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Chronic Kidney Disease and Coronary Artery Disease

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Abstract

Chronic kidney disease (CKD) and coronary artery disease (CAD) are conditions that, when present together, is considered a high-risk feature. Despite the high prevalence, few studies are dedicated to studying CAD specifically in individuals with CKD, and it is a common exclusion criterion in most trials. This fact leads to gap in the evidence for the management of CAD, which, sometimes, results in undertreatment of CKD patients. In this chapter, authors present peculiarities related to CAD among patients with CKD from physiopathology to diagnostic and therapeutic decisions. An evidence-based approach was used to explore this high-risk subset of CAD patients.

Keywords: chronic kidney disease, coronary artery disease, atherosclerosis, coronary artery bypass graft, percutaneous coronary intervention

1. Background

The association between chronic kidney disease (CKD) and coronary artery disease (CAD) has been the subject of numerous studies recently. Not only because of the frequent association between the two entities, but also because of the aggregate risk when both conditions are present in the same individual.

Despite the high prevalence, few studies are dedicated to studying CAD specifically in individuals with CKD. In fact, CKD, especially in its final stages, is a common exclusion criterion in large studies. This fact resulted in a gap in the evidence for the management of CAD, which, sometimes, results in undertreatment of CKD patients.

This chapter aims to explore the association between CAD and CKD, approaching from pathophysiology to available evidence for the treatment of these conditions.

2. Coronary atherosclerosis and renal failure

Another scenario where there is a profound interaction between renal failure and the cardiovascular system is with regard to coronary atherosclerosis. It is known that chronic kidney disease adds risk to coronary events. The relationship between renal disease and cardiovascular mortality can be found even in the early stages of disease [1] and increases as kidney function deteriorates [2] (see **Table 1** for the stages of CKD according to the National Kidney Foundation KDOQI Clinical Practice Guidelines [3]). It is also known that the population with CAD and CKD has higher mortality regardless of the treatment used for coronary disease [4].

Several epidemiological studies have demonstrated that CKD is an independent risk factor for cardiovascular events.

The Framingham Heart Study was one of the first to associate chronic kidney disease with cardiovascular events in the general population. Of the 6233 study participants, stage 2 CKD was found in 246 men and 270 women. Of these, 81% were not diagnosed with cardiovascular disease at the start of the study. After 15 years of follow-up, there was a tendency for a higher incidence of cardiovascular events in the male population with stage 2 CKD [5]. Data from the Atherosclerosis Risk in the Communities study also confirm an increase in the risk of cardiovascular events in this same population [6]. When GFR is considered as a continuous variable, this study points to a 5–6% increase in cardiovascular risk for each loss of 10 mL/min/1.73 m^2 of GFR. Go and colleagues also demonstrated, in a cohort study of 1,120,295 patients, comprised of approximately 9.6% of diabetics and 6.3% of CAD patients, a risk of death of about 1.2 times higher associated with an GFR 45–59 mL/min/1.73 m^2 when compared to those with GFR ≥60 mL/min/1.73 m^2 [7]. There was a growing risk as the lowest GFR was considered, culminating with a relative risk of about 5.9 in those patients with RFG <15 mL/min/1.73 m^2.

There is also a worse prognosis associated with renal failure in populations with established heart disease. The Valsartan in Acute Myocardial Infarction Trial (VALIANT) looks at the influence of GFR, even in its early stages, in a population at high risk for cardiovascular

Stages	GFR (mL/min/1.73 m^2)	CKD
0	>90	Risk group for CKD. Absence of renal injury
1	>90	Normal renal function. Presence of kidney damage
2	89–60	Discrete or functional CKD
3	59–30	Moderate or laboratory CKD
4	29–15	Severe or clinical CKD
5	<15	Terminal or pre-dialytic CKD

Table 1. Staging and classification of CKD.

events [8]. This study accompanied patients after acute myocardial infarction complicated by systolic ventricular dysfunction or symptoms of congestive heart failure (CHF) who were randomized to either valsartan, captopril or both. After adjusting for the received treatment and comorbidities, a risk of 1.14 times greater risk for cardiovascular death was found in patients with an GFR of 60–74 mL/min/1.73 m^2 (95% CI 1.02–1.27) and 1.10 times for combined events (cardiac mortality, re-infarction, CHF and stroke) when compared to the population with normal renal function. A factor that may have contributed to these findings is that the CKD population was undertreated when compared to the population with normal renal function, receiving invasive stratification (27.5% vs. 34.7%) and beta-blockers (71.9% vs. 74.7%) to a lesser extent than those with preserved renal function.

2.1. Mechanisms of cardiovascular complications in CKD

As previously described, kidney disease, even in its early stages, poses an increased risk of cardiovascular events. Even initial lesions such as a discrete fall in GFR or microalbuminuria (including patients with normal GFR) are associated with increased cardiac mortality, AMI or stroke. The main pathophysiological mechanism involved in this complex relationship appears to be endothelial dysfunction.

2.1.1. Endothelial dysfunction

Endothelial dysfunction is one of the initial events of the so-called atherosclerotic gait. It is present in both small and large vessels. Reducing the bioavailability of nitric oxide (NO) is one of the main mechanisms involved in endothelial dysfunction in patients with GFR. In this context, it is important to highlight the role of asymmetric dimethyl arginine (ADMA), which is derived from protein catabolism and competitive inhibitor of NO synthase produced mainly in the endothelium, the heart and the smooth cells and is clarified by the kidneys. When in high concentrations, as in individuals with GFR, it blocks the entry of L-arginine at the cellular level, leading to a reduction in NO synthesis. This leads to increased peripheral vascular resistance, intimal hyperplasia of the vessels and consequent increase in blood pressure with remodeling of the same. Recent studies have pointed to ADMA as an independent marker of cardiovascular risk in individuals with CAD [9].

2.1.2. Albuminuria

The correlation between macroalbuminuria and microalbuminuria with endothelial dysfunction measured in peripheral vessels is something that has been demonstrated and is a consequence of glomerular hyperfiltration. Thus, albuminuria has been identified not only as a consequence of the renal aggression that precedes the fall of GFR, but also as powerful marker of cardiovascular risk. Like GFR, albuminuria increases cardiovascular risk even at minimal levels. This risk increases as the albuminuria level rises, defined as normal albumin excretion (<30 mg/g), to microalbuminuria (30–300 mg/g) and, finally, with macroalbuminuria (>300 mg/g).

Several studies have demonstrated the role of albuminuria as a marker of cardiovascular risk. The Irbesartan Diabetic Nephropathy Trial (IDNT) studied 1715 subjects with type 2 DM, hypertension and macroalbuminuria, randomizing them to receive irbesartan, amlodipine or placebo. In a post-hoc analysis of Anavekar [10], univariate analysis showed an increase in cardiovascular risk proportional to the value of albuminuria. Multivariate analysis confirmed albuminuria as an independent risk factor. The (Reduction of End Points in NIDDM with Angiotensin II Antagonist Losartan (RENAAL) study [11] showed similar results, demonstrating a 1.92-fold higher risk of cardiovascular events in the group with albuminuria >3000 mg/g when compared to the dose group <1500 mg/g. The HOPE [12] study got a RR of 1.83 for cardiac death and 1.61 for the combined outcome of AMI or stroke in the population with albuminuria >17.7 mg/g. In addition, subsequent analyzes of HOPE suggest that albuminuria as low as 4.4 mg/g already translates into increased cardiovascular risk, suggesting that it behaves as a continuous variable [13].

2.1.3. Systemic arterial hypertension

Hypertension is present in most patients with CKD and atherosclerotic disease. The activation of the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system and sodium retention plays an important role in the development of hypertension. Recently, renalase, a regulator of cardiac function and blood pressure produced by the kidney, has been discovered. This regulator metabolizes catecholamines and has hypotensive action. Its absence may be responsible for adrenergic hyperreactivity leading to endothelial dysfunction and cardiac and vascular remodeling [9].

The activation of RAAS occurs in several ways in kidney disease. Angiotensin II stimulates NAD (P) H oxidase, leading to superoxide anion formation and contributing to endothelial dysfunction and cardiac remodeling. In addition, when angiotensin II stimulates the AT 1 receptor, there is generation of reactive oxygen species (ROS) with release of inflammatory mediators, including cytokines, adhesion molecules, PAI-1 (plasminogen activator inhibitor-1), among others. These events eventually promote the progression of atherosclerosis.

2.1.4. Inflammation

Atherosclerosis has been considered as an inflammatory condition. CKD patients are known as 'inflamed patients' since we have evidence of measurable inflammatory markers such as C-reactive protein (CRP), fibrinogen, interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), factor VIIc, factor VIIIc, plasmin-antiplasmin complex, D-dimer, E-selectin, VCAM-1 and ICAM1, as well as the deleterious effects of the inflammatory process in this population [9]. The poor nutrition of these patients, evidenced by low levels of albumin, pre-albumin and transferrin, has been suggested as a possible mechanism of activation of the inflammatory process. In addition, oxidative stress, the accumulation of modified molecules after synthesis, nonenzymatic glycosylation products or other products normally cleansed by the kidney also have their role in triggering inflammation [9]. Consequently, we have alterations in the endothelium and lipoproteins leading to accelerated atherosclerosis.

CRP has been particularly studied in the chronic kidney population, being found at higher levels in the terminal CKD population than in the normal population. CRP has been shown to be an excellent marker of cardiovascular risk in this population [14, 15].

The inflammation also seems to be related to the vascular calcification process, so common in patients with CKD, markedly in those in advanced stages of the disease. Calcification may be present in the medial layer of vessels, smooth muscle cells, medial muscular arteries and valvular system. As calcification progress, the capacitance of the arterial vessels is reduced, promoting the progression of systemic arterial hypertension (SAH) and left ventricular hypertrophy (LVH). The mechanisms involved in the CKD calcification process are complex and include the passive precipitation of Ca and P in the presence of high concentrations of these ions in the extracellular, in addition to the effect of inducers of osteogenic transformation, formation of hydroxyapatite and deficiency of calcification inhibitors such as osteoprotegerin and fetuin-A. In addition, high levels of leptin, common in patients with CKD due to reduced GFR, can induce calcification via hypothalamic receptors, stimulating osteoblastic beta-adrenergic receptors, generating ROS and inducing bone morphogenetic protein-2 (BMP-2). BMPs are regulators of bone formation, acting on receptors (BMPRs) that modulate gene expression. BMP-2 and BMP-4 are promoters of calcification, while BMP-7 behaves as an inhibitor of this process. BMP-7 is expressed mainly in the kidney and its reduction is proportional to the loss of renal function (**Figure 1**) [9].
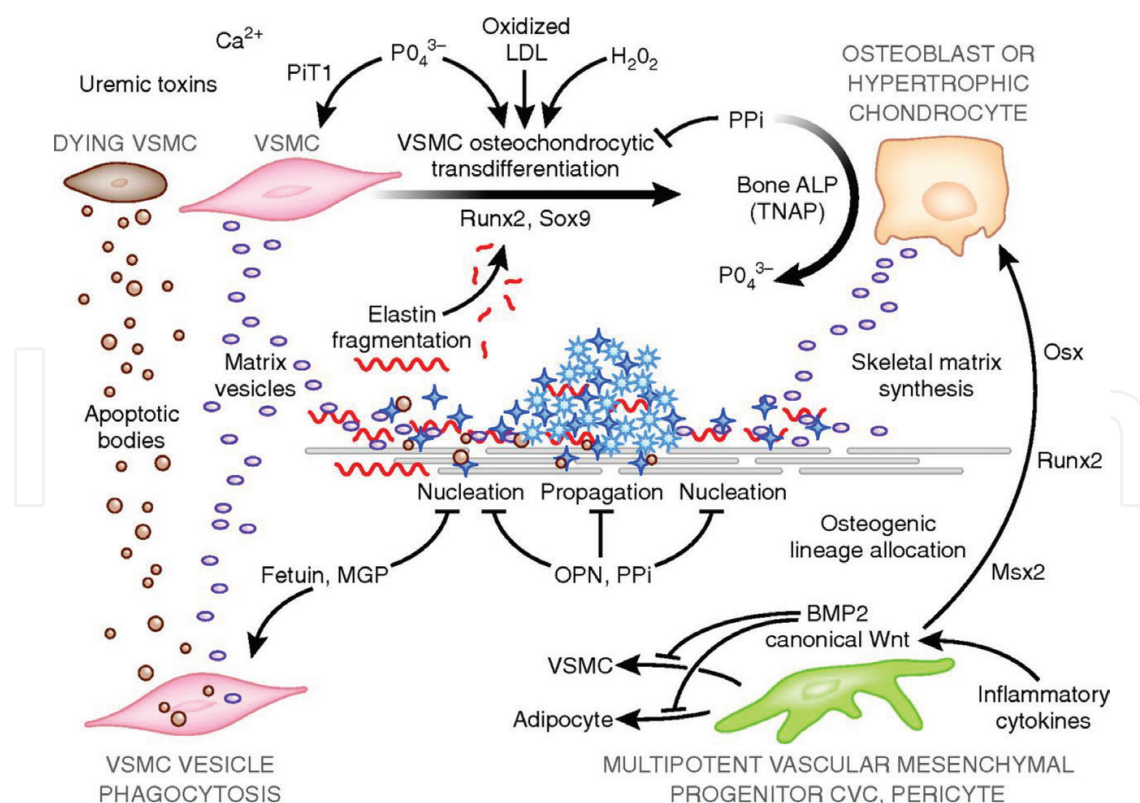

Figure 1. Atherosclerosis and calcification in renal failure. Extracted from Mizobuchi et al. [35].

3. Particularities in the diagnosis and treatment of CAD in patients with renal insufficiency

The incidence of coronary disease in the CKD population is high. Gowdak and colleagues observed a 47% incidence of angiographically significant CAD among patients with terminal CKD awaiting renal transplantation [16]. Interestingly, even in the population without traditional risk factors (SAH, DM, obesity, dyslipidemia and smoking), the observed incidence of CAD was 26%, and may reach 100% among those with all risk factors mentioned above.

The best method to investigate or stratify CAD in this population is still a matter of dispute. The presence of endothelial dysfunction, LVH, hypertension and volume overload in chronic renal patients should be considered when choosing the best method.

Some studies have considered that a more aggressive strategy should be used, since the non-invasive methods do not have good accuracy in the prediction of events in this population, especially in those with terminal CKD. In an attempt to validate a strategy for diagnosis of significant CAD in a population of chronic dialysis patients, a study conducted at the Heart Institute of the Hospital das Clínicas of the USP Medical School (InCor-HCFMUSP) confirms that the documented coronary angiography and the presence of DM were good predictors of cardiovascular events. The sensitivity, specificity and positive and negative predictive values of myocardial scintigraphy with dipyridamole were 70, 74, 69 and 71%, respectively. It is worth noting that scintigraphy did not diagnose CAD in a significant number of patients with CAD confirmed by coronary angiography [16, 17]. These data confirm that the invasive strategy remains the gold standard in the diagnosis and stratification of risk in this population. It is important to remember that the use of iodinated contrast (especially in the population with discrete to moderate CRF) may worsen the renal function of these individuals, and the need for hemodialysis in cases of contrast-induced nephropathy is not uncommon. This, in addition to being an invasive, more expensive and less available method, does not authorize us to indicate routine coronary angiography for patients with CKD in the investigation and/or stratification of CAD. Clinical judgment should weigh the risk factors already mentioned to select the population that will benefit most from the invasive examination.

The use of new methods for the diagnosis of CAD, such as coronary angiotomography, calcium score and magnetic resonance imaging has also been studied in this population. In a recently published study, the calcium score applied to a population of renal transplant candidates had a good correlation with angiographic CAD for diagnosis, as well as being a good predictor of cardiovascular events when above 400 Agatston [18]. Magnetic resonance imaging has its importance mainly in the evaluation of previous infarctions, ischemia and myocardial viability in this population [19].

4. Treatment of CAD in patients with CKD

Treatment of coronary disease is based on optimized medical therapy associated or not with interventional procedures (surgical revascularization or angioplasty). The population with CAD and CKD has peculiarities that should not be forgotten when choosing the best therapeutic strategy.

The population of chronic renal failure with CAD is certainly a subgroup that benefits as much as possible from full clinical management because it is a group of patients with multiple comorbidities and an accelerated atherosclerosis [20]. In spite of this recommendation, the population with renal dysfunction is frequently undertreated, which surely contributes to the worse prognosis of this special population [21].

Interventional therapy in patients with chronic kidney disease with CAD seems to be beneficial in some situations, especially when we consider their high atherosclerotic load and angiographic complexity.

A retrospective study by Reddan, conducted at Duke University, analyzed 4584 patients with CAD who underwent clinical treatment, percutaneous coronary intervention (PCI) or myocardial revascularization (CABG), who were stratified according to GFR, followed and evaluated for cardiovascular events. In this study, a benefit of percutaneous treatment over clinical treatment was observed in the population with mild to moderate CRF, but not among those with terminal CKD. When comparing myocardial revascularization surgery with medical treatment, we observed that, curiously, the benefit of surgery is greater as the severity of renal failure progresses [4].

In our setting stands out a subanalysis of MASS II [22], conducted by Lopes and collaborators at InCor - HCFMUSP. In this publication, 611 patients from the original study, randomized to medical treatment, PCI or CABG, were stratified by GFR in 3 categories (RFG ≥ 90, between 89 and 60 or between 59 and 30 mL/min/1.73 m^2) and classified as with normal renal function (n = 112/18%), mild (n = 349/57%) or moderate (n = 150/25%), respectively. The results point to a higher mortality among the population with moderate CRF, compared to the other two groups. In addition, it was observed that among patients with mild CRF, patients submitted to surgery had a higher survival rate free of cardiovascular events and lower mortality in 5 years compared to the population submitted to angioplasty or in exclusive medical treatment.

Lima and collaborators evaluated in a registry-type study 763 diabetic patients with CAD of the MASS group stratified according to renal function and followed for about 5 years. Of note is the high rate of CKD patients when applied clearance estimated by Cockcroft-Gault, with almost 65% of patients with some degree of CKD having clearance <90 mL/min. Even in an exclusively diabetic population, the presence of CKD was associated with higher mortality regardless of the treatment received, with survival rates of 91.1%, 89.6% and 76.2% for the preserved function, mild and moderate CKD, respectively (p = 0.001). When compared to the drug treatment, the surgical treatment was associated with lower combined event rates in the stratum with discrete CKD (86.2% versus 65.7% for CABG and TM respectively, p < 0.001) and additional revascularization in all function strata studied.

4.1. Interventional treatment in patients with end-stage CKD

This is a population where, despite the interventional therapy chosen, there is a higher risk of morbidity and mortality when compared to the general population. A patient undergoing CABG has a 4.4-fold greater risk of in-hospital death, a 3.1-fold increase in mediastinitis, and a 2.6-fold increase in stroke than a nondialysis patient. Some studies point to the safety of angioplasty in this population, especially in single-vessel patients [23]. However, when we compare angioplasty with surgical revascularization, it seems to bring greater cardiovascular

protection to these patients [24]. This can be attributed to a higher rate of restenosis in this population, which is derived from a close association with diabetes mellitus, accelerated atherosclerosis and vascular calcification [25].

Several studies in chronic coronary disease have evaluated the performance of the subpopulation of chronic renal patients in their trials. In a post-hoc analysis of the ARTS study [26], 142 patients with moderate CKD with multiarterial CAD were randomized to receive surgery or angioplasty and followed for 5 years. Regardless of the revascularization method chosen, patients with moderate CRF had more cardiovascular events (death, stroke, nonfatal AMI or additional revascularization) than the population with mild or normal renal function. When we compared the strategies, we observed that there was no significant difference in mortality (RR: 1.18, 95% CI: 0.51–2.72, p = 0.81), but a greater number of events combined in the angioplasty group (RR: 1.56, 95% CI: 1.03–2.37, p = 0.04), mainly due to additional revascularizations (29% vs. 9.6% p = 0.005).

The BARI study [27] evaluated 3608 patients (randomized and from the registry), stratifying them into two groups: with and without CRF, which was defined as baseline serum creatinine greater than 1.5 mg/dL. Of the total, 1517 patients were submitted to surgery and 2091 to angioplasty. Of these, 76 patients were considered to have chronic renal failure. This population was older and had a higher proportion of hypertensive and diabetic patients. Among patients undergoing PCI, chronic kidney disease had a higher incidence of in-hospital mortality and cardiogenic shock. In addition, this population was more susceptible to the presence of angina, hospitalizations due to cardiac reasons and less time for additional revascularization compared to the normal population. In 7 years, the population with CKD had a higher incidence of general (RR: 2.2, p < 0.001) and heart (RR: 2.8, p < 0.001) than the population with normal renal function.

Although we consider the benefit of pharmacological stents on conventional stents with regard to the lower incidence of restenosis, recent studies comparing pharmacological stents with CABG in this population show a greater benefit of the latter, especially at the expense of lower rate of additional revascularization [28]. A recent study by Marui and colleagues from the CREDO-Kyoto registry demonstrated that in 388 patients with dialytic CKD, similar incidences of general and cardiac death were observed when CABG compared with PCI in a long-term follow-up. The latter strategy, however, was associated with higher rates of AMI and additional revascularization [29].

In the post-hoc analysis of the FREEDOM study [30], comparison of interventional strategies among diabetic patients with CAD in the presence of renal dysfunction defined by estimated clearance <60 mL/min did not demonstrate superiority of CABG on PCI with first-generation pharmacological stent at MACCE rate at 5-year follow-up.

Charytan et al. [31] in a collaborative study including 10 randomized prospective studies of 3993 subjects demonstrated similar survival rates at 5 years when patients with CKD class 3–5 underwent CABG or PCI (HR 0.99, CI 0.67–1.46). However, AMI-free survival among patients with CKD class 3–5 was higher among those undergoing surgical treatment (HR: 0.49; CI: 0.29–0.82). Consistent with other studies, CABG was associated with lower rates of additional revascularization than PCI, regardless of the renal function stratum considered.

Recently, a meta-analysis by Bundhun's et al. [32] included 18 studies involving a larger number of patients (n = 69,456, 29,239 underwent CABG and 40,217 underwent PCI). This present analysis observed a benefit of CABG in reducing mortality when compared to PCI in long-term follow-up only (OR: 0.81, 95% CI: 0.70–0.94, p = 0.007 for nondialytic, OR: 0.81, 95% CI: 0.69–096, P = 0.01 for dialytic). It is also worth mentioning a benefit in reducing additional revascularizations among those submitted to CABG in almost all studies that included this outcome. Of note, however, is the heterogeneity of the included studies, with different definitions for CKD, in addition to follow-up times ranging from 1 month to 8 years.

Off-pump CABG was also evaluated in some studies because of the theoretical benefit of a less aggressive procedure than on-pump CABG. These studies have demonstrated a lower need for blood products and dialysis in the postoperative period, shorter hospital stay in intensive care and mechanical ventilation, but with no difference in mortality in the medium term [24, 33]. Consistent with these previous results, recently published data from the Coronary Artery Bypass Grafting Surgery Off-pump Revascularization Study, comparing on-pump versus off-pump CABG, showed a reduced risk of perioperative acute renal injury associated with off-pump CABG. In spite of this, no renal protection was observed at the 1-year follow-up associated with this surgical strategy [34].

5. Final considerations

CKD has a negative impact on the prognosis of individuals with CAD regardless of the treatment. There are no peculiarities in the indication of revascularization in this population, and attention must be paid to the greater clinical and angiographic severity of this population. The drug treatment should be applied considering the potential limitations of the use of some classes among those with terminal CKD, however, avoiding at all costs under-treatment. There is still no consensus on the best therapeutic strategy for CAD (e.g. interventional versus conservative; PCI versus CABG) for those with CKD. The studies are heterogeneous and almost completeness formed by observational records, post-hoc analyses of large trials or meta-analyses. In spite of this, some clarity seems to emerge from these publications: (1) the greater the angiographic severity/severity of CKD, the greater is the benefit of surgical revascularization; (2) in the subpopulations with discrete/moderate CKD, there is no clear evidence of surgery on the other treatments; and (3) surgery is associated with less need for additional revascularization independently of the status of renal function, which suggests that this benefit is associated with the revascularization method itself, rather than the patient's renal status.

We await the results of the ISCHEMIA-CKD study (ClinicalTrials.gov Identifier: NCT01985360), designed to study patients with documented (at least moderate) ischemia and severe renal dysfunction (GFR <30 or on dialysis) randomized to an initial strategy of coronary angiography and interventional treatment plus optical medical therapy or optimal medical therapy alone. Its results will surely bring answers to pertinent questions not yet answered in this common clinical scenario.

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