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Review Article

Adrenal Vein Sampling: How I Do It

Abstract

Adrenal vein sampling (AVS) is an uncommonly performed interventional procedure. However, it is essential in the management of patients with primary aldosteronism and several other rare hormonal disorders. AVS can be technically challenging, largely from difficulty with right adrenal vein catheterization. Recently described technical modifications have improved the likelihood of successful sampling in every case. This paper highlights the author's approach to patient selection and step-by-step details of his technique.

Keywords: *Adrenal vein sampling, primary aldosteronism, hypertension*

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Introduction

Adrenal vein sampling (AVS) is one of the oldest procedures still performed by interventional radiologists (IRs). The technique was first reported in the mid-1960s as a means to identify the site(s) of hormone-producing adrenal or extra-adrenal tumors causing hypertension.[1,2] The procedure gained popularity over the following two decades but then lost favor in the 1990s as cross-sectional imaging techniques such as computed tomography (CT) and magnetic resonance (MR) became widely used and refined. However, the significant limitations of CT and MR in determining the sources of excess hormone production are now well recognized and have caused a resurgence of interest in AVS.

The most common indication for AVS is subtype analysis in hypertensive patients with laboratory proven primary aldosteronism (PA, Conn syndrome).[3] Another much less common reason for doing sampling is the evaluation of patients with virilization syndrome or Cushing syndrome in whom detection of excess adrenal gland hormone release may guide operative therapy.[4,5] In PA, aldosterone production is exaggerated, not suppressed by sodium loading, and not properly regulated by normal feedback mechanisms.[3] PA is present in about 5%–10% of hypertensive patients. By far the most common causes are adrenal aldosteronoma or bilateral adrenal hyperplasia. While medical therapy is effective in all of these conditions, laparoscopic adrenalectomy is generally recommended for patients with unilateral disease.[3] Unfortunately, imaging alone is not sufficient to make the correct choice between medical therapy and operation. For example, there is a significant rate of discordance between CT imaging findings and AVS results in subtype classification of patients with PA.[3,6,7] CT findings predict the wrong diagnosis in over one-third of cases.[7] It is true that the recent multicenter, randomized SPARTACUS trial did not show a significant difference in intensity of antihypertensive drugs given or clinical benefit from management based on AVS compared with CT imaging alone.[8] However, there has been substantial criticism of that study,[9] and most authorities in the field continue to insist on AVS prior to operation for PA in all but very special cases (see below).

There is abundant evidence that morbidity and mortality risk is higher with PA related hypertension than with essential hypertension.[3] It is also clear that appropriate treatment with either mineralocorticoid antagonists (MA, such as spironolactone and eplerenone) or laparoscopic adrenalectomy (for unilateral disease) will restore normal serum potassium, decrease blood pressure, and number of antihypertensive medications required for good control, and limit cardiac and renal dysfunction. Nonetheless, most experts advocate surgery when unilateral disease is proven.

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Patient Selection

Because PA is an uncommon disease, the American Endocrine Society recommends selective screening of patients with sustained high blood pressure.[3] Screening is done by calculation of the serum aldosterone/renin ratio (ARR), which is elevated in patients with PA. These assays are quite sensitive to a variety of factors, including the use of many blood pressure medications, hypokalemia, sodium intake, and patient position. A typical threshold for PA diagnosis is ARR >20–25. However, very low measured plasma renin activity (PRA) may spuriously elevate the ARR ratio. Thus, some guidelines for PA diagnosis require plasma aldosterone concentration (PAC) to be >15 (or >10) ng/dL.[3] In almost all patients, a positive ARR value should be confirmed with a secondary physiologic test to demonstrate a lack of suppression of aldosterone. Endocrinologists typically order an oral salt loading test or intravenous (IV) saline infusion test. The lack of suppression of urinary or serum aldosterone, respectively, proves autonomous excess production. Rarely, it may be reasonable to proceed with AVS with only equivocal evidence for PA (e.g., the patient cannot tolerate discontinuation of MA, borderline ARR level but strongly positive secondary test).

After the diagnosis of PA is made, patients almost always proceed to imaging of the adrenal glands. CT is preferred over MR and should be performed using dedicated protocols for evaluating the adrenal glands and their venous drainage. However, as noted above, AVS must always follow CT scanning except in several circumstances:[3]

- Probable adrenocortical carcinoma (based on the size >4 cm and characteristic imaging features) that requires operation
- Young patient (<35 years old) with spontaneous hypokalemia, PAC >30 ng/dL, and CT showing typical cortical adrenal adenoma with entirely normal contralateral gland
- Familial subtypes of PA that are not amenable to surgery (typically a patient <20 years old with family history of PA or of stroke at <age 40 years)
- A patient who is completely unwilling to have an operation or in whom surgery would be too risky.

Preprocedure Evaluation and Preparation

Because the diseases that require AVS are generally uncommon, and few interventionalists do these procedures, IRs who offer this service will often receive referrals from many different providers often outside their home institutions. Clear communication with these referring physicians is essential. Laboratory results and imaging studies should be obtained and reviewed. Some outside providers may need guidance in obtaining appropriate laboratory studies to support the diagnosis of PA and the need for AVS. Some may have their own opinions regarding the method of sampling (e.g., with or without stimulation, see below). For some conditions, such as the search for sources of virilizing hormone, gonadal vein sampling should be done as well. In atypical cases, the IR should always confirm that all of the necessary assays will be performed on behalf of the endocrinologist.

While not absolutely necessary, a preprocedure phone consult or clinic visit with the patient is very helpful. It ensures that the patient and family fully understand the rationale for the procedure, what the patient will experience, the expected results of the study, and the possibility that a definitive answer will not be obtained. Results may take 1–2 weeks if samples must be sent to an outside laboratory for aldosterone or other specialized assays. While adverse events are rare, they should be discussed in advance, including the small possibility of adrenal hemorrhage or venous thrombosis or rupture. The IR can ensure that important issues will be addressed before the case is scheduled, such as the need for anticoagulant adjustment.

In patients with PA from unilateral disease, treatment with MA drugs or amiloride for blood pressure management will lead to a rise in PRA with associated elevation of aldosterone on the unaffected side, which can result in a false negative study for lateralization. Ideally, these agents should be held for at least 4–5 weeks before sampling. However, preliminary data from one recent study suggest that a shorter withdrawal period may be adequate. In that report, PRA was found to be adequately suppressed in 94% of patients off MA drugs for 2 weeks.[10] Standard guidelines recommend peripheral alpha-1 adrenergic receptor blockers, hydralazine, and some calcium channel blocking agents as substitute agents. Patients are reminded to continue all other prescribed antihypertensive medications and oral potassium supplements through the morning of the procedure. While hypokalemia is a well-known feature of PA, it is only present in a minority of patients. Nonetheless, severe hypokalemia can negatively impact the results and make the procedure unsafe to perform with moderate sedation.

Perhaps the most important but under-recognized requirement for a successful AVS program is very close cooperation with the laboratory medicine service. The lack of advance notice about cases or absence of strict protocols for labeling, transport, and handling of blood specimens can lead to errors in the hormone assays. The interventionalist doing AVS should develop and monitor workflow systems with laboratory medicine leadership (at the physician and technologist levels) to ensure that no errors are made. For unusual cases, the IR should confirm, in advance, the sample volumes necessary for all assays requested and instructions for specific tube types and specimen handling (e.g., on ice).

While imaging is not absolutely necessary before AVS, the IR should review any available cross-sectional studies, particularly abdominal CT scans or prior nondiagnostic

AVS angiograms. In particular, it may be useful to identify the point of entry of the right adrenal vein into the inferior vena cava (IVC) with respect to bony landmarks to guide the catheterization procedure.

Sampling Procedure

Most experienced IRs perform AVS by sequential rather than simultaneous catheterization of the right and left adrenal veins. Simultaneous sampling of both veins through separate femoral vein access sites theoretically avoids errors related to temporal variations in hormone production. In practice, however, no significant reduction in accuracy seems to occur with sequential catheterization.[11,12] This is particularly true when sampling is done with stimulation for the evaluation of PA. In this common practice, an adrenocorticotropic hormone analog such as cosyntropin (Cortrosyn) is given by continuous IV infusion at 50 μg/h starting at least 30 min before catheterization and continued throughout the procedure. Stimulation has several beneficial effects, including increased aldosterone secretion from aldosteronomas, reduction in temporal and stress-induced fluctuations over the sampling period, and increased adrenal vein cortisol levels which will raise confidence that proper catheterization was done.[3] Opponents will argue that the sensitivity of the analysis is reduced. While there is no clear consensus on the use of stimulation during AVS for PA, many IRs with large AVS practices choose to use it.

The procedure is usually done with moderate sedation. After femoral vein catheterization, heparin 3000 units IV may be given to prevent adrenal vein thrombosis during cannulation. The peripheral blood sample is obtained through the 5 Fr femoral vein sheath. For each sample, at least 2 mL of blood are aspirated as waste. It is critical that no contrast material be present in the specimens. For patients with PA, 4 mL of blood is aspirated into a syringe and handed off the field to a technician for transfer to and labeling of sample tubes. A flow sheet should be maintained by the technician listing each sample (numbered in order) including sampling time and venous site.

The left adrenal vein is typically catheterized with a 4 or 5 Fr Simmons 2 catheter. In some patients with an unusually long left renal vein, a Simmons 3 catheter may be needed. After the catheter is reformed in the IVC, the left renal vein is entered. The catheter is withdrawn at the groin as the catheter tip advances into the vein. With slowly continued withdrawal at the groin, the catheter tip will reverse direction and move centrally. At about the left lateral border of the spine, the catheter tip will typically pop-up into the left phrenic adrenal vein trunk [Figure 1]. Variations in anatomy of the left adrenal vein are rare but must be appreciated by the operator, including the left adrenal vein directly entering the IVC, the gonadal vein, or the lower moiety of a circumaortic left renal vein.[13-15]

Gentle venography (no more than 2–3 mL) will confirm the location. If the catheter tip position is tenuous, it may be helpful to introduce a coaxial microcatheter to provide a few centimeters of additional length to stabilize the position in the vein [Figure 2]. Venography should demonstrate the left phrenic adrenal vein trunk and clearly identify the confluence of phrenic and adrenal vein tributaries [Figure 1]. Sampling in or central to the adrenal vein tributary is critical. Incorrect sampling may occur if the catheter tip advances into the phrenic tributary. The blood sample is obtained as described above, with slow aspiration to avoid entraining blood from the renal vein. Venography is repeated to confirm that the catheter position has been maintained. If the position has changed, discard the specimen and recatheterize the vein.

A 4 Fr RDC catheter (Cordis Corporation, Hialeah, Florida USA) is used to engage the right adrenal vein [Figure 3]. If unsuccessful, the operator should try a 4 Fr cobra or 4 Fr Simmons 1 catheter. Typically, the right adrenal vein enters the IVC at about the T11-T12 level. Ideally, the entire surface of the 90º sector of the right posterior quadrant of the IVC is interrogated from T11 to L1. To start, the catheter tip is placed on the back wall of the IVC at about T11 and withdrawn to about L1. If a vein is not engaged, the catheter is then rotated a few degrees clockwise at the groin, advanced superiorly to T11, and withdrawn again. This maneuver is repeated over and over as the tip gradually approaches the right lateral wall of the IVC. When the catheter tip enters a vessel, gentle venography with 1–2 mL of contrast is done [Figure 4]. If the main hepatic veins or right renal vein are entered, the operator should make a note of these locations and search only below or above these levels, respectively. If an inferior right hepatic vein is detected, formal venography

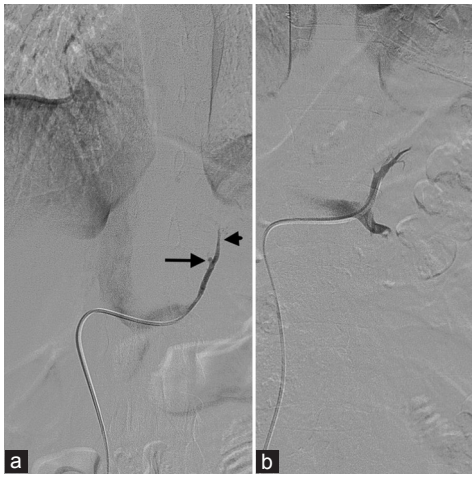

Figure 1: Left adrenal venography for venous sampling. (a) Catheter tip is situated in the main left phrenic adrenal trunk. Note the left adrenal vein tributary (arrowhead) and the left phrenic tributary (arrow). (b) In another patient, the catheter tip has entered the left adrenal vein trunk. Such superselective catheterization is not necessary

should be done. In a significant percentage of patients, the right adrenal vein will arise from the central portion of this vessel[16] [Figure 5].

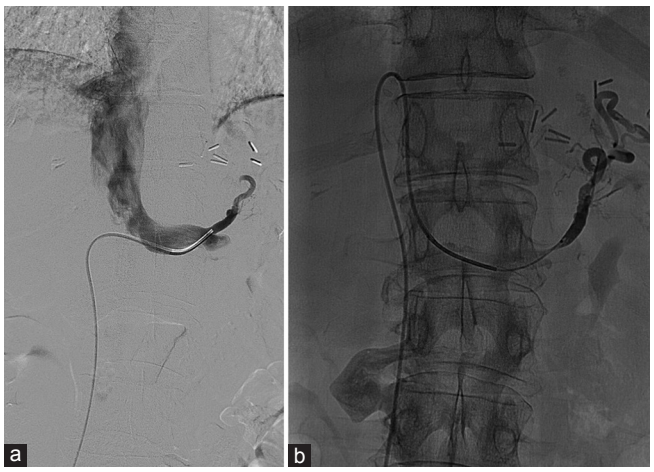

Figure 2: Inadequate left adrenal vein sampling. (a) Sampling was done with the catheter tip barely in the phrenicoadrenal vein trunk. With continuous cosyntropin infusion, rapid peripheral cortisol was 28.7 mg/dL, and selective vein cortisol was 59.9 mg/dL; catheter likely withdrew from the vein during blood aspiration. (b) A coaxial microcatheter was advanced into the phrenicoadrenal trunk to obtain an appropriate sample. Selective vein cortisol was 553.8 mg/dL

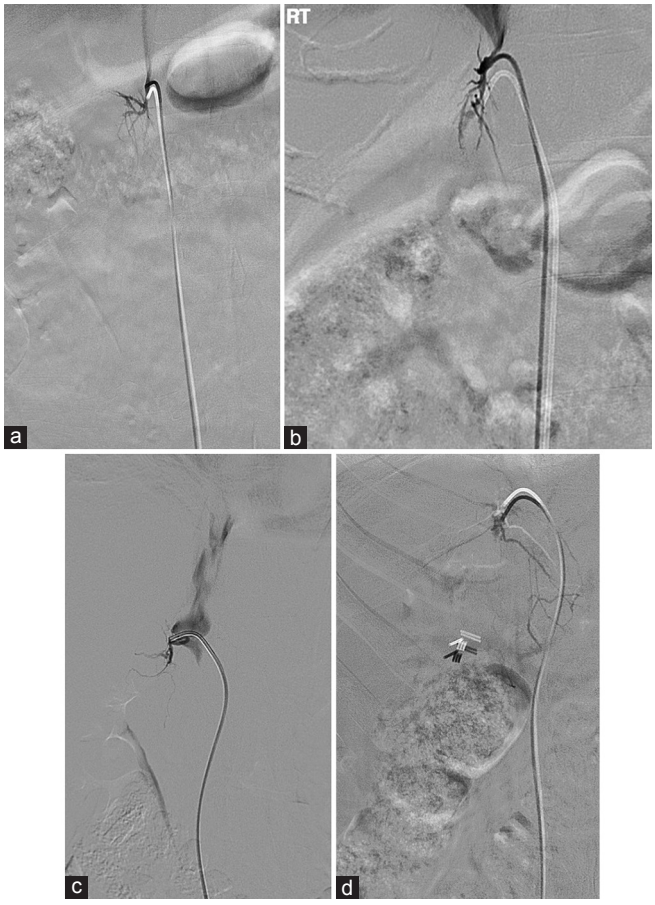

Figure 4: Typical right adrenal venography (a-c). Atypical right adrenal venography (d) proven by cortisol analysis

Typically, the right adrenal vein has 4–5 tributaries that converge in a "delta" configuration to a very short central trunk that enters the IVC directly [Figure 4]. The parenchymal stain is usually negligible. This appearance must be distinguished from small hepatic veins [Figure 6]. Injection of those veins is typically associated with prominent sinusoid stain or communication with hepatic vein collaterals. Sometimes, the right adrenal vein has an unusual pattern. A useful sign that the correct vessel has been cannulated is filling of an inferior emissary vein, which is almost pathognomonic of the right adrenal vein [Figure 7].[17] But whenever in doubt, a blood sample should be taken.

It is characteristic of right AVS that blood aspiration is slow and difficult. Easy rapid flow should suggest malposition of the catheter. Aspiration often causes a "ratcheting" vibration in the catheter shaft. Very slight manipulations of the catheter (up/down and right/left) and intermittent rather than continuous aspiration may assist with blood withdrawal. Another very useful trick is to insert a soft-tipped microwire into the catheter

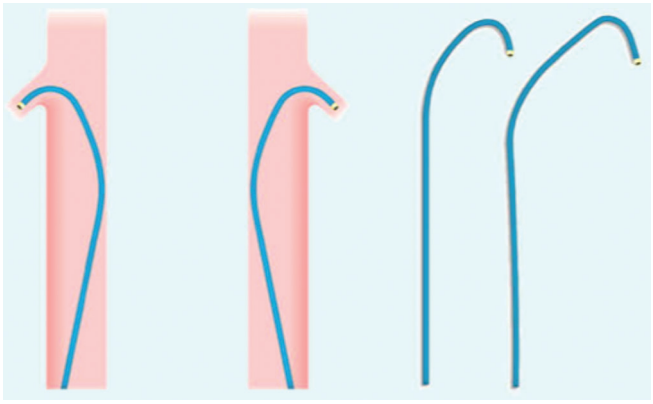

Figure 3: Four French RDC catheter (Cordis Corporation, Hialeah, Florida USA)

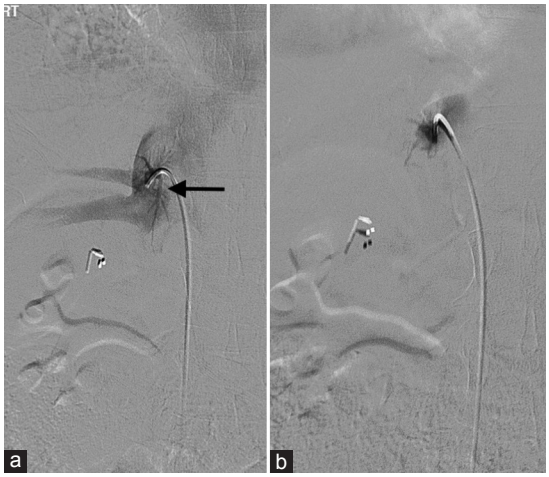

Figure 5: (a) Right adrenal vein (arrow) arises centrally near the inferior accessory hepatic vein entry into the inferior vena cava. (b) Selective catheterization of the adrenal vein for sampling

fitted with a hemostatic valve.[18] Once the right adrenal vein trunk is engaged, the microwire is gently advanced a short distance into the vessel [Figure 8]. This step will stabilize the catheter tip and facilitate blood aspiration. After the sample is obtained, venography is repeated to confirm that the tip remains in the adrenal vein.

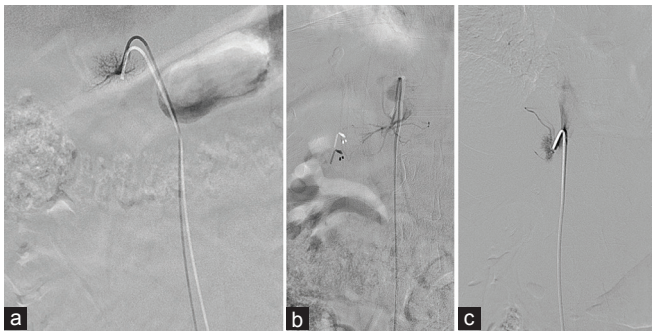

Figure 6: (a-c) Examples of hepatic venography which should not be confused with adrenal venography

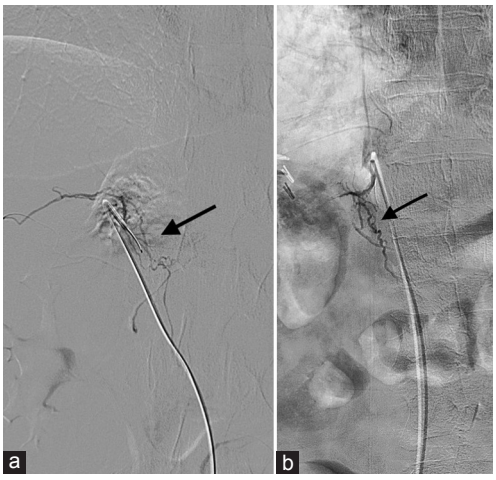

Figure 7: (a and b) Right adrenal veins associated with inferior emissary veins (arrow)

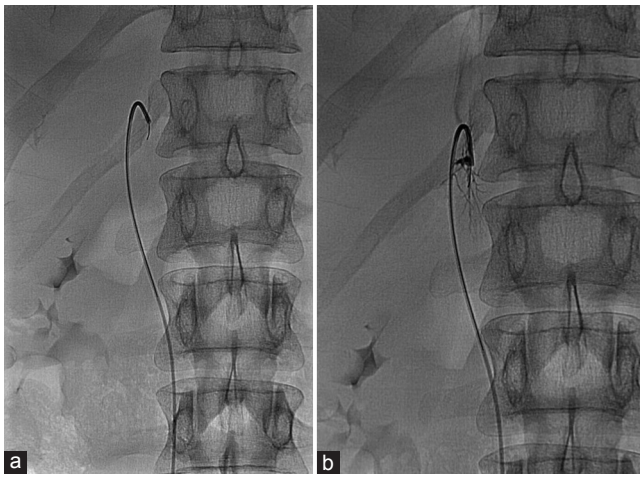

Figure 8: Microwire used to stabilize catheter position (a) and assist with aspiration from the right adrenal vein (b)

Confirmation of Proper Sampling

Catheterization is rarely a problem with the left adrenal vein. When right adrenal venography is characteristic and postsampling venography confirms a stable position, proper sampling is also likely to have occurred. When venography of the putative right adrenal vein is atypical or possibly represents hepatic vein, some operators will perform C arm CT venography to confirm the location.[19] However, the most accurate method to ensure correct sampling is rapid cortisol analysis of specimens before ending the procedure.[20] Most laboratories can perform this analysis within 45–60 min. The disadvantages of this added step are prolonged sedation time, patient inconvenience, and loss of valuable IR room time. On the other hand, the patient and operator are certain that a diagnostic study has been done before the procedure is over. Once the cortisol levels return, a selectivity index is calculated (selective vein cortisol/peripheral vein cortisol). When continuous cosyntropin stimulation is used, a selectivity index >4 confirms proper sampling of that adrenal gland. When the right-sided index is low, catheterization of the wrong vein has occurred. When the left-sided index is low, the catheter was either too deep into the inferior phrenic vein or catheter tip moved during aspiration [Figure 2]. Patients only require 1–2 h of observation after sheath withdrawal.

Laboratory Analysis and Interpretation

Once aldosterone levels have returned, the lateralization index is calculated (higher [vein aldosterone/vein cortisol] ÷ lower [vein aldosterone/vein cortisol]). When stimulation was done during sampling, lateralization is confirmed when the index is ≥4.[3] Values between 3 and 4 are nondiagnostic and may warrant repeat AVS.

If sampling is not successful, the IR and referring physician should consider a second attempt. In that case, it may be useful to obtain high resolution, thin cut contrast-enhanced CT imaging with attention to adrenal veins to guide the second procedure. In one recent report, a diagnostic study was obtained in 60% of cases on the second attempt and 20% of cases on the third attempt.[21]

Complications

AVS is a remarkably safe procedure. Significant adverse events are very uncommon. They include the usual rare complications associated with venography from the femoral vein (e.g., bleeding, thrombosis, contrast reaction, and contrast nephropathy). The specific complication of this procedure is injury to the (usually right) adrenal vein from catheterization itself or more commonly over injection of contrast, leading to vein rupture, vein thrombosis, gland or perigland hematoma, or adrenal infarction. This complication occurs in <1% of cases in high volume centers.[3] Some of these events may produce flank or abdominal pain during or soon after the procedure.

Pain often increases over the 1st day, may require opioid analgesics, and subsides over a period of 2–3 days. The treatment is virtually always conservative.

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Conflicts of interest

There are no conflicts of interest.

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