine hypertension. Moreover, individuals prescribed Midodrine may encounter typical side effects such as scalp tingling, piloerection, and urinary retention. The recommended dosage ranges from 2.5 to 10 mg administered twice or thrice daily. **IIa / B-R**
- **Droxidopa** demonstrates effective improvement in symptoms associated with NOH in conditions like Parkinson's disease and has shown potential in reducing falls according to small-scale studies. Nevertheless, its application may be restricted by factors like supine hypertension, and potential side effects, including headache, dizziness, and nausea, should be considered. The

recommended dosage ranges from 100 to 600 mg administered three times daily. **IIa / B-R**

- **Fludrocortisone** enhances plasma volume, providing relief from OH symptoms. Its consistent use may offer preventive benefits for OH, especially in post-space flight scenarios such as with astronauts, although the potential limitation of supine hypertension should be acknowledged. In cases of existing supine hypertension, alternative medications are recommended over fludrocortisone. Common side effects include edema, hypokalemia, and headaches, while more severe reactions like adrenal suppression and immunosuppression are associated with doses exceeding 0.3 mg per day. The recommended daily dosage ranges from 0.05 to 0.3 mg. **IIa / C-LD**
- For patients experiencing autonomic failure and non-responsive NOH with other treatments, **Pyridostigmine** has the capacity to enhance orthostatic tolerance by elevating peripheral vascular resistance and BP. However, potential side effects encompass nausea, vomiting, abdominal cramping, sweating, salivation, and urinary incontinence. The recommended dosage ranges from 30 to 60 mg administered twice or thrice daily. **IIb / C-LD**
- **Octreotide** could provide advantages for individuals experiencing syncope and facing recurrent postprandial or NOH that is resistant to other treatments. The recommended dose is 0.2–1.6 mg/kg per day, administered subcutaneously. **IIb / C-LD**
- **Ephedrine**, a sympathomimetic drug, is FDA-approved for treating clinically significant hypotension during the perioperative period, especially in situations where general anesthesia induces vasodilation and hypotension. It is frequently chosen to manage hypotension resulting from spinal or epidural anesthesia, particularly in obstetrics. Caution is advised in patients with hypotension and concurrent tachycardia. The intravenous dosage for anesthesia-induced hypotension is an initial 5 to 10 mg dose, repeatable as needed, with a maximum total cumulative dose of 50 mg.
- **Dopamine** is recommended for managing cardiogenic shock as an alternative agent. In septic shock cases, it acts as an adjunctive agent alongside norepinephrine, with intravenous dosages ranging from 0.5 to 20 mcg/kg/minute in cardiogenic shock and 2 to 5 mcg/kg/minute (potentially escalating to 20 mcg/kg/minute) in septic shock. Caution is advised due to potential side effects, including an increased risk of tachycardia and other tachyarrhythmias, including ventricular arrhythmias. **Strong, high-quality evidence.**
- **Dobutamine** is indicated to support patients in septic shock not achieving hemodynamic goals with norepinephrine alone. It's also used in short-term

management of acute decompensated heart failure. It is administered intravenously at 2 to 5 mcg/kg/minute (usually 2 to 10 mcg/kg/minute). Cardiovascular effects may occur, underscoring the importance of cautious administration and monitoring to balance therapeutic benefits and potential risks. **Weak recommendation.**

- **Norepinephrine** serves as a potent vasoconstrictor for septic shock-induced hypotension. Initial doses range from 0.05 to 0.15 mcg/kg/minute, with the usual dose from 0.025 to 1 mcg/kg/minute. It's also used in severe chronic heart failure. Despite its effectiveness, side effects such as increased heart rate, hypertension, and reduced blood flow require careful monitoring and titration for optimal outcomes. **Strong, high- quality evidence.**
- **Epinephrine**, acting as a vasoconstrictor in hypotension and septic shock, enhances cardiac output and restores blood pressure. It's considered adjunctive when initial vasopressors are insufficient. Initial doses range from 0.05 to 0.2 mcg/kg/minute, titrated to 0.02 to 0.5 mcg/kg/minute. Effective in stabilizing hemodynamics, its potential side effects, including increased heart rate and elevated blood pressure, necessitate vigilant monitoring. **Low quality evidence.**
- **Vasopressin** acts in hypotension and septic shock by inducing vasoconstriction. It's considered adjunctive when initial catecholamine vasopressors are insufficient. Doses range from 0.01 to 0.04 units/minute, with adjustments based on the patient's response. While generally well-tolerated, hyponatremia and decreased cardiac output may occur, emphasizing the need for close monitoring. No specific recommendations from health technology assessment (HTA) bodies exist for vasopressin. **Strong, moderate quality evidence.**

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of OH.

These recommendations should be used to support and not supplant decisions in individual patient management.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

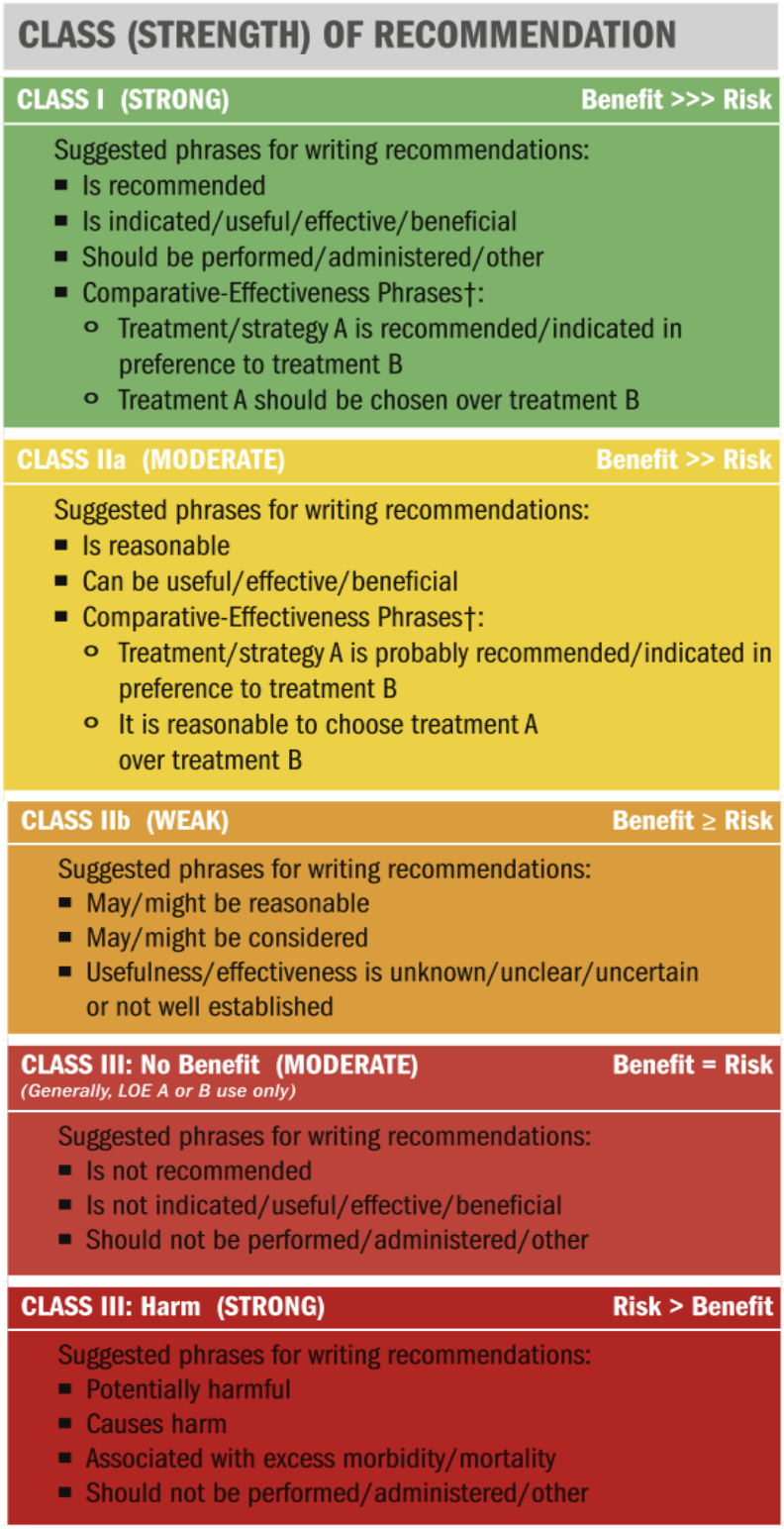
Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

Appendix B. PubMed Search Methodology Terms

Query	Filters	Search Details	Results
((((Hypotension [MeSH Terms]) OR (Vascular Hypotension[Title/Abstract])) OR (Low Blood Pressure[Title/Abstract])) OR (Blood Pressure, Low[Title/Abstract])) OR (Hypotension, Vascular[Title/Abstract])	In the last 5 years	("Hypotension"[MeSH Terms] OR "vascular hypotension"[Title/Abstract] OR "low blood pressure"[Title/Abstract] OR "blood pressure low"[Title/Abstract] OR "hypotension vascular"[Title/Abstract]) AND (y_5[Filter])	3,711

Appendix C. Level of Evidence



CLASS (STRENGTH) OF RECOMMENDATION

CLASS I (STRONG) — **Benefit >>> Risk**

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

CLASS IIa (MODERATE) — **Benefit >> Risk**

Suggested phrases for writing recommendations:
- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

CLASS IIb (WEAK) — **Benefit ≥ Risk**

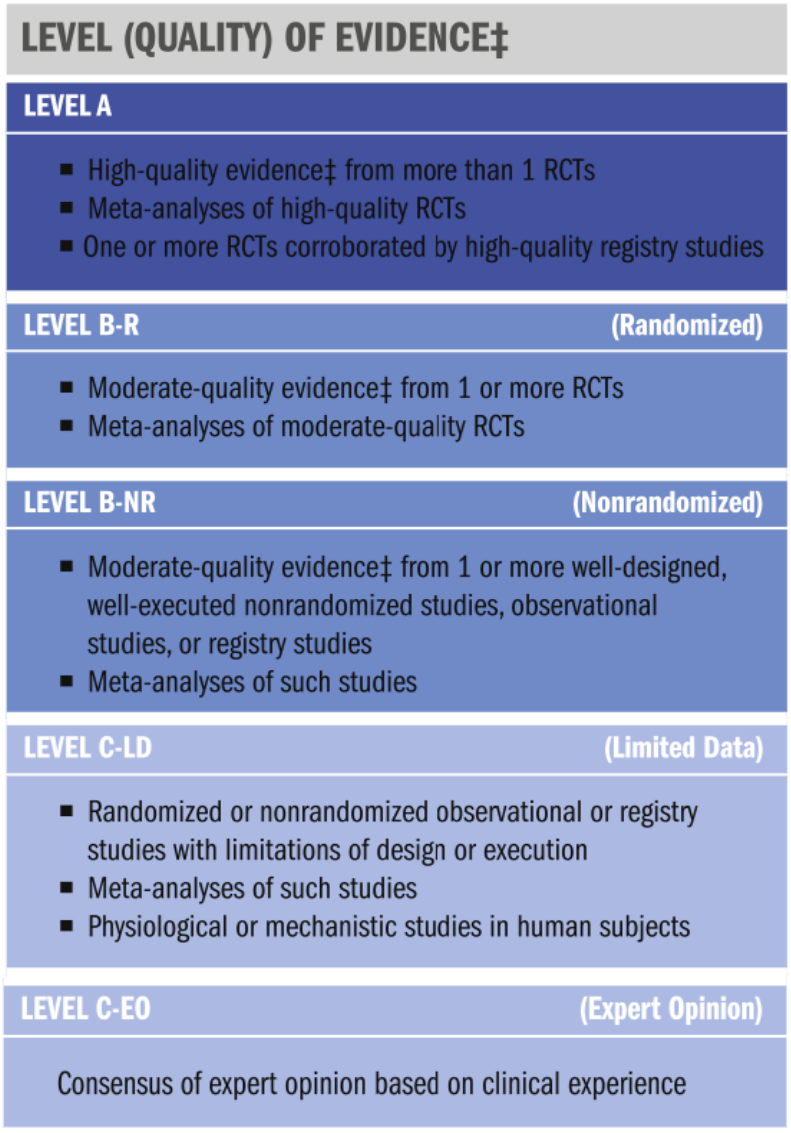
Suggested phrases for writing recommendations:
- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

CLASS III: No Benefit (MODERATE) — **Benefit = Risk**
(Generally, LOE A or B use only)

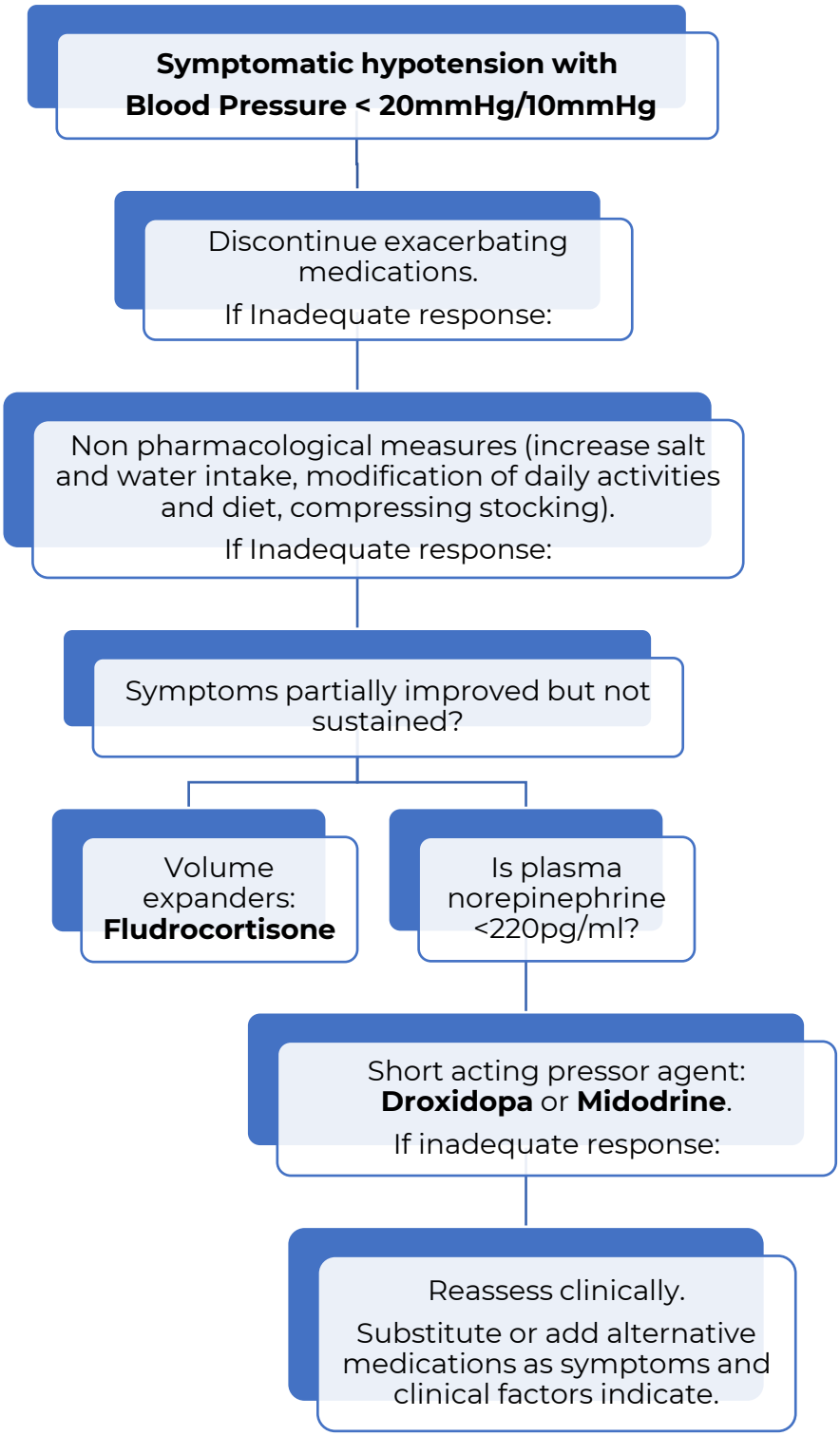
Suggested phrases for writing recommendations:
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

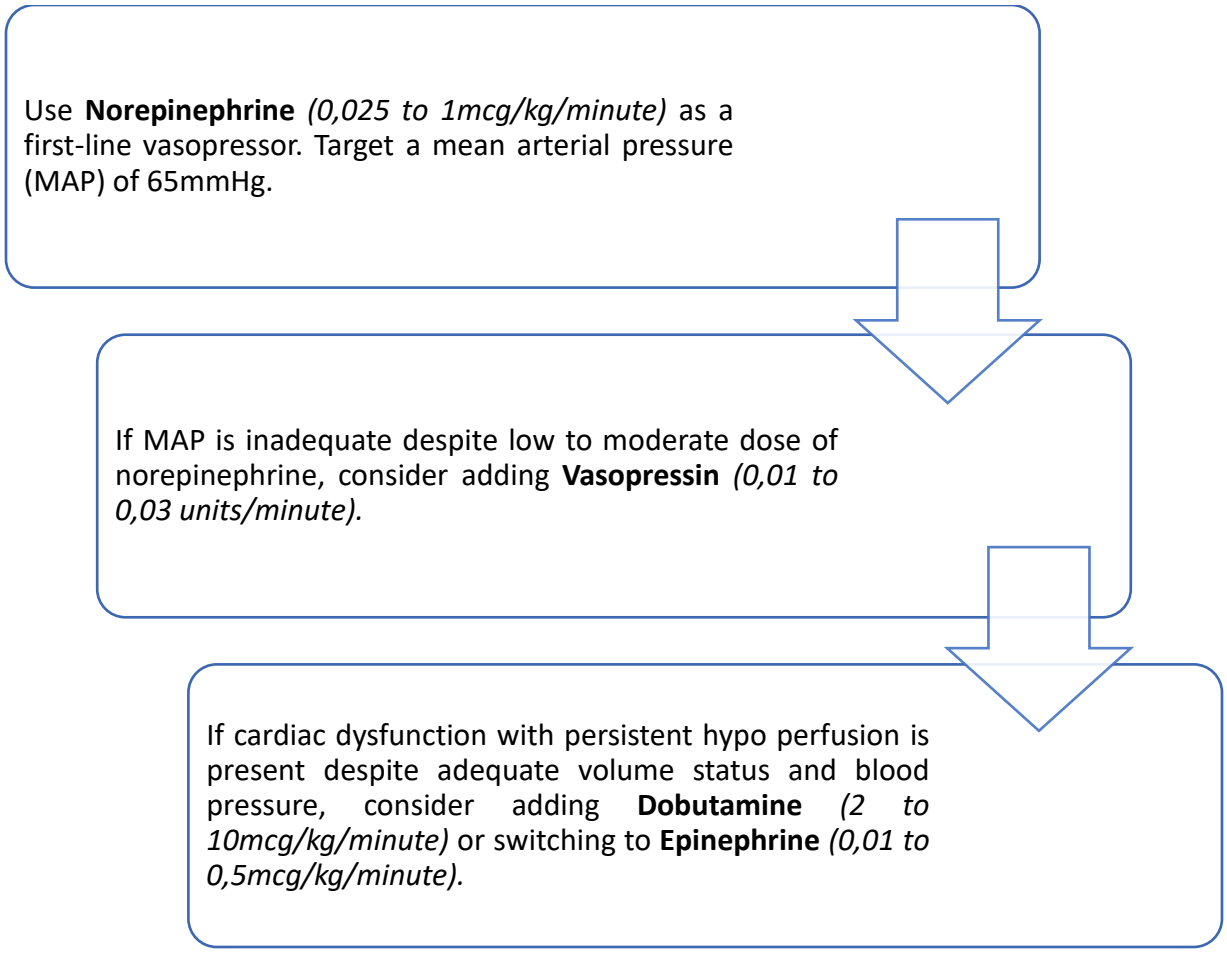
CLASS III: Harm (STRONG) — **Risk > Benefit**

Suggested phrases for writing recommendations:
- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other


LEVEL (QUALITY) OF EVIDENCE‡
LEVEL A
High-quality evidence‡ from more than 1 RCTs
Meta-analyses of high-quality RCTs
One or more RCTs corroborated by high-quality registry studies
LEVEL B-R (Randomized)
Moderate-quality evidence‡ from 1 or more RCTs
Meta-analyses of moderate-quality RCTs
LEVEL B-NR (Nonrandomized)
Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
Meta-analyses of such studies
LEVEL C-LD (Limited Data)
Randomized or nonrandomized observational or registry studies with limitations of design or execution
Meta-analyses of such studies
Physiological or mechanistic studies in human subjects
LEVEL C-EO (Expert Opinion)
Consensus of expert opinion based on clinical experience

Appendix D. Treatment Algorithm of Hypotension




Use **Norepinephrine** *(0,025 to 1mcg/kg/minute)* as a first-line vasopressor. Target a mean arterial pressure (MAP) of 65mmHg.
If MAP is inadequate despite low to moderate dose of norepinephrine, consider adding **Vasopressin** *(0,01 to 0,03 units/minute).*
If cardiac dysfunction with persistent hypo perfusion is present despite adequate volume status and blood pressure, consider adding **Dobutamine** *(2 to 10mcg/kg/minute)* or switching to **Epinephrine** *(0,01 to 0,5mcg/kg/minute).*