

Anesthetic Management of Pheochromocytoma

Derek T Woodrum, Sachin Kheterpal

Assistant Professors, Department of Anesthesiology, University of Michigan, Dearborn, USA

Correspondence: Derek T Woodrum, Assistant Professor, Department of Anesthesiology, University of Michigan 1500 East Medical Center Drive, 1H247UH, SPC 5048, Ann Arbor, MI 48109-5048, USA, Phone: 734-936-4280, e-mail: dwoodrum@med.umich.edu

ABSTRACT

The anesthetic management of pheochromocytoma is complicated and challenging. However, preoperative pharmacologic preparation has greatly improved perioperative outcome, and modern anesthetic drugs combined with advanced monitoring contribute to intraoperative stability. There is great regional and international variation in which intraoperative anesthetic technique is employed and there are little data to suggest one approach over another. Nevertheless, most management principles are universal. Progress lies in improved data collection that is increasingly available with electronic anesthesia information systems.

Keywords: Pheochromocytoma, Intraoperative anesthesia.

INTRODUCTION

Surgical resection of a pheochromocytoma represents one of the greatest challenges faced by anesthesiologist. Hemodynamic instability is common and sudden with severe hemodynamic changes occurring frequently during the operation. Historically, perioperative mortality rates were high but dramatically decreased with modern preoperative pharmacologic preparation and improvements in intraoperative management.¹ Nevertheless, anesthetic management of patients with pheochromocytoma remains complex and involved. An understanding of tumor physiology and receptor pharmacology serves to inform pharmacologic preparation and intraoperative medical management decisions. The vast majority of anesthetic and surgical literature for pheochromocytoma is derived from case reports and relatively small case series; thus, class 1 evidence from randomized prospective controlled trials is limited. Many institutions have “in-house” approaches to anesthesia for pheochromocytoma, and practice patterns therefore vary significantly. However, there are fundamental principles consistent across countries and major institutions.

The incidence of pheochromocytoma is difficult to accurately report, though it is estimated at 500-1600 cases per year for a prevalence of 1:6500 to 1:2500 in the United States.² Some of the uncertainty may reflect historic inconsistency on the precise definition of a pheochromocytoma—is secretory carotid body tumor a pheochromocytoma? What about a minimally secretory tumor at the skull base? The World Health Organization clarified the nomenclature in 2004³ when it described pheochromocytoma as an intra-adrenal paraganglioma. Other paragangliomas are also derived from chromaffin cells, including tumors in juxta-aortic locations and

carotid body tumors. Collectively, these are referred to as extra-adrenal paragangliomas.

Due to their neural crest origin, almost all pheochromocytomas secrete an excess of catecholamines and/or catecholamine breakdown products. Up to 20% of head and neck paragangliomas are also secretory⁴ and biochemical screening is mandatory for these tumors as well. Epinephrine, norepinephrine (and their metabolites metanephrine and normetanephrine) along with dopamine are the most common causes of hemodynamic disturbances that lead to clinical presentation. Although pheochromocytoma is the cause of sustained hypertension in < 0.1% of all hypertensive patients, nearly 50% of patients with pheochromocytoma have sustained hypertension. In the other half, a more classically described constellation of symptoms, paroxysms of hypertension, palpitations, diaphoresis, headache and feelings of doom, is present at diagnosis.

Most patients with pheochromocytomas now present for resection after careful preoperative pharmacologic preparation, but the literature is rife with descriptions of more dire and urgent presentations of shock,⁵ cardiomyopathy,⁶⁻⁸ orthostatic hypotension^{9,10} or even cardiovascular collapse.¹¹

PREOPERATIVE WORK-UP

The current recommendations are for patients to be tested for fractionated elevations of catecholamine breakdown products—metanephrine and normetanephrine rather than their parent catecholamines—in plasma, urine or both if available. Testing in this manner has nearly 100% sensitivity.^{2,12,13} Urinary vanillylmandelic acid assays, by comparison, are only 64% sensitive in adults.² The reason to measure breakdown products over parent catecholamines is because chromaffin cells

intratumorally metabolize the parent moieties independent of paroxysmal catecholamine release. Testing for catecholamine metabolites may therefore increase sensitivity.^{14,15} Of course, the anesthesiologist is not commonly involved in preoperative diagnosis but occasionally may be called upon to assist medical and surgical colleagues in diagnostic recommendations from the preoperative clinic, particularly when seeing patients (e.g. carotid body tumors) where secretory implications may have been overlooked.

The patient's daily medications should be reviewed, as many can impact catecholamine release. Certain amphetamines in weight loss drugs (e.g. ephedra, sibutramine) may cause displacement of catecholamines from storage vesicles or have direct action on adrenoceptors. Tricyclic antidepressants, selective norepinephrine (NE) reuptake inhibitors, and monoamine oxidase inhibitors all may decrease NE reuptake or influence NE metabolism. Dopamine receptor antagonists, such as haloperidol or droperidol may provoke catecholamine release from the tumor.

The remainder of the preoperative work-up should focus on end-organ manifestations of the paroxysmal or sustained hypertension. A metabolic panel screens for kidney dysfunction and preoperative glucose levels are noted. An EKG will frequently show evidence of left ventricular hypertrophy reflecting compensation against chronic hypertension. ST changes, decreased QRS voltage and QTc prolongation are common¹⁶ and generally not indicative of coronary artery disease. The EKG abnormalities generally resolve after alpha blockade or surgical resection. There are myriad reports of preoperative cardiomyopathy (as a consequence of chronic catecholamine excess) and preoperative echocardiography should be considered in all patients.

PHARMACOLOGIC PREPARATION

The most critical element to safe perioperative care of the pheochromocytoma patient is adequate preoperative blockade against the effects of catecholamines.¹⁷ Many advocate preoperative blockade for extra-adrenal paraganglioma even with normal measured levels of catecholamines.² While small series have not detected an outcome difference in patients with or without preoperative alpha blockade,¹⁸ it remains the standard of care and widely accepted as a critical step in surgical preparation. The main goals of preoperative blockade are to normalize blood pressure, heart rate and function of other organs; restore volume depletion; and prevent surgery-induced catecholamine storm with its attendant risks to the cardiovascular system.¹⁹ Several different approaches may be employed (blockade of catecholamine synthesis or blockade of downstream effect) but it is standard to provide preoperative blockade for at least 10-14 days preoperatively.^{13,19} Roizen and colleagues developed criteria over two decades ago that represent the goal response to pharmacologic preparation. They include no in-hospital blood pressure > 160/90 mmHg for 24 hours prior to surgery, blood pressure not lower than 80/45 mmHg during the standing phase of orthostatic testing, no ST or T wave changes for a week prior to surgery, and no

more than five premature ventricular contractions per minute. Initially, these criteria pertained to inpatient preparation but outpatient preparation has become standard and feasible in most cases.²⁰

The choice of preoperative drug used for blockade is heavily influenced by regional or international practice patterns as well as by drug availability.¹⁹ Alpha-adrenoreceptor antagonists, calcium channel blockers, and angiotensin converting enzyme (ACE)-inhibitors have all been used²¹⁻²³ with success. That aside, the most common drug used in the United States is phenoxybenzamine. It is given at initial doses of 10 mg twice daily to effect an irreversible, noncompetitive alpha-adrenergic blockade. The dose is increased until symptoms resolve or side effects (postural hypotension, nasal congestion, etc.) appear. The preoperative treatment duration is traditionally 10-14 days, though shorter periods have been used successfully.²⁴ An optimal duration of treatment has not been convincingly established or universally agreed upon. Other alpha-adrenoreceptor blockers with alpha-1 specificity have been employed²² in situations where phenoxybenzamine is not tolerated or in uninsured patients (phenoxybenzamine is an expensive medication). Prazosin (Minipress; 2-5 mg twice or three times daily), terazosin (Hytrin; 2-5 mg daily), and doxazosin (Cardura; 2-8 mg daily) are short-acting competitive antagonists. As such, they should also be dosed on the morning of surgery for sustained effect. A small study at the Mayo and Cleveland Clinics compared phenoxybenzamine preparation with alpha-1-specific blockade. No difference in ultimate outcome was reported, but the phenoxybenzamine group required more intraoperative phenylephrine, and the alpha-1-specific group experienced higher maximal blood pressure.²⁵ Urapadil use has been reported successfully in 17 patients but required intravenous administration for three days prior, which may limit its utility in routine clinical practice. It is not approved by the Food and Drug Administration for use in the United States but it is available in Europe.²⁶

Beta-adrenoreceptor blockade is commonly added to treat tachyarrhythmias accompanying alpha-blockade. They should not be used before or in absence of alpha-blockade, as the alpha-agonist effect of secreted epinephrine will be unopposed and may lead to severe hypertension. Metoprolol (Lopressor; 25-50 mg two or three times daily), atenolol (Tenormin; 12.5-25 mg twice or three times daily) and propranolol (Inderal; 20-80 mg twice or three times daily) are the usual choices. Labetolol and carvedilol are not commonly utilized for alpha or beta blockade because they have alpha to beta-antagonist activity ~1:7, which is not appropriate as monotherapy preparation.

Calcium channel blockers have received increasing amounts of attention and use in the recent years. They have been used in patients intolerant to phenoxybenzamine and in predominantly normotensive patients because they do not cause the hypotension seen with alpha-adrenoreceptor blockade. Amlodipine (Norvasc; 10-20 mg daily), nifedipine (Adalat; 30-90 mg daily), verapamil (Calan-SR; 180-540 mg daily) and nifedipine (Cardene; 60-90 mg daily) are all options.

An alternate preparation approach is to use metyrosine to inhibit catecholamine synthesis. Metyrosine is a tyrosine analog that inhibits the enzyme tyrosine hydroxylase, which itself is the rate-limiting step in catecholamine formation.²⁷ It has benefit in patients with large or metastatic tumor burden, in those with hypertension even on high doses of phenoxybenzamine, and in those with highly biochemically active tumors. It has been reported to decrease the hypertension caused by tumor manipulation intraoperatively, and some have described “smoother” hemodynamics when administered.²⁸ Its use should be adjunctive to alpha-adrenoreceptor blockade.²⁹

Finally, octreotide usage has been reported. It has been noted that some pheochromocytomas possess specific somatostatin binding sites, which led to the hypothesis that octreotide may have antisecretory potential.³⁰ However, in a placebo-controlled trial there was no difference in plasma catechol levels after octreotide monotherapy and its use is not routine.

MONITORS

An arterial line should be placed before induction of anesthesia. This should be undertaken in a calm manner,²⁸ remembering the significant role of the sympathetic nervous system in the pathogenesis of hypertension and hypertensive crises.³¹ The authors recommend placement by an experienced provider in the preoperative area after administration of an anxiolytic (typically midazolam 2-4 mg IV) and liberal use of local anesthetic combined with small doses (25-100 mcg) of intravenous fentanyl. Strong consideration should be given to the placement of central venous access for three reasons: First, it is likely that vasopressors will need to be administered after adrenal vein ligation and into the postoperative period. This is due to the disparate effect duration of phenoxybenzamine (1-2 days) and catecholamines (minutes). Secondly, larger-bore central venous access allows for rapid volume expansion during and after the adrenal vein dissection. Finally, a central venous line (CVL) provides measurement of central venous pressures. It is certainly true that some patients do not require vasopressors beyond a low-moderate dose of alpha-agonist (e.g. phenylephrine) after tumor removal. This would not require a CVL for safe intravenous delivery, but currently there are no accurate predictors of which patients are most likely to need central administration of vasopressors, such as norepinephrine or vasopressin. Until predictive models exist, each patient should be carefully considered for central venous access. CVL placement is generally performed under anesthesia in the post-induction/preincision period, but some advocate for preoperative placement as a “test stimulus” to determine quality of preoperative alpha-blockade.

Pulmonary artery catheters are used rarely³² and are no longer a standard component of care for the routine assessment of volume status. They remain a useful consideration if patients have pre-existing cardiac disease, significant catecholamine-induced cardiomyopathy or in patients whose intraoperative volume status is ambiguous. At the authors’ institution, systolic

pressure variation (or pulse pressure variation) is widely used as a valuable monitor of intravascular volume status. It utilizes the underlying principle that positive pressure mechanical ventilation affects vena cava, pulmonary artery, and aortic blood flow—with subsequent changes in systolic blood pressure.³³ The alterations in blood flow and systemic blood pressure vary over the respiratory cycle allowing the anesthesiologist to calculate the difference between the highest and lowest blood pressure. Systolic pressure variation is higher in the setting of hypovolemia, as blood vessels are more susceptible to compression by positive pressure with lower intravascular volume.³⁴ A systolic blood pressure variation of 0-5 mmHg suggests hypervolemia, 5-10 mmHg indicates euolemia, and > 10 mmHg suggests intravascular depletion. This monitoring approach has been well validated against the gold standard of transesophageal echocardiography.³⁵ It is limited by the need for sinus rhythm and a closed chest, but otherwise is readily applicable for pheochromocytoma resection and volume management therein. It has been shown to be superior to CVP as an ongoing monitor of volume status³⁶ and predictor of response to fluid challenge. It is inexpensive, does not require additional equipment, and can be assessed in the OR on most monitors.³⁷ Systolic pressure variation has been reported as a valuable volume assessment tool, specifically for pheochromocytoma management.³⁸

Transesophageal echocardiography has become standard of care in many cardiac surgical operations due to its ability to rapidly determine volume status, detect myocardial ischemia, diagnose and monitor valvular anomalies, and to guide inotropic or vasopressor support in cardiomyopathy. It also guides several phases of cardiopulmonary bypass. It has drawbacks of high equipment costs, need for advanced training by specialty providers, and the potential for missed or inaccurate diagnoses. As such, it has limited application in pheochromocytoma except in cases of intracardiac pheochromocytoma, severe catecholamine-induced cardiomyopathy or cardiovascular collapse. In rare instances, it may have utility in determining intravascular volume status.

INTRAOPERATIVE MANAGEMENT

A general anesthetic is almost always employed for pheochromocytoma resection. As mentioned before, a myriad of approaches has been used and almost all drugs in the lexicon of anesthesia have been utilized in various combinations as part of a balanced anesthetic.^{21, 32, 39, 40} There are no firm conclusions and few formal recommendations to be made when describing exact anesthetic technique. The most important aspects are adequate preoperative blockade, recognition of preoperative intravascular volume depletion, and heightened vigilance coupled with precise, prompt care of hemodynamic instability.

Mirroring the lack of evidence regarding the best drug to effect preoperative blockade, there is little evidence that one intraoperative anesthetic approach or another will influence the outcome. It is almost certainly true that careful preoperative

preparation is the most important contributor to intraoperative hemodynamic stability. Several principles guide intraoperative management, but no convincing studies exist to advocate the use of one particular drug as the “key” to intraoperative stability. Indeed, the clinical recommendations from the proceedings of the First International Symposium on Pheochromocytoma¹³ do not mention intraoperative anesthetic care. There are at least equal parts of art and science when it comes to the intraoperative anesthetic portion of the management. From the surgical perspective a laparoscopic approach has become commonplace. Though typically well-tolerated, laparoscopic insufflation has been associated with spikes in hypertension.²⁶ It has been reported that lower insufflations pressures may attenuate hypertensive episodes during laparoscopic resection.⁴¹

Induction Agents

Propofol, sodium thiopental, and etomidate are commonly used for the IV induction of anesthesia. No studies compare the drugs and all are useful in establishing rapid onset of general anesthesia. Ketamine should be avoided due to its sympathomimetic properties.

Inhalational Agents

All inhalational agents have been used during pheochromocytoma resection. Nitrous oxide has no contraindications⁴² and has been used in routine pheochromocytoma^{32,43} as well as those treated during pregnancy.⁴⁴ Sevoflurane and isoflurane are commonly used in modern anesthesia while desflurane is best avoided due to its ability to cause significant sympathetic stimulation.^{45,46} Halothane has the ability to sensitize the myocardium to the arrhythmogenic effects of catecholamines, and is therefore no longer used in pheochromocytoma resection.^{40,47}

Pain Medications

Fentanyl and hydromorphone are commonly used in pheochromocytoma resection. Large boluses of morphine are to be avoided given concerns for histamine release causing substantial catecholamine release and potential hypertensive crisis. Indeed, histamine stimulation was historically used in the diagnosis of pheochromocytoma before modern biochemical assays supplanted provocative studies.⁴⁸ Ketamine is avoided for pain control due to its sympathomimetic characteristics. Remifentanyl has the advantages of profound potency, rapid titratability, and extremely short half life. This allows rapid titration with changes in surgical stimulation, but postsurgically it provides no pain relief and postoperative pain control measures should be promptly instituted after discontinuing the infusion. Several reports detail the use of remifentanyl to control hemodynamics during resection, but frequently very high doses are required with inconsistent effect.^{43,49} Furthermore, it is almost always used as an adjunct to other vasoactive agents such that single-agent effect is difficult to determine.^{50,51} Larger

studies or an accumulation of reported evidence is needed to determine even its expected efficacy. Remifentanyl’s major utility may be to blunt the sympathetic response to tracheal intubation or surgical incision.

It is important to understand that patients with pheochromocytoma have multiple sources of catecholamine excess. In addition to adrenal parenchymal stores, sympathetic neurons themselves may store excess catecholamines as a reuptake response to high circulating levels.³¹ Times of sympathetic surge expose patients to the release of these catecholamines and potentially contribute to blood pressure spikes and hypertensive crises. As such, patients should be treated with appropriate analgesia during any awake interaction or line placement, and maintained at an appropriately deep plane of anesthesia during orotracheal intubation, incision, and during retractor placement.

Treatment of Pre-excision Hypotension

Brief episodes of hypotension are relatively common during the course of a pheochromocytoma resection. In the time period before adrenal vein clamping, the treatment of hypertensive spikes may outlast the brief stimulus (e.g. retractor placement) and accompanying catecholamine effect resulting in paroxysms of hypotension. In these instances, small doses of direct-acting alpha-agonist (e.g. phenylephrine 50-100 mcg) should be considered if volume status is appropriately replete. Drugs with indirect or direct alpha and beta-agonist effect (ephedrine or epinephrine) should be avoided.

Antiemetics

Droperidol is commonly used as a prophylactic antiemetic medication during general anesthesia. In modern times, a very small dose of 0.625 mg IV contributes to effective antiemetic in the postoperative period. In addition to the well-known concern of QT prolongation, several reports have noted an association with hypertensive crisis in pheochromocytoma. This may be due to a reserpine-like effect⁵² or due to inhibition of an otherwise inhibitory dopaminergic receptor in the adrenal medulla.⁵³ Blockade of this inhibitory receptor would allow for excess catechol secretion. Nevertheless, at the authors’ institution, a small (0.625 mg) intravenous dose is commonly used without a noted untoward effect. It is worth remembering that historically, droperidol doses were almost always vastly higher (12-50 mg)^{54,55} and used in patients without alpha-adrenoreceptor blockade. In some, a small dose of droperidol is likely to be safe and used frequently in combination with other antiemetics, such as dexamethasone or diphenhydramine at our institution. Individual practitioners may wish to delay droperidol administration until after adrenal vein ligation. Metoclopramide is commonly avoided due to its ability to stimulate catecholamine secretion from pheochromocytoma tissue.⁵⁶

Intraoperative Hypertension

Spikes in blood pressure are very common during pheochromocytoma resection even in well-prepared patients.

Tumor manipulation can lead to brief, very high levels of circulating short-acting catecholamines. Different approaches can be taken for the prevention and treatment of hypertensive spikes. Preventative measures include preoperative pharmacologic preparation, deep-plane anesthesia (hemodynamics permitting) and effective sympatholysis with adequate inhalational depth, short-acting opioid administration (fentanyl or remifentanyl), and facilitation of surgical exposure by use of muscle relaxants, such as vecuronium or cisatracurium. It is also common to administer a "background" infusion of nitroprusside or nitroglycerine if baseline blood pressure allows. Other medicines have been advocated for intraoperative use. Nicardipine is used to prevent or treat blood pressure spikes and has a similar advantage of rapid titratability.⁵⁷ Magnesium sulfate infusion has been used with increasing frequency in the past decade.⁵⁸⁻⁶⁰ It decreases release of catecholamine stores, is a potent alpha-adrenoreceptor antagonist, effects mainly arteriolar vasodilation, and acts as an antiarrhythmic to epinephrine.⁶¹ Dose ranges have been reported between 1 and 2 mg/hour and bolus doses of 20-40 mcg/kg have been used.^{60,62,63} Dexmedetomidine has also been used during pheochromocytoma resection.⁶⁴⁻⁶⁶ It is a centrally acting alpha-2 agonist (similar to clonidine, which also has alpha-1 agonist effects) and may be beneficial to intraoperative hemodynamics through activation of presynaptic alpha-2 receptors and subsequent decreased norepinephrine release. Like so many reports of various drugs used in pheochromocytoma anesthesia, reports are limited and their use is based on pharmacodynamic profile and successful use in other arenas.

As mentioned above, the greatest care and most dense pharmacologic preparation will not prevent all spikes in blood pressure during tumor manipulation. It is important to remember that these spikes are likely to be short-lived due to the pharmacokinetics of catecholamines. Nevertheless, significant hypertension should not be tolerated and the best treatment matches the expected duration of the spikes. Short acting agents, such as esmolol (10-50 mg IV), labetalol (5-20 mg IV) or phentolamine (1-5 mg IV) may be delivered as boluses with relatively short duration of effect. Background levels of inhalational agent and vasoactive infusions (nitroglycerin or nitroprusside, magnesium, nicardipine, etc.) are also titrated to blood pressure control.

It is very difficult to comment on or determine the benefit of a single drug or a single described multi-drug technique for intraoperative anesthesia, as randomized trials do not exist. Even a cursory review of the literature reveals various combinations such as labetalol infusion;⁶⁷ prazosin and metoprolol;⁴¹ dexmedetomidine, remifentanyl, sodium nitroprusside, and labetalol;⁶⁶ nitroglycerin infusion, esmolol and clonidine.⁶⁸ In short, no data support the evidence-based use of one intraoperative approach over another.

Postresection Hypotension

Adrenal vein ligation marks the effective removal of the catecholamine source from the circulation. Hypotension after

ligation occurs frequently and can be severe, consistent with the short half life (minutes) of norepinephrine and epinephrine. Additional factors include the ongoing presence of preoperative alpha blockade and intravascular hypovolemia. Good communication from the surgical team is mandatory as the blood pressure lowering infusions are abruptly stopped when the adrenal vein is ligated. Postligation hypotension is treated with fluid resuscitation (vascular capacitance may increase rapidly) and temporary vasopressor use is common. A pure alpha-agonist, such as phenylephrine is commonly used but norepinephrine or epinephrine may be required (and should be administered centrally). Several reports detail the use of vasopressin to treat postligation hypotension, particularly in the setting of catecholamine-resistant hypotension.⁶⁹⁻⁷² It has been noted that chronic exposure to catecholamines may lead to receptor down-regulation, in which case vasopressin may be useful because its effects are mediated through noncatecholamine vasopressin receptors. Another theory is that chronic exposure to catecholamines may down-regulate hypothalamic vasopressin synthesis⁶⁹ preventing the release of endogenous vasopressin from its storage site in the posterior pituitary during hypotension after adrenal vein ligation. Regardless of which vasopressor is used, the infusion(s) can frequently be weaned over the ensuing 2-12 hours; durations longer than 24 hours are uncommon.

CONCLUSION

As frequently noted, it is difficult to extract any consistent recommendation from the literature regarding intraoperative anesthetic management of pheochromocytoma resection. Indeed, a PubMed literature search on <http://www.ncbi.nlm.nih.gov/pubmed> (November 1, 2010) for "pheochromocytoma" or "phaeochromocytoma" + anesthesia, limited to "English language" and "randomized controlled trial" returns only two manuscripts: One about the influence of insufflation pressure during laparoscopic adrenalectomy⁴¹ and the other not truly satisfying the definition of a randomized trial.²⁶ The same search limited instead to "letters," "case reports," and "editorials" returns 227 manuscripts over the past 30 years.

Nevertheless, progress in the anesthetic management of pheochromocytoma is possible. A critical innovation that has created the opportunity for such progress is the use of electronic, automatically recorded blood pressure and heart rate measurements by anesthesia information management systems to study intraoperative hemodynamics during pheochromocytoma resection. This dense data collection will allow for careful definitions of "blood pressure variability" or "significant hypertension" so that larger case series between institutions may be effectively compared. Anecdotal reports of "stability" or "brief hypertensive episode" will eventually be replaced by precise, universal definitions driven by availability of granular, accessible data. The enormous expansion of outcome reportings will extend to pheochromocytoma when consistent patterns of intraoperative management can be linked to outcome databases.

Despite certain advances to come, it is likely that a specific intraoperative anesthetic protocol for pheochromocytoma will never exist across institutions or countries. A conscientious, attentive anesthetic in a well-prepared patient is almost certainly more important than which drug or drug combination is selected.

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