

Chapter 2

Vasopressors and Inotropes

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Introduction

Medication errors and adverse drug events occur more frequently in the intensive care unit compared to general care units.¹ Adverse drug events become more likely as patients receive more medications. Sentinel events and medication errors are more common as the number of failing organs increases.^{2,3} Vasopressors are frequently associated with adverse drug events and they are considered high-alert drugs by the Institute of Safe Medication Practices due to their increased potential to cause harm.^{4,6} Vasopressors and inotropes are used in patients with the highest acuity and under stressful situations which adds to the potential for errors. In addition, dosing guidelines, ranges and units are not always standardized across agents at specific institutions or for a certain agent across institutions. The literature is disparate with respect to dosing recommendations. With the exception of vasopressin, we report the dosing of these agents in a weight-based manner. This should enhance dosing consistency to help minimize errors. We encourage institutions to adopt this dosing scheme to reduce discrepancies associated with their administration. Moreover, using a weight based dosing strategy in an era of increasing obesity raises the question of whether actual, adjusted or ideal body weight should be used when administering vasopressors. No data are available to select an appropriate weight and trials evaluating the use of vasopressors rarely report the body weight used in cases of obesity. With the exception of milrinone, we encourage the use of ideal body weight for all weight-based dosing strategies because these agents possess short half-lives, rapid onsets, and low volumes of distribution but may be associated with severe adverse events when higher weights are used resulting in higher

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doses in heavier patients. Moreover, these agents are rapidly titrated to clinical response, so starting at lower doses based on ideal body weight is prudent.

This chapter discusses the safety concerns of select vasopressors and inotropes encountered in intensive care units. Published adverse reactions with these agents are summarized.

Dobutamine (DOB)

Dosing Considerations

Dobutamine's (DOB) clinical activity is primarily mediated by beta (β)-receptor agonism. Frequently observed effects of DOB include increased cardiac output (CO), decreased systemic vascular resistance (SVR), and tachycardia. Commonly cited dosing ranges of 2–20 mcg/kg/min may need to be exceeded to achieve adequate response which may enhance the likelihood of adverse events. DOB doses of 40 mcg/kg/min have been reported but higher doses may be needed depending on the clinical situation.⁷ The increased risk of adverse events at elevated doses must be balanced with potential benefits of the higher dose. Lack of adequate fluid resuscitation prior to or concomitant use of other inotropes may increase the risk of adverse events.

Obesity: Data are not available for use in critically ill obese patients. However, since many institutions use weight based dosing for DOB, ideal body weight should be used to avoid excessive dosing of a drug with low volume of distribution and short half-life in over weight patients. The rate should be verified to ensure the correct dose is being administered.

Thinness/emaciation: There are no reports of dosing considerations in underweight or nutritionally depleted patients. Dobutamine doses should be titrated to the lowest dose required for goal hemodynamic response.

Kidney Injury: Dobutamine is mainly metabolized by the liver and catechol-O-methyl transferase (COMT). The pharmacokinetics of DOB in patients with renal insufficiency has not been studied. Dobutamine does not require specific dose changes for renal insufficiency.

Hemodialysis/Continuous Renal Replacement Therapy: The pharmacokinetics of DOB has not been studied. Dose adjustments should be titrated to hemodynamic response.

Liver Dysfunction: Dobutamine is metabolized by COMT and by conjugation to inactive metabolites. Dose adjustments are not necessary for hepatic insufficiency.

Hypothermia: Therapeutic hypothermia may decrease enzymatic metabolism of medications including DOB leading to higher serum concentrations. The clinical significance of this is unknown, therefore no initial dose adjustments are recommended and dose adjustments should be based on hemodynamic response.⁸

Safety Concerns

Safety concern	Rationale	Comments/recommendations
Extravasation	While DOB displays β -selective inotropic and vasodilatory properties, the L-enantiomer possesses α -agonistic properties. ⁹ Therefore, extravasation may cause vasoconstrictive related adverse events. Few case reports have been published regarding DOB extravasation, treatment, and outcomes ¹⁰	DOB should be administered via a central catheter whenever possible. If not readily available, a central catheter should be placed as soon as possible. If extravasation and vasoconstriction are evident, phentolamine (10 mg/10 ml NS) may be given in and around the extravasation site via hypodermic syringe ¹¹
Tachyarrhythmia/ myocardial ischemia	β -adrenergic effects may contribute to tachycardia, tachyarrhythmia, and potentially myocardial ischemia. Effects may be greater in the elderly, those with preexisting cardiac ischemia or dysrhythmias, hypovolemia, or when used in combination with other inotropes and vasopressors ^{12,13}	Dose related increases in heart rate are predictable. Doses exceeding 20 mcg/kg/min are more likely to cause tachyarrhythmias and produce ischemic changes on electrocardiogram. When DOB was used in combination with norepinephrine (NE), lower heart rates were noted compared with other vasopressors alone. ¹⁴ Cardiac monitoring should include telemetry for heart rate and rhythm and serial troponin concentrations if ischemia is suspected. Echocardiography may be required
Glucose abnormalities	Administration of sympathomimetics may cause gluconeogenesis and insulin resistance ¹⁵	DOB has been shown to cause hyperglycemia in animal studies. Serum glucose should be monitored and corrected with insulin as clinically indicated ^{15,16}
Hypotension	DOB may cause hypotension due to β -agonist induced vasodilation	Hypotension may occur in states of hypovolemia leading to rebound tachycardia. ¹² Blood pressure should be frequently monitored and verified
Allergic reaction	DOB contains sodium bisulfite	Allergic reactions to bisulfite may occur. Eosinophilic myocarditis has been linked to DOB use. ¹⁷ White blood cell count with differential should be monitored

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Safety concern	Rationale	Comments/recommendations
Drug-drug interactions	DOB is metabolized by COMT. While pharmacokinetic drug interactions between COMT inhibitors (entacapone, tolcapone) may enhance DOB activity, close monitoring and frequent dose titration to the lowest effective dose is recommended DOB is alkaline labile. Caution should be used when coadministering medications through shared lines with DOB	Pharmacodynamic interactions such as the concomitant administration of other vasopressors and inotropes may increase DOB activity and enhance the likelihood of adverse effects. Interactions should not deter the use of additional agents in patients requiring supplemental therapy to reach hemodynamic goals. Medications that alter blood pressure (vasodilators, negative inotropes, etc.) may enhance or reduce the effectiveness of DOB. DOB should be administered through a dedicated lumen of a central venous catheter

Dopamine (DA)

Dosing Considerations

Dopamine's (DA) clinical activity is dose-dependent. Lower doses of 0.5–3 mcg/kg/min primarily stimulate dopamine receptors, intermediate doses of 3–10 mcg/kg/min stimulate beta (β)-receptors, and higher doses 10–20 mcg/kg/min stimulate alpha (α)-receptors.⁷ Mixed actions may occur at doses above or below these commonly cited ranges. DA doses in excess of 50 mcg/kg/min have been reported but higher doses may be needed depending on the clinical situation. The increased risk of adverse events at elevated doses must be balanced with diminishing potential benefits of the higher dose. Additional or alternative vasopressor support may be needed if cardiovascular goals are not met within the standard dosing range. Lack of adequate fluid resuscitation prior to or concomitant vasopressor use may increase the risk of adverse events.

Obesity: Data are not available regarding dosing in critically ill obese patients. However, since DA is dosed in units based on weight, ideal body weight should be used to avoid excessive dosing of a drug with low volume of distribution and short half-life in over weight patients. The rate should be verified to ensure the correct dose is being administered.

Thinness/emaciation: There are no reports of dosing considerations in underweight or nutritionally depleted patients. Dopamine doses should be titrated to the lowest dose required for goal hemodynamic response.

Kidney Injury: Only a small amount of DA is excreted unchanged in the urine. Dopamine has been used at low doses in cases of acute or chronic renal insufficiency in attempts to increase urine production or prevent worsening renal function. The results of a large study of critically ill patients with acutely worsening renal function showed no benefit to “low-dose” or “renal-dose” DA.¹⁸ Dopamine does not require specific dose adjustments for renal insufficiency. The dose should be titrated to hemodynamic response.

Hemodialysis/Continuous Renal Replacement Therapy: Dopamine does not require specific dosage adjustments and should be titrated to hemodynamic response during dialysis.

Liver Dysfunction: Dopamine is metabolized by COMT and monoamine oxidase (MAO) to inactive metabolites. Dose adjustments are not necessary for hepatic insufficiency.

Hypothermia: Therapeutic hypothermia may decrease enzymatic metabolism of medications including DA leading to higher serum concentrations. The clinical significance of this is unknown, therefore no initial dose adjustments are recommended and dose adjustments should be based on hemodynamic response.⁸

Safety Concerns

Safety concern	Rationale	Comments/recommendations
Extravasation	DA possesses dopamine, β , and α receptor activity which can cause vasoconstriction and skin sloughing, ischemia, gangrene and necrosis if extravasation occurs. Reports of adverse events have been published regarding DA extravasation ¹⁹	DA should be administered via a central catheter whenever possible. If not readily available, a central catheter should be placed as soon as possible. Only dosages ≤ 5 mcg/kg/min should be administered peripherally. If extravasation is noted, phentolamine (10 mg/10 ml NS) may be given in and around the extravasation site via hypodermic syringe ¹¹
Peripheral ischemia	Higher dose DA (≥ 10 mcg/kg/min) acts as a potent vasoconstrictor that can cause peripheral ischemia (digits, skin, etc.) via α -adrenergic effects. Ischemia has been reported at lower doses as well. Inadequate volume resuscitation prior to and during vasopressor administration may increase the risk of ischemia	Fluid assessment and adequate resuscitation should be initiated prior to and during DA administration. Assessment of peripheral circulation and ischemia should be done frequently while receiving DA. Venous oxygen saturation should be maintained at $\geq 70\%$. The lowest effective dose of DA should be used to achieve hemodynamic goals and tapered off as soon as possible

Safety concern	Rationale	Comments/recommendations
Gastrointestinal ischemia and impaired motility	DA may increase hepato-splanchnic blood flow in septic patients by enhancing CO but DA impairs hepato-splanchnic metabolism leading to impaired hepatic energy balance when compared to norepinephrine. DA may contribute to mesenteric ischemia in septic shock and impedes gastrointestinal motility via DA-2 receptor stimulation ²⁰⁻²⁴	DA impairs hepato-splanchnic and mesenteric mucosal perfusion in hypotensive patients. Serum lactate concentrations and liver function enzymes should be monitored frequently. Gastrointestinal function (e.g. aspirated gastric residual, bowel distension or pain, bowel movements) should be assessed routinely as DA decreases gastric motility
Glucose abnormalities	Administration of sympathomimetics may cause gluconeogenesis and insulin resistance	DA has been shown to increase serum glucose, glucagon and insulin even at low doses (i.e., 2 mcg/kg/min). Serum glucose concentrations should be monitored and corrected with insulin as clinically indicated ^{15,25}
Nephrotoxicity	"Low or renal-dose" DA is not renal protective and does not improve kidney function. Higher doses of DA may increase arterial constriction and decrease renal blood flow	Negative results found in a large prospective trial of "low-dose" DA suggest there is no renal protective benefit. ¹⁸ Fluid status, urine production and serum markers of renal function (BUN, creatinine) should be monitored frequently
Tachyarrhythmia/myocardial ischemia	β -adrenergic receptor stimulation may contribute to tachycardia, tachyarrhythmia, and potentially myocardial ischemia. Effects may be greater in the elderly, those with preexisting cardiac ischemia or dysrhythmias, hypovolemia, or when used in combination with other inotropes and vasopressors ²⁶	Tachyarrhythmias may occur at doses as low as 3 mcg/kg/min. Sinus tachycardia, supraventricular tachycardia, and premature ventricular complexes may occur with DA. The largest trial of 1,679 patients in shock compared DA with NE and showed DA was associated with higher rates of atrial fibrillation (A-fib) and ventricular tachycardia leading to more patients being withdrawn from the DA group compared to NE (6.1% vs. 1.6%). Another trial of 252 patients with fluid resuscitated septic shock showed patients who received DA were more likely to develop sinus tachycardia, A-fib, and PVC compared to NE. ^{27,28} Cardiac monitoring should include telemetry for heart rate and rhythm and serial troponin concentrations if ischemia is suspected. Echocardiography may be required

Safety concern	Rationale	Comments/recommendations
Endocrine	DA suppresses prolactin secretion from the anterior pituitary gland. ^{29,30} DA has been reported to lower thyrotropin and thyroid hormone secretion in critically ill patients ³⁰	A 6 h DA infusion of 2.5 mcg/kg/min can decrease prolactin concentrations by 80%. Higher doses may suppress prolactin to a greater extent. ^{29,30} The clinical significance of prolactin suppression is unknown. A prospective study showed a three-fold decrease in TSH response to TRH in critically ill patients receiving DA. ³⁰ TSH and T3/T4 should be intermittently monitored
Pulmonary	DA may increase pulmonary artery occlusive pressure, and cause pulmonary edema and intrapulmonary shunting	Studies confirm increased pulmonary pressures as well as increased pulmonary shunting in patients treated with DA. ³¹ Arterial blood gas analyses and the extent of respiratory support should be assessed routinely. In severe cases, echocardiography and/or pulmonary artery catheterization may aid monitoring
Drug-drug interactions	DA is metabolized by MAO and COMT. While pharmacokinetic drug interactions between MAO inhibitors (including linezolid, selegiline, phenelzine, isocarboxazid, tranylcypromine) and COMT inhibitors (entacapone, tolcapone) may enhance DA activity, close monitoring and frequent dose titration to the lowest effective dose is recommended DA is alkaline labile. Caution should be used when coadministering medications through shared lines with DA	Pharmacodynamic interactions such as the concomitant administration of other vasopressors and inotropes may increase DA activity and enhance the likelihood of adverse effects. Interactions should not deter the use of additional agents in patients requiring supplemental therapy to reach hemodynamic goals. Medications that lower blood pressure (vasodilators, negative inotropes, etc.) will decrease the effectiveness of DA. DA should be administered through a dedicated lumen of a central venous catheter

Epinephrine (EPI)

Dosing Considerations

Epinephrine's (EPI) clinical activity is mediated by alpha (α)-receptor and beta (β)-receptor agonism. Tachycardia, increased CO, and increased SVR are generally observed with EPI use. Commonly cited dose ranges of 0.01–3 mcg/kg/min may need to be exceeded to achieve adequate response which may enhance the likelihood of adverse events.⁷ Lack of adequate fluid resuscitation prior to or concomitant vasopressor use may increase the risk of adverse events.

Obesity: Data are not available for use in critically ill obese patients. However, since many institutions use weight based dosing for EPI, ideal body weight should be used to avoid excessive dosing of a drug with low volume of distribution and short half-life in over weight patients. The mixed concentration and rate should be verified to ensure the correct dose is being administered.

Thinness/emaciation: There are no reports of dosing considerations in underweight or nutritionally depleted patients. Epinephrine doses should be titrated to the lowest dose required for goal hemodynamic response.

Kidney Injury: Only a small proportion of EPI is excreted unchanged in the urine. The pharmacokinetics of EPI in patients with renal insufficiency has not been studied. Epinephrine does not require specific dose changes for renal insufficiency.

Hemodialysis/Continuous Renal Replacement Therapy: The pharmacokinetics of EPI has not been studied. Doses should be titrated to hemodynamic response.

Liver Dysfunction: Epinephrine is metabolized by COMT and MAO to inactive metabolites. Dose adjustments are not necessary for hepatic insufficiency.

Hypothermia: Therapeutic hypothermia may decrease enzymatic metabolism of medications including EPI leading to higher serum concentrations. The clinical significance of this is unknown, therefore no initial dose adjustments are recommended and dose adjustments should be based on hemodynamic response.⁸

Safety Concerns

Safety concern	Rationale	Comments/recommendations
Extravasation	EPI is a potent vasoconstrictor that can cause skin sloughing, ischemia, gangrene and necrosis if extravasation occurs. Reports of adverse events have been published regarding EPI extravasation ¹⁹	EPI should be administered via a central catheter. If not readily available, a central catheter should be placed as soon as possible. If extravasation is noted, phentolamine (10 mg/10 ml NS) may be given in and around the extravasation site via hypodermic syringe ¹¹

Safety concern	Rationale	Comments/recommendations
Peripheral ischemia	EPI is a potent vasoconstrictor that can cause peripheral ischemia (digits, skin, etc.) via α -adrenergic effects. Inadequate volume resuscitation prior to and during vasopressor administration may increase the risk of ischemia. Higher doses of EPI may increase the risk of peripheral ischemia	Fluid assessment and adequate resuscitation should be initiated prior to and during EPI administration. Assessment of peripheral circulation and ischemia should be done frequently while receiving EPI. Venous oxygen saturation should be maintained at $\geq 70\%$. The lowest effective dose of EPI should be used to achieve hemodynamic goals and tapered off as soon as possible
Tachyarrhythmia/ myocardial ischemia	β -adrenergic effects may cause tachycardia, tachyarrhythmia, and potentially myocardial ischemia. Dysrhythmias and/or ischemia occur irrespective of concomitant disease states or therapies; however, risk is greatest in those with preexisting cardiac disease or dysrhythmias, hypovolemia, or when used in combination with other inotropes and vasopressors ²⁶	In a large prospective trial of 277 patients, EPI significantly increased heart rate compared with NE. ³² Another study of 330 patients showed no difference in tachyarrhythmias between EPI and NE with DOB. ¹⁴ EPI may cause demand ischemia and ST segment deviations in patients after single doses as low as 0.1–0.3 mg. ³³ Cardiac monitoring should include telemetry for heart rate and rhythm and serial troponin concentrations if ischemia is suspected. Echocardiography may be required
Gastrointestinal ischemia	EPI decreases hepato-splanchnic and mesenteric blood flow and oxygen delivery ^{20,21}	Serum lactate concentrations and liver function enzymes should be monitored frequently ^{20,21,34,35}
Lactic acidosis	EPI increases serum lactate concentration by decreasing hepato-splanchnic oxygenation, increasing calorogenesis, and enhancing the breakdown of glycogen leading to increased lactate concentrations ^{14,32}	Multiple clinical trials have shown statistically higher serum lactate concentrations in patients treated with EPI compared with other vasopressors. Increases in lactate are variable but significant acidosis is possible. ^{14,32,35} Arterial blood gas analyses and serum lactate concentrations should be monitored frequently
Glucose abnormalities	Administration of sympathomimetics may cause gluconeogenesis and insulin resistance ¹⁵	EPI has the highest propensity to cause hyperglycemia compared to other vasopressors. ^{15,32,36} Serum glucose should be monitored and corrected with insulin as clinically indicated

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Safety concern	Rationale	Comments/recommendations
Nephrotoxicity	Vasopressors can cause renal artery constriction and decreased filtration via α -adrenergic receptors	Animal data suggest EPI may reduce renal blood flow but urine production may increase due to higher MAP in vasodilatory shock ³⁷
Drug-drug interactions	EPI is metabolized by MAO and COMT. While pharmacokinetic drug interactions between MAO inhibitors (including linezolid, selegiline, phenelzine, isocarboxazid, tranylcypromine) and COMT inhibitors (entacapone, tolcapone) may enhance EPI activity, close monitoring and frequent dose titration to the lowest effective dose is recommended EPI is alkaline labile. Caution should be used when coadministering medications through shared lines with EPI	Pharmacodynamic interactions such as the concomitant administration of other vasopressors and inotropes may increase EPI activity and enhance the likelihood of adverse effects. Interactions should not deter the use of additional agents in patients requiring supplemental therapy to reach hemodynamic goals. Medications that lower blood pressure (vasodilators, negative inotropes, etc.) will decrease the effectiveness of EPI. EPI should be administered through a dedicated lumen of a central venous catheter

Isoproterenol (ISO)

Dosing Considerations

Isoproterenol's (ISO) clinical activity is mediated by beta (β)-receptor agonism. ISO primarily acts as an inotrope causing increased CO, tachycardia, and vasodilation to decrease SVR. ISO possesses high arrhythmogenic potential and is not commonly used as an inotrope. Commonly cited dosing ranges of 0.01–0.3 mcg/kg/min may need to be exceeded to achieve adequate response which may enhance the likelihood of adverse events. Dose should be titrated to the lowest effective dose and only escalated as clinical or ventricular response allows. ISO infusions of 30 mcg/min have been reported. Lack of adequate fluid resuscitation prior to or concomitant inotrope use may increase the risk of adverse events.³⁸

Obesity: Data are not available for use in critically ill obese patients. However, since many institutions use weight based dosing for ISO, ideal body weight should be used to avoid excessive dosing of a drug with low volume of distribution and short half-life in over weight patients. The rate should be verified to ensure the correct dose is being administered.

Thinness/emaciation: There are no reports of dosing considerations in underweight or nutritionally depleted patients. Isoproterenol doses should be titrated to the lowest dose required for goal hemodynamic response.

Kidney Injury: The pharmacokinetics of ISO in patients with renal insufficiency has not been studied. Isoproterenol does not require specific dose changes for renal insufficiency.

Hemodialysis/Continuous Renal Replacement Therapy: The pharmacokinetics of ISO has not been studied. Dose adjustments should be titrated to hemodynamic response.

Liver Dysfunction: Isoproterenol is metabolized by COMT to inactive metabolites. Dose adjustments are not necessary for hepatic insufficiency.³⁸

Hypothermia: Therapeutic hypothermia may decrease enzymatic metabolism of medications including ISO leading to higher serum concentrations. The clinical significance of this is unknown, therefore no initial dose adjustments are recommended and dose adjustments should be based on hemodynamic response.

Safety Concerns

Safety concern	Rationale	Comments/recommendations
Cardiac dysrhythmias, tachyarrhythmias, ventricular arrhythmia, atrial arrhythmia/myocardial ischemia	ISO causes increased heart rate and shortened atrioventricular nodal conduction. This may generate atrial and/or possibly serious ventricular arrhythmias. ISO decreases diastolic filling time and diastolic coronary perfusion. β -adrenergic effects may increase myocardial oxygen demand and induce ischemia	Dose related increases in heart rate are predictable. Increased risk of ventricular arrhythmia exists when ISO is dosed to a heart rate of 130 bpm. The ISO infusion rate should be decreased or temporarily discontinued if the heart rate reaches 110 bpm. ³⁸ ISO is rarely used because it is associated with serious arrhythmias but it is used to treat slow prolonged QT-interval. The lowest effective dose of ISO should be used to reach goal clinical response and tapered off as soon as possible. Myocardial ischemia also occurs in adults and children after inhaled ISO. Intravenous use has been reported to cause myocardial ischemia and worsen myocardial injury. ISO is not recommended in patients with a history of cardiovascular disease or active myocardial ischemia. ³⁸⁻⁴⁰ Cardiac monitoring should include telemetry for heart rate and rhythm, blood pressure, and serial troponin concentrations if ischemia is suspected. Echocardiography may be required

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Safety concern	Rationale	Comments/recommendations
Gastrointestinal ischemia	ISO increases cardiac output but preferentially decreases hepato-splanchnic and mesenteric blood flow in favor of skeletal muscle blood flow ⁴¹	Serum lactate concentrations and liver function enzymes should be monitored frequently ²¹
Glucose abnormalities	Administration of sympathomimetics may cause gluconeogenesis and insulin resistance ^{15,36}	ISO may cause hyperglycemia but not to the same extent as EPI. Serum glucose concentrations should be monitored and corrected with insulin as clinically indicated
Pulmonary	ISO decreases pulmonary vascular resistance and may overcome hypoxic pulmonary vasoconstriction ^{42,43}	ISO may increase intrapulmonary shunting especially in patients with parenchymal lung disease leading to decreased arterial oxygenation. ^{42,43} Arterial blood gas analyses and the extent of respiratory support should be assessed routinely. In severe cases, echocardiography and/or pulmonary artery catheterization may aid monitoring
Hypotension	ISO may cause hypotension due to β -agonist vasodilation	ISO increases pulse pressure and possibly systolic pressure but tends to cause an overall decrease in mean arterial and diastolic pressures due to vasodilation. Hypotension may be exacerbated by hypovolemia. Blood pressure should be frequently monitored and verified
Allergic reaction	ISO contains sodium bisulfite ³⁸	Allergic reactions to bisulfite may occur. White blood cell count with differential should be monitored
Drug-drug interactions	ISO is metabolized by COMT. While pharmacokinetic drug interactions between COMT inhibitors (entacapone, tolcapone) may enhance ISO activity, close monitoring and frequent dose titration to the lowest effective dose is recommended	Pharmacodynamic interactions such as the concomitant administration of other vasopressors and inotropes may alter ISO activity and enhance the likelihood of adverse effects. Interactions should not deter the use of additional agents in patients requiring supplemental therapy to reach hemodynamic goals. Medications that alter blood pressure (vasodilators, negative inotropes, etc.) may enhance or reduce the effectiveness of ISO
	ISO is alkaline labile. Caution should be used when coadministering medications through shared lines with ISO	ISO should be administered through a dedicated lumen of a central venous catheter

Milrinone (MIL)

Dosing Considerations

Milrinone (MIL) is a phosphodiesterase III inhibitor which leads to increased cardiac contractility, CO, heart rate, and decreased SVR through vasodilation. A loading dose of 50 mcg/kg over 20 min may be administered, however many clinicians opt not to give a loading dose prior to the infusion due to concerns of hypotension. Commonly cited dosing ranges of 0.125–1 mcg/kg/min may need to be exceeded to achieve adequate response which may enhance the likelihood of adverse events. Lack of adequate fluid resuscitation prior to or concomitant inotrope use may increase the risk of adverse events.

Obesity: Data are not available for use in critically ill obese patients. Package labeling provides dosing recommendations for patients based on actual body weight to a maximum weight of 120 kg.⁴⁴ Given a published volume of distribution ranging 0.3–0.47 L/kg an adjusted body weight may be used for initiation in cases of morbid obesity with close titration to desired clinical response.

Thinness/emaciation: There are no reports of dosing considerations in underweight or nutritionally depleted patients. Milrinone doses should be titrated to the lowest dose required for goal hemodynamic response.

Kidney Injury: Milrinone is largely excreted unchanged in the urine (80–85%) therefore dose adjustments are needed for renal insufficiency. Package labeling recommends initial dose adjustments as follows: 0.2 mcg/kg/min for a calculated creatinine clearance <5 mL/min/1.73m², 0.23 mcg/kg/min for a calculated creatinine clearance of 5–10 mL/min/1.73m², 0.28 mcg/kg/min for a calculated creatinine clearance of 10–20 mL/min/1.73m², and further incremental rate increases of 0.05 mcg/kg/min for every increase in calculated creatinine clearance of 10 mL/min/1.73m² up to 0.5 mcg/kg/min for a calculated creatinine clearance >50 mL/min/1.73m².³⁵ Doses may be further adjusted based on hemodynamic response to a maximum of 0.75 mcg/kg/min in those without renal failure. No adjustment in loading dose is required (if given).⁴⁴

Hemodialysis/Continuous Renal Replacement Therapy: While MIL is removed by continuous renal replacement therapy, pharmacokinetic analysis estimates the half-life of MIL to be 20 h (compared to 2.3 h in heart failure patients without renal failure).⁴⁵ No data are available to guide dosing in dialysis patients and extreme caution is advised due to the prolonged half-life.

Liver Dysfunction: Milrinone is minimally metabolized via conjugation and oxidation to inactive metabolites. Dose adjustments are not necessary for hepatic insufficiency.

Hypothermia: There are no reports of dosing considerations during therapeutic hypothermia, therefore dose adjustments should be based on hemodynamic response.

Safety Concerns

Safety concern	Rationale	Comments/recommendations
Hypotension	MIL is a phosphodiesterase III inhibitor which causes smooth muscle relaxation ^{12,13,46-48}	Hypotension requiring therapeutic intervention may occur with MIL. ^{12,13,46-50} Not administering a loading dose may lessen the occurrence of hypotension. ^{46,47} MIL should be decreased or stopped and vasopressors (NE, DA, EPI, phenylephrine, vasopressin) may need to be instituted if hypotension is severe. ⁵⁰ Cardiac monitoring should include telemetry for heart rate and rhythm and blood pressure should be frequently verified. Echocardiography may be required
Tachyarrhythmia/ myocardial ischemia	MIL may cause increases in heart rate, atrial, and ventricular arrhythmias. ^{12,13,46,48,49} Inotropic and chronotropic properties of MIL may increase myocardial oxygen demand and induce ischemia ^{12,13,49}	Dose-related increases in heart rate are expected. MIL may lead to ischemic myocardial changes due to increasing oxygen demand. Caution should be used in patients with myocardial ischemia. Cardiac monitoring should include telemetry for heart rate and rhythm and serial troponin concentrations if ischemia is suspected. Echocardiography may be required
Glucose abnormalities	Animal models suggest MIL may cause insulin resistance ⁵¹	Human data linking MIL to hyperglycemia are lacking. Serum glucose should be monitored and corrected with insulin as clinically indicated
Thrombocytopenia/ altered platelet activation	MIL is structurally related to amrinone, a medication that may cause thrombocytopenia via action of an acetylated metabolite. MIL does not share this metabolite. However, reports of thrombocytopenia have been published in clinical trials ⁴⁴	The reported incidence of thrombocytopenia with MIL use varies between studies from 0.4% in package labeling to 58% in a small pediatric trial used during open heart surgery. The majority of studies indicate a low risk of thrombocytopenia likely related to procedures or other medications and not directly linked to MIL ^{44,52,53}

Safety concern	Rationale	Comments/recommendations
Drug-drug interactions	MIL increases cyclic adenosine monophosphate, which may inhibit platelet activation ⁴⁸	Conflicting data exist regarding altered platelet activity. Initial studies suggest platelet function and hemostasis was not inhibited by either amrinone or MIL. ^{52,54} However, a recent in vitro study suggests that higher MIL concentrations can inhibit adenosine diphosphate and arachidonic acid induced platelet activation ⁵⁵ Patients should be monitored for signs and symptoms of bleeding. Hemoglobin, hematocrit, and platelets should be followed as clinically indicated
	Pharmacokinetic drug interactions have not been reported with MIL. Pharmacodynamic interactions with other cardiovascular medications may occur	Concomitant use of other cardiovascular medications is common. Monitoring blood pressure and heart rate is standard of practice. Co-administration is often successful with close hemodynamic monitoring
	Intravenous compatibility should be checked prior to coadministering medications through shared lines with MIL	MIL should be administered through a dedicated lumen of a central venous catheter

Norepinephrine (NE)

Dosing Considerations

Norepinephrine’s (NE) clinical activity is mediated by alpha (α)-receptor agonism and some beta (β)-1-receptor agonism although tachycardia is not generally seen with NE. NE primarily acts as a vasoconstrictor to increase SVR. Commonly cited dosing ranges of 0.05–3 mcg/kg/min may need to be exceeded to achieve adequate response, which may enhance the likelihood of adverse events.⁷ Lack of adequate fluid resuscitation prior to or concomitant vasopressors use may increase the risk of adverse events.

Obesity: Data are not available for use in critically ill obese patients. However, since many institutions use weight based dosing for NE, ideal body weight should

be used to avoid excessive dosing of a drug with low volume of distribution and short half-life in over weight patients. The mixed concentration and rate should be verified to ensure the correct dose is being administered.

Thinness/emaciation: There are no reports of dosing considerations in underweight or nutritionally depleted patients. Norepinephrine doses should be titrated to the lowest dose required for goal hemodynamic response.

Kidney Injury: 4–16% of NE is excreted unchanged in the urine. The pharmacokinetics of NE in patients with renal insufficiency has not been studied. Norepinephrine does not require specific dose changes for renal insufficiency. The dose should be titrated to hemodynamic response.

Hemodialysis/Continuous Renal Replacement Therapy: The pharmacokinetics of NE has not been studied; therefore no initial dose adjustments are required and titration should be based on clinical response. Norepinephrine has been used to increase MAP in patients who become hypotensive during dialysis.

Liver Dysfunction: Norepinephrine is metabolized by COMT and MAO to inactive metabolites. Dose adjustments are not necessary for hepatic insufficiency.

Hypothermia: Therapeutic hypothermia may decrease enzymatic metabolism of medications including NE leading to higher serum concentrations. The clinical significance of this is unknown, therefore no initial dose adjustments are recommended and dose adjustments should be based on hemodynamic response.⁸

Safety Concerns

Safety concern	Rationale	Comments/recommendations
Extravasation	NE is a potent vasoconstrictor that can cause skin sloughing, ischemia, gangrene and necrosis if extravasation occurs. Reports of adverse events have been published regarding NE extravasation ¹⁹	NE should be administered via a central catheter. If not readily available, a central catheter should be placed as soon as possible. If extravasation is noted, phentolamine (10 mg/10 ml NS) may be given in and around the extravasation site via hypodermic syringe ¹¹
Peripheral ischemia	NE is a potent vasoconstrictor that can cause peripheral ischemia (digits, skin, etc.) via α -adrenergic effects. Inadequate volume resuscitation prior to and during vasopressor administration may increase the risk of ischemia. Higher doses of NE may increase the risk of peripheral ischemia	Fluid assessment and adequate resuscitation should be initiated prior to and during NE administration. Assessment of peripheral circulation and ischemia should be done frequently while receiving NE. Venous oxygen saturation should be maintained at $\geq 70\%$. The lowest effective dose of NE should be used to achieve hemodynamic goals and tapered off as soon as possible

Safety concern	Rationale	Comments/recommendations
Gastrointestinal ischemia	NE possesses variable effects on hepato-splanchnic and mesenteric blood flow in hypotensive patients. Most reports suggest minimal differences to improved blood flow and/or oxygen consumption when compared to EPI or DA ²⁰⁻²²	NE alone or in combination with DOB improves hepato-splanchnic and mesenteric blood delivery compared to other agents in hypotensive patients. Serum lactate concentrations and liver function enzymes should be monitored frequently ²¹
Glucose abnormalities	Administration of sympathomimetics may cause gluconeogenesis and insulin resistance ^{15,36}	NE dose correlates to hyperglycemic events. Serum glucose concentrations should be monitored and corrected with insulin as clinically indicated ^{15,36}
Nephrotoxicity	A decrease in creatinine clearance has been shown in healthy, non-hypotensive volunteers with NE administration. Vasopressors can cause renal artery constriction and decreased filtration. However, NE with fluid resuscitation may improve renal perfusion and filtration in hypotensive patients ³⁷	Decreased urine production in sepsis-related hypotension may be due to hypovolemia and efferent arteriole vasodilatation. This may be reversed by fluid resuscitation and NE. Compared to high dose DA, NE is more likely to achieve MAP goals and enhance urine production. ³⁷ Fluid status, urine production and serum markers of renal function (BUN, creatinine) should be monitored frequently
Bradycardia or other arrhythmias	NE possesses β_1 -agonist properties that may induce tachyarrhythmias. Increases in SVR may cause reflex bradycardia ²⁶	Studies of NE in shock report reflex bradycardia. CO remains constant or increases with NE. Tachycardia is most likely to occur at higher doses but tachyarrhythmias are less frequent than with DA or EPI. ^{27,28,32} Cardiac monitoring should include telemetry for heart rate and rhythm and serial troponin concentrations if ischemia is suspected. Echocardiography may be required

(continued)

Safety concern	Rationale	Comments/recommendations
Drug-drug interactions	NE is metabolized by MAO and COMT. While pharmacokinetic drug interactions between MAO inhibitors (including linezolid, selegiline, phenelzine, isocarboxazid, tranylcypromine) and COMT inhibitors (entacapone, tolcapone) may enhance NE activity, close monitoring and frequent dose titration to the lowest effective dose is recommended NE is alkaline labile. Caution should be used when coadministering medications through shared lines with NE	Pharmacodynamic interactions such as the concomitant administration of other vasopressors and inotropes may increase NE activity and enhance the likelihood of adverse effects. Interactions should not deter the use of additional agents in patients requiring supplemental therapy to reach hemodynamic goals. Medications that lower blood pressure (vasodilators, negative inotropes, etc.) will decrease the effectiveness of NE. NE should be administered through a dedicated lumen of a central venous catheter

Phenylephrine

Dosing Considerations

Phenylephrine's clinical activity is mediated by alpha (α)-receptor agonism and acts mainly as a vasoconstrictor to increase SVR. Commonly cited dosing ranges of 0.2–5 mcg/kg/min may need to be exceeded to achieve adequate response, which may enhance the likelihood of adverse events.⁷ Lack of adequate fluid resuscitation prior to or concomitant vasopressor use may increase the risk of adverse events.

Obesity: Data are not available for use in critically ill obese patients. However, since many institutions use weight based dosing for phenylephrine, ideal body weight should be used to avoid excessive dosing of a drug with low volume of distribution and short half-life in over weight patients. The mixed concentration and rate should be verified to ensure the correct dose is being administered.

Thinness/emaciation: There are no reports of dosing considerations in underweight or nutritionally depleted patients. Phenylephrine doses should be titrated to the lowest dose required for goal hemodynamic response.

Kidney Injury: Phenylephrine is mainly metabolized by MAO with up to 16% of an intravenous dose excreted in the urine unchanged. The pharmacokinetics of phenylephrine in patients with renal insufficiency has not been studied. Phenylephrine does not require specific dose changes for renal insufficiency.^{56,57}

Hemodialysis/Continuous Renal Replacement Therapy: The pharmacokinetics of phenylephrine has not been studied; therefore no initial dose adjustments are required and titration should be based on clinical response. Phenylephrine may be used to increase MAP in patients who become hypotensive during dialysis.

Liver Dysfunction: Phenylephrine is primarily metabolized by MAO to inactive metabolites. Dose adjustments are not necessary for hepatic insufficiency.^{56,57}

Hypothermia: Therapeutic hypothermia may decrease enzymatic metabolism of medications including phenylephrine leading to higher serum concentrations. The clinical significance of this is unknown, therefore no initial dose adjustments are recommended and dose adjustments should be based on hemodynamic response.

Safety Concerns

Safety concern	Rationale	Comments/recommendations
Extravasation	Phenylephrine is a potent vasoconstrictor that can cause skin sloughing, ischemia, gangrene and necrosis if extravasation occurs. Phenylephrine extravasation may lead to tissue ischemia and necrosis ¹⁹	Phenylephrine should be administered via a central line. If not readily available, a central catheter should be placed as soon as possible. If extravasation is noted, phentolamine (10 mg/10 ml NS) may be given in and around the extravasation site via hypodermic syringe ¹¹
Peripheral ischemia	Phenylephrine is a potent vasoconstrictor that can cause peripheral ischemia (digits, skin, etc.) via α -adrenergic effects. Inadequate volume resuscitation prior to and during vasopressor administration may increase the risk of ischemia. Higher doses of phenylephrine may increase the risk of peripheral ischemia	Fluid assessment and adequate resuscitation should be initiated prior to and during phenylephrine administration. Assessment of peripheral circulation and ischemia should be done frequently while on phenylephrine. Venous oxygen saturation should be maintained at $\geq 70\%$. The lowest effective dose of phenylephrine should be used to achieve hemodynamic goals and tapered off as soon as possible

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Safety concern	Rationale	Comments/recommendations
Gastrointestinal ischemia	Phenylephrine may decrease hepato-splanchnic and mesenteric blood flow and oxygen delivery	When NE was changed to phenylephrine in late septic shock, decreases in splanchnic blood flow, oxygen delivery and intramucosal pH were noted which reversed when NE was reinstated. Increased serum lactate concentrations and decreased lactate uptake have been noted. Conversely, the same investigators found no differences in regional perfusion between NE and phenylephrine in early phase septic shock. ^{58,59} Despite mixed data, signs of hepato-splanchnic and mesenteric ischemia should be assessed. Serum lactate concentrations and liver function enzymes should be monitored frequently ²¹
Glucose abnormalities	Phenylephrine is selective for α -receptors and therefore carries the lowest risk for hyperglycemia of the catecholamines ¹⁵	Phenylephrine may precipitate hyperglycemic events. Serum glucose concentrations should be monitored and corrected with insulin as clinically indicated
Nephrotoxicity	Vasopressors can cause renal artery constriction and decreased filtration via α -adrenergic receptors. However, phenylephrine with fluid resuscitation may improve renal perfusion and filtration in hypotensive patients ³⁷	Decreased urine production in sepsis related hypotension may be due to hypovolemia and efferent arteriole vasodilatation. This may be reversed by fluid resuscitation and phenylephrine. In late septic shock, creatinine clearance was decreased when NE was changed to phenylephrine. The same authors found no difference in creatinine clearance when phenylephrine was compared to NE in early septic shock. ^{37,59} Fluid status, urine production and serum markers of renal function (BUN, creatinine) should be monitored frequently

Safety concern	Rationale	Comments/recommendations
Bradycardia and cardiac function	Phenylephrine does not stimulate β -adrenergic receptors. Increases in SVR may cause reflex bradycardia. Of all vasopressors, phenylephrine is the least likely to cause arrhythmias ^{26,56}	Reflex bradycardia may occur with phenylephrine. CO remains constant or increases with phenylephrine in septic shock. Because phenylephrine may decrease cardiac index in cardiac patients, caution is warranted when used in cases of severe cardiac dysfunction and impaired myocardial performance. Phenylephrine is less likely to cause arrhythmias when compared to DA or NE and is indicated to terminate paroxysmal supraventricular tachycardia. ^{26,56} Cardiac monitoring should include telemetry for heart rate and rhythm and serial troponin concentrations if ischemia is suspected. Echocardiography may be required
Drug-drug interactions	Phenylephrine is metabolized by MAO. ⁵⁷ While pharmacokinetic drug interactions between MAO inhibitors (including linezolid, selegiline, phenelzine, isocarboxazid, tranylcypromine) may enhance phenylephrine activity, close monitoring and frequent dose titration to the lowest effective dose is recommended Phenylephrine is alkaline labile. Caution should be used when coadministering medications through shared lines with phenylephrine	Pharmacodynamic interactions such as the concomitant administration of other vasopressors and inotropes may increase phenylephrine activity and enhance the likelihood of adverse effects. Interactions should not deter the use of additional agents in patients requiring supplemental therapy to reach hemodynamic goals. Medications that lower blood pressure (vasodilators, negative inotropes, etc.) will decrease the effectiveness of phenylephrine. Phenylephrine should be administered through a dedicated lumen of a central venous catheter

Vasopressin (VASO)

Dosing Considerations

Vasopressin's (VASO) vasoconstrictive activity is mediated by agonism of vasopressin (V)-1 receptors to increase SVR. In septic shock, VASO is often used as adjunctive therapy to catecholamine vasopressors at doses of 0.01–0.04 units/min that reflect physiologic replacement of a relative vasopressin deficiency. In cases of hepatorenal syndrome, VASO is commonly titrated by 0.04 units/min to achieve an increase in MAP of 10 mmHg, urine production, or a maximum dose of 0.4 units/min. Close attention to infusion rates is needed, as dosing in the USA is in units per minute while dosing in many other countries is in units per hour.

Obesity: Data are not available for the use of VASO in critically ill obese patients. Vasopressin is not dosed based on weight and is not titrated when used as a vasopressor in septic shock. The mixed concentration and rate should be verified to ensure the correct dose is being administered

Thinness/emaciation: There are no reports of dosing considerations in underweight or nutritionally depleted patients.

Kidney Injury: Vasopressin is mainly metabolized by vasopressinase with only 5–10% excreted unchanged the urine. The pharmacokinetics of VASO in patients with renal insufficiency are not significantly altered and do not require dose adjustment.⁵⁶ Vasopressin may be used at moderate to high doses to improve renal function in hepatorenal syndrome.

Hemodialysis/Continuous Renal Replacement Therapy: Vasopressin is not removed by hemodialysis and requires no specific dose adjustments. Vasopressin has been used to increase tolerability of fluid removal during dialysis.⁵⁶

Liver Dysfunction: No specific dose adjustments are required for patients with liver dysfunction. Vasopressin may be used in high doses in patients with hepatorenal syndrome.

Hypothermia: Therapeutic hypothermia may decrease enzymatic metabolism of medications including VASO leading to higher serum concentrations. The clinical significance of this is unknown, therefore no initial dose adjustments are recommended and dose adjustments should be based on hemodynamic response.⁸

Safety Concerns

Safety concern	Rationale	Comments/recommendations
Extravasation	VASO is a potent vasoconstrictor that can cause skin sloughing, ischemia, gangrene and necrosis if extravasation occurs. Reports of adverse events have been published regarding VASO extravasation	Although VASO may be administered subcutaneously for other indications, it should be given via a central catheter whenever possible when it is administered intravenously. If not readily available, a central catheter should be placed as soon as possible. If extravasation occurs, the infusion should be stopped, warm compresses applied, and the site of administration elevated. A trial of local vasodilator may be considered, however this presents a risk in the hypotensive patient
Peripheral ischemia	VASO is a potent vasoconstrictor that may cause peripheral ischemia (digits, skin, etc.) via V_1 -receptor effects. Inadequate volume resuscitation prior to and during vasopressor administration may increase the risk of ischemia. Higher doses of VASO may increase the risk of peripheral ischemia ⁶⁰	Fluid assessment and adequate resuscitation should be initiated prior to and during VASO administration. Assessment of peripheral circulation and ischemia should be done frequently while on VASO. Ischemic skin lesions have been reported to occur at rates as high as 30% when VASO is added to NE in resistant shock. ⁶¹ In a randomized trial of 776 septic shock patients, ischemic digits occurred more frequently with VASO compared to NE but not statistically higher and infrequently overall ⁶²
Gastrointestinal ischemia	VASO decreases hepato-splanchnic and mesenteric perfusion. VASO has been used to treat variceal hemorrhage and hepatorenal syndrome because it constricts the hepato-splanchnic vasculature to decrease perfusion ^{21,60,63}	Hepato-splanchnic ischemia and decreased gastric blood flow is usually observed with doses exceeding 0.04 units/min; however, lower doses of VASO may cause mesenteric vasoconstriction. Increased transaminases and total bilirubin have been reported with VASO likely due to impaired hepato-splanchnic blood flow. ^{21,63} Serum lactate concentrations and liver function enzymes should be monitored frequently ²¹

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Safety concern	Rationale	Comments/recommendations
Cardiac ischemia and function	VASO may decrease CO as a result of reduced stroke volume. Animal and human models show mixed data suggesting a potential to cause cardiac ischemia at doses ≥ 0.04 units/min ^{64,65}	While animal models suggest VASO causes cardiac ischemia, human trials have not shown this adverse effect when compared to other agents. ^{62,65} Use as an adjunct vasopressor in septic shock may lower heart rate compared to NE alone. ⁶² Decreased stroke volume and CO may occur in hyperdynamic vasodilatory shock. Caution is warranted in patients with severe cardiac dysfunction, ischemic cardiac disease, coronary artery disease, atherosclerosis, cardiomyopathies, or congestive heart failure. In patients requiring high doses of VASO for indications other than shock, adding nitroglycerin may be used to decrease myocardial ischemia and improve cardiovascular function. Cardiac monitoring should include telemetry for heart rate and rhythm and serial troponin concentrations if ischemia is suspected. Echocardiography may be required
Hematological	VASO receptors are found on platelets and may contribute to the release of von Willebrand factor and enhanced platelet aggregation ⁶⁰	Multiple studies have shown an association between VASO treatment and decreased platelet counts. No change is evident in global coagulation at an infusion of 0.067 units/min. ^{60,63,66} Platelet count and coagulation parameters should be monitored serially
Endocrine	Stimulation of VASO receptors may lead to increased prolactin concentrations ⁶⁰	Serum prolactin concentrations in vasodilatory shock are higher when patients are treated with VASO and NE compared to NE or VASO alone. The clinical significance of this finding is unknown ⁶⁰
Electrolyte imbalance	VASO is also an agonist of V_2 receptors which may lead to decreased free water excretion and hyponatremia ⁶⁰	Although doses used for vasoconstriction are higher than those needed to decrease free water excretion in the kidney, hyponatremia has been reported as a rare adverse event in clinical trials. Many case reports of serious hyponatremia using VASO analogs have been reported. ^{60,62} Fluid status and serum sodium concentration should be routinely monitored

Safety concern	Rationale	Comments/recommendations
Drug-drug interactions	Pharmacokinetic drug-drug interactions are minimal with VASO. Pharmacodynamic interactions leading to additive toxicities are a concern when VASO is added to other vasopressor agents. The risk of increased ischemic events due to enhanced vasoconstriction needs to be considered versus prolonged hypotension when adjunctive VASO is being contemplated Caution should be used when coadministering medications through shared catheters with VASO	Additive vasoconstriction and ischemia must be considered when adding VASO to other vasopressors. The risk of excessive vasoconstriction should be weighed against the benefit of increased MAP and decreased NE dose to maintain adequate hemodynamic response. VASO should be administered through a dedicated lumen of a central venous catheter

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Kane-Gill, S.; Dasta, J. (Eds.)

2011, X, 160 p., Hardcover

ISBN: 978-0-85729-605-4