

AHA PRESIDENTIAL ADVISORY

Penicillin Reactions in Patients With Severe Rheumatic Heart Disease: A Presidential Advisory From the American Heart Association

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ABSTRACT: Secondary antibiotic prophylaxis with regular intramuscular benzathine penicillin G (BPG) is the cornerstone of rheumatic heart disease management. However, there is a growing body of evidence that patients with rheumatic heart disease who have severe valvular heart disease with or without reduced ventricular function may be dying from cardiovascular compromise following BPG injections. This advisory responds to these concerns and is intended to: (1) raise awareness, (2) provide risk stratification, and (3) provide strategies for risk reduction. Based on available evidence and expert opinion, we have divided patients into low- and elevated-risk groups, based on symptoms and the severity of underlying heart disease. Patients with elevated risk include those with severe mitral stenosis, aortic stenosis, and aortic insufficiency; those with decreased left ventricular systolic dysfunction; and those with no symptoms. For these patients, we believe the risk of adverse reaction to BPG, specifically cardiovascular compromise, may outweigh its theoretical benefit. For patients with elevated risk, we newly advise that oral prophylaxis should be strongly considered. In addition, we advocate for a multifaceted strategy for vasovagal risk reduction in all patients with rheumatic heart disease receiving BPG. As current guidelines recommend, all low-risk patients without a history of penicillin allergy or anaphylaxis should continue to be prescribed BPG for secondary antibiotic prophylaxis. We publish this advisory in the hopes of saving lives and avoiding events that can have devastating effects on patient and clinician confidence in BPG.

Key Words: AHA scientific statements ■ antibiotic prophylaxis ■ heart valve diseases ■ penicillin G benzathine ■ rheumatic heart disease

More than 39 million people have rheumatic heart disease (RHD).¹ The vast majority live in low- and middle-income countries. In these settings, RHD is often diagnosed late, after severe valvular heart disease or cardiovascular complications have already developed. Without access to advanced medical or surgical therapy, people living with RHD in low- and middle-income countries have a high mortality rate and low life expectancy.²

Injectable benzathine penicillin G (BPG), given via intramuscular injection every 3 to 4 weeks for a prolonged period (eg, 10 years, until age 40 years, lifelong),^{3–5} is

the cornerstone of RHD prevention (preventing rheumatic fever recurrence) and management. However, adoption of BPG has been suboptimal. Poor uptake is multifactorial, but fear of anaphylaxis and subsequent death causes some patients to resist receiving injections and health care professionals to resist administering them.⁶ The true risk of anaphylaxis following a BPG injection is low.⁷ Regardless of frequency, sentinel incidents are long remembered in affected communities, creating anxiety among patients, families, and health care professionals that substantially reduces BPG delivery. Further, there have been serious enough

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concerns about adverse reactions to BPG that its use has been severely curtailed or even banned in some parts of India and Africa.⁶ This, of course, has a devastating effect on RHD control.

Until recently, deaths in the minutes and hours after BPG injection have been presumed to be anaphylactic related. However, a growing number of anecdotal reports of immediate or nearly immediate BPG-related deaths, many of which did not have features of classical anaphylaxis, point to cardiovascular compromise as the possible cause of some BPG-related deaths.⁶ A cardiovascular cause for BPG-related death has important ramifications, namely for implementation of strategies to prevent or abort these adverse events, and for considering the possibility that there may be patients in whom less effective prophylaxis with oral antibiotics may be warranted.

As the evidence base for adverse BPG reactions among patients with RHD remains sparse, and no formal research has been conducted on risk mitigation, there is not yet sufficient evidence to inform a guideline or scientific statement. However, we believe an advisory is urgently needed to raise awareness, provide risk stratification, and give guidance on easily implementable protocols to reduce risk and overcome reluctance to administer and receive secondary prophylaxis around the world. This is particularly timely in light of the 2018 World Health Assembly resolution on RHD control.⁸

ANAPHYLAXIS OR CARDIOVASCULAR COMPROMISE

Serious adverse events following BPG administration are frequently attributed to (presumably penicillin) anaphylaxis because of the association with a known allergen and rapid progression to collapse. Although some BPG reactions are the direct result of anaphylaxis, publications dating back >50 years make it clear that not all severe BPG reactions in patients with RHD are anaphylactic.⁹ Recently, a growing number of anecdotal reports¹⁰ of immediate or nearly immediate BPG-related deaths, many of which did not have features of classical anaphylaxis, prompted a case review.⁶ In that series, 10 cases from 5 countries were reported. Only 3 met criteria for possible anaphylaxis; the other 7 cases showed remarkable similarity: A patient with severe valvular RHD who lost consciousness almost immediately after BPG injection and could not be resuscitated.⁶ Similarly, a review of the Khartoum RHD registry recently reported on >800 children with RHD.¹¹ In that series, 3 young children, over a span of only a few months, experienced collapse and immediate death following BPG injection, despite receiving appropriate intervention for presumed anaphylaxis.

No anaphylaxis symptoms, other than collapse, were noted, but all 3 had severe mitral regurgitation with resultant heart failure.

These data suggest that cardiovascular compromise, rather than anaphylaxis, may be responsible for some sudden deaths that occur immediately after BPG injection, in particular in patients with severe valvular heart disease. Marantelli and colleagues,⁶ as part of the case review previously mentioned, outlined the physiological cascade of responses that may precipitate these events. Although the mechanisms vary slightly based on the distribution of underlying structural heart disease, it is postulated that pain or fear of BPG administration drives a physiological response precipitating decompensation that includes vasovagal hypotension, bradycardia (in some cases), and syncope, quickly leading to decreased coronary perfusion, ventricular arrhythmias, and sudden cardiac death.

Although there is no direct evidence yet to support this mechanism of death, we believe it is highly plausible and supported by 4 arguments. First, there is a consistent association between adverse outcomes after BPG injections and severity of RHD.^{6,11,12} Anaphylaxis, compared with cardiac compromise, would show equal distribution across severity of RHD proportionate to the number of BPG injections delivered, yet sudden deaths occur disproportionately in young people with severe, symptomatic RHD. Second, there is a clear discrepancy of adverse BPG events between patients receiving BPG for RHD prophylaxis and those receiving BPG for other indications. Most data are from women receiving BPG to prevent mother-to-child transmission of syphilis, with few reports of adverse BPG reactions, despite a large number of doses of BPG being given.^{13–16} Third, there has been an apparent lack of response to appropriate anaphylaxis treatment in many patients, which also casts doubt that anaphylaxis is the cause of death. Although the patient response to resuscitation efforts, including administration of adrenaline, is not part of any diagnostic criteria for anaphylaxis, in clinical practice, adrenaline is highly effective in reversing immediate symptoms. However, the 2019 case series of adverse drug reactions to BPG found that although 8 of 9 patients received adrenaline, 7 were unable to be resuscitated. Finally, there has consistently been a striking lack of other anaphylactic symptoms among patients with severe RHD who experienced sudden death. Although hypotension and loss of consciousness can be features of an anaphylactic death, they are most often preceded by tachycardia along with respiratory, cutaneous, or gastrointestinal manifestations, which have been notably absent from these reports.

The following are clinical features comparing vasovagal collapse with anaphylaxis¹⁷:

1. Onset: A vasovagal episode is generally immediate, usually within minutes of, or during, medication administration. Anaphylaxis onset is usually within 15 minutes of medication administration but can occur within hours.
2. Respiratory symptoms or signs: With a vasovagal episode, breathing is generally normal (it may be shallow, but not labored). With anaphylaxis, a patient may demonstrate cough, wheeze, hoarseness, stridor, signs of respiratory distress (rapid breathing, cyanosis, or retractions), or upper airway swelling.
3. Cardiovascular symptoms or signs: A vasovagal episode may present with bradycardia, weak or absent peripheral pulses, a strong carotid pulse, hypotension (usually transient and corrects in patients once in a supine position), and loss of consciousness (which usually improves once supine or in a head-down position). Anaphylaxis may present with tachycardia, weak or absent carotid pulses, hypotension that is sustained and has no improvement without specific treatment, and loss of consciousness with no improvement once supine or in a head-down position.
4. Skin symptoms or signs: A vasovagal episode may present with generalized pallor and cool, clammy skin. Anaphylaxis may present with pruritis, generalized skin erythema, urticaria, or angioedema.
5. Gastrointestinal symptoms or signs: Gastrointestinal symptoms are similar in vasovagal and anaphylaxis cases. Both can present with nausea and vomiting, although anaphylaxis can also be associated with more cramping and diarrhea.
6. Neurologic symptoms or signs: With vasovagal episodes, the patient generally feels faint or lightheaded. With anaphylaxis, the patient has a sense of severe anxiety and distress.

RISK IDENTIFICATION

The most important factor predisposing patients to cardiac compromise appears to be the severity of the underlying valvular heart disease. Patients with severe valve disease, regardless of the valve in question, have little cardiovascular reserve and may not compensate well to pain on injection, vasovagal syncope, or volume and pressure shifts associated with administration of BPG. Adrenaline administration, although appropriate and lifesaving for anaphylaxis, may contribute to further cardiovascular compromise precipitated through tachycardia and decreased time for ventricular filling. Patients with severe mitral stenosis who depend on increased preload to maintain cardiac output may be at the highest risk, followed by those with severe aortic

stenosis and severe aortic insufficiency. Additionally, many of the reported deaths have occurred in patients with severe mitral regurgitation in the setting of symptomatic heart failure and left ventricular dysfunction.¹⁸ Thus, we believe that while well-compensated severe mitral regurgitation does not have increased risk and is not a contraindication to BPG, symptomatic patients with severe mitral regurgitation, in particular those who are cachectic and have decreased left ventricular systolic function, are at elevated risk. Because patients with severe MR often straddle (or move back and forth between) low- and elevated-risk categories, this group requires frequent individualized assessment of risk, with adjustment regarding oral versus injectable penicillin for patients as needed.

In many settings, we believe that there are also modifiable environmental conditions that may contribute to increased risk in vulnerable patients. Vagal reactions are likely exacerbated by conditions more common in low- and middle-income countries where the majority of fatal BPG reactions have been reported. Often, patients presenting to injection clinics for BPG in low- and middle-income countries appear dehydrated or hungry after having traveled long distances, waiting hours for injections, and sometimes having experienced a recent intercurrent illness—explaining why patients who have tolerated injections in prior months might have a reaction without significant change in their underlying disease. In addition, many receive injections in settings where routine hemodynamic monitoring is unavailable, making it more challenging to distinguish anaphylaxis from a cardiovascular collapse.

RISK MITIGATION

Based on the available evidence presented in this advisory, the expert working group believes patients with RHD who have severe valvular heart disease or heart failure may be at elevated risk of cardiovascular compromise and sudden death following BPG administration. In addition, the benefit of secondary prophylaxis is questionable given that the purpose of secondary prophylaxis is to prevent progression to severe valve lesions. Thus, we believe the risk of adverse reactions to BPG in patients at elevated risk outweighs its theoretical benefit. For these patients at elevated risk, we newly advise that oral prophylaxis, if reliably available and affordable, should be strongly considered (Table 1). We recognize in making this recommendation that there are availability concerns associated with oral prophylaxis in some settings, which will need to be considered. In many cases, regular prescribing of oral long-term prophylaxis would require a commitment from government in order to ensure availability. Additionally, although unequivocally inferior, reducing the risk of acute rheumatic fever

Table 1. Advisory Panel Conclusions for Prophylaxis Based on Risk of Death From Vasovagal Compromise

	Low risk	Elevated risk*
Structural cardiac disease	<ol style="list-style-type: none"> 1. Borderline RHD 2. Mild or moderate aortic regurgitation 3. Mild or moderate MR 4. Asymptomatic severe mitral regurgitation[†] 5. Mild or moderate mitral stenosis 6. Patients with postsurgical or interventional RHD patients who have no more than moderate residual valvular heart disease and preserved left ventricular function 	<ol style="list-style-type: none"> 1. Severe aortic insufficiency 2. Severe mitral stenosis 3. Severe aortic stenosis 4. Ventricular dysfunction (EF <50%) 5. Severe symptoms (NYHA class III or IV)[‡]
Secondary prophylaxis	Intramuscular BPG prophylaxis unless otherwise contraindicated [§]	Oral antibiotics (preferably penicillin) prophylaxis unless otherwise contraindicated [§]

BPG indicates benzathine penicillin G; EF, ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; and RHD, rheumatic heart disease.

*Risk selection should be based on the *most severe component of valvular disease* (ie, if mild MR but severe aortic regurgitation, then highest-risk categorization). American College of Cardiology/American Heart Association (AHA) classification for valvular heart disease.²²

[†]We recognize that patients with isolated severe MR make up the largest and most heterogeneous group who stand to benefit from this advisory; often straddling (or moving back and forth between) low- and elevated-risk categories. The decision regarding oral versus injectable penicillin for patients in this group should be adjusted on a case-by-case basis as needed.

[‡]Includes symptoms caused by nonstructural contributing factors such as atrial fibrillation and anemia.

[§]Contraindications for BPG or oral penicillin prophylaxis include prior allergic or hypersensitivity reactions, with best practice including formal allergy testing to confirm when available.

^{||}Guidelines for oral prophylaxis can be drawn from AHA⁵ or World Health Organization²¹ recommendations or from local guidelines and best practices, where they exist.

recurrence by 87% compared with 96% with BPG, high adherence to oral penicillin provides reasonable protection against recurrent group A beta-haemolytic streptococci infection (71% versus 91% with BPG),¹⁹ and eliminates the risk of injection-related vasovagal syncope, which may lead to increased mortality in this elevated-risk group. Guidelines for oral prophylaxis can be drawn from American Heart Association (AHA)⁵ or World Health Organization (WHO)²⁰ recommendations or from local guidelines and best practices, where they exist. Adherence support for those taking oral prophylaxis deserves special attention (at least twice-daily dosing) and should be tailored as needed to promote high adherence.

If BPG is preferred, we advise that, if possible, it be given to patients at elevated risk in a monitored setting by individuals experienced in cardiopulmonary resuscitation and proper cardiopulmonary resuscitation equipment. As no standardized severity scale for RHD exists, utilization of the American College of Cardiology/AHA classification for valvular heart disease selecting for the valve most severely affected is a reasonable approach for classifying patients at elevated risk.²¹

For patients with less than severe valvular heart disease and preserved ventricular function, we believe there is a yet to be understood but low risk of cardiovascular compromise should a vasovagal reaction occur. However, even given this presumed low risk, we advocate for a multifaceted strategy for vasovagal risk reduction in all patients with RHD receiving BPG, as most of these recommendations are simple, can be implemented in most locations, and have the potential to save lives. However, at the same time, we emphasize that the inability to institute all of these recommendations in an individual setting should not preclude BPG

administration. As current guidelines recommend, all low-risk patients without a history of penicillin allergy or anaphylaxis should be prescribed BPG for secondary

Table 2. Standard Best Practices for BPG Administration Including Recommendations to Reduce the Risk of Vasovagal Reactions

Standard best practice for BPG administration
<ol style="list-style-type: none"> 1. BPG should be given by people trained in intramuscular injection and in recognition and treatment of anaphylaxis and vasovagal reactions 2. Pain reduction and reassurance techniques should be used, and patients and guardians should be counseled about the signs/symptoms of vasovagal reactions 3. Volume of diluent should be the minimum recommended by the manufacturer 4. If possible, an anaphylaxis kit (minimum epinephrine) should be available (preferably in the room) wherever BPG is given 5. If a patient or clinician recognizes signs/symptoms of presyncope, the patient should lie back down, and, if at low risk, attempt counterpressure maneuvers (eg, leg crossing, hand grip) 6. Patients should be monitored for at least 30 min after injection for any signs of anaphylaxis or vasovagal syncope 7. Countries/programs should have in place a mechanism for BPG adverse events reporting
Best practice to reduce the risk of vasovagal reactions triggered by BPG injection*
<ol style="list-style-type: none"> 1. Minimize pain of injection (see #2 above) 2. Have the patient drink 500 mL of water 30–60 min before injection[†] 3. Have the patient eat a snack 30–60 min before injection 4. Administer BPG in supine position[‡] 5. Have the patient remain supine for at least 5 min after injection and rise slowly

BPG indicates benzathine penicillin G.

*Inability to institute all of these recommendations in an individual setting should not preclude BPG administration.

[†]If administering BPG to a patient with compromised ventricular function, hydration recommendations need to be customized by a health care professional.

[‡]Some patients and health care professionals may prefer a standing position for BPG administration, and these preferences should be handled on an individual basis.

prophylaxis given its superior efficacy in the prevention of recurrent rheumatic fever.¹⁹

For all patients receiving BPG, we emphasize that standard best practice should include reducing injection pain and patient anxiety, both of which are known risk factors for injection-related syncope.²² A range of pain reduction strategies exists for BPG injections including firm pressure to the site for 10 seconds before injection, application of an ice pack before injection, and the use of simple analgesics such as paracetamol before the injection.²³ In addition, patients should be well-hydrated before injection. Consumption of 500 mL of water has been shown to prevent reflex syncope by increasing vascular constriction and blood pressure, with cardiovascular effects peaking ~30 minutes after ingestion and lasting for 60 minutes, although clinicians should

modify this recommendation as appropriate when considering the patient with reduced ventricular function.^{24–28} We also advise that patients eat at least a small amount of food within 60 minutes before receiving an injection.^{29,30} Finally, acknowledging that patient and clinician preferences may impact this decision, we advise administration of BPG in patients in the supine position, which limits venous pooling in the lower extremities, and remaining supine for 5 to 10 minutes following injection with slow return to the standing position (Table 2).

We also believe that health care professionals who administer BPG should be taught to recognize vasovagal symptoms (sweating, lightheadedness, nausea, ringing in the ears, blurred or reduced vision, sudden feeling of hot/cold, pallor, dilated pupils, yawning) and should educate their patients as appropriate. Patients

Table 3. Research Priorities in the Pathogenesis, Impact, and Prevention of Severe BPG Reactions

Issue	Research priority	Comment
1. Defining the extent and nature of the problem	A. An international registry of severe BPG reactions	Existing literature consists mainly of anecdotal reports and retrospective studies with a high likelihood of bias, low quality of evidence, and lack of understanding of the role of potential comorbidities ^{6,10,16,37} Can define: Incidence with appropriate denominators (per injection, per patient-year) Severity Predisposing features (eg, severity of underlying heart disease) Clinical features, particularly to discern anaphylaxis from other reactions
	B. Prospective cohort studies	Can collect higher-quality epidemiological data and also more detailed information routinely (eg, baseline echocardiograms, blood pressure monitoring during injections) Could be used to monitor impact of implementing new guidelines and recommendations. If done in a population-based way and in multiple countries, could document impact of new guidelines in just a few years Potential to piggyback on existing initiatives such as the REMEDY study ²
2. Understanding perceptions of BPG, policy implications, and human impact of severe reactions and of policy changes	A. Qualitative and quantitative studies of perceptions and impact	In some countries or jurisdictions, bans have been placed on BPG administration because of concerns around safety, and in others there has been a lack of confidence among patients, leading to low adherence rates Define extent and nature of concerns among patients, clinicians, decision-makers, and wider community, and compare with scientific evidence Document individual, family, and community impact of severe reactions and implementation of policy responses
	B. Policy research	Document range of policy responses to perceived or real risks of BPG Document impact of policy responses on confidence in BPG and on outcomes (eg, rheumatic fever recurrences, mortality) Inform recommendations around reinstating BPG, particularly how to build, sustain, and regain trust, especially in underserved and under-resourced communities
3. Ensure quality and supply of BPG and oral penicillin	A. Build on existing studies with systematic data collection to document active ingredient and impurity levels in supplies and evidence of stockouts	Requires international coordination and leadership
4. Determine clinical risk and mitigating factors	A. Detailed clinical studies including clinical trials of mitigating medications or clinical protocols	Could be embedded in prospective studies, such as in 1B
	B. Implementation science to evaluate new recommendations put into practice at scale, especially in resource-limited settings	Requires increased training of implementation scientists locally, to provide credible and culturally relevant approaches

BPG indicates benzathine penicillin G; and REMEDY, Global Rheumatic Heart Disease Registry.

Table 4. Case Examples

Case	Category	Advice (also use clinical judgment)
A 17-y-old boy has moderate mitral stenosis, mild aortic insufficiency, and normal ventricular function who is taking medications and does not currently have symptoms	Low risk	Continue BPG
A 16-y-old girl taking warfarin after mitral valve replacement 1 y ago, currently with normal ventricular function and asymptomatic	Low risk	Continue BPG
A 14-y-old patient with moderate mitral stenosis and normal ventricular function who has marked breathlessness with light walking to school	Elevated risk (symptomatic—NYHA class III)	Consider oral prophylaxis
An 18-y-old patient with severe mitral stenosis and mild symptoms who is awaiting surgery	Elevated risk (severe mitral stenosis)	Consider oral prophylaxis

BPG indicates benzathine penicillin G; and NYHA, New York Heart Association.

with presyncopal symptoms should lie back down immediately and leg elevation should be used, if possible, to increase cerebral vascular flow. A cool damp cloth or ice pack applied to the face and neck may further attenuate symptoms and avoid loss of consciousness. Although symptoms can often be reversed through early initiation of counterpressure maneuvers (isometric contractions such as hand grip or leg crossing), which can increase cerebral blood flow velocity and cerebral oxygenation,^{31–33} they are generally contraindicated in patients with heart failure and in those with critical valvular stenosis and, thus, should be reserved for patients in the low-risk category.

SKIN TESTING FOR BPG ALLERGY

Although the assessment of patients for penicillin allergy is largely outside the scope of this advisory, we wish to acknowledge that BPG skin testing, using dilute BPG before injection, has been widely practiced in many parts of the world including African countries, Iran, and Nepal.³⁴ It is possible that the practice stems from the 2001 WHO guidelines on acute rheumatic fever and RHD, which state that: “health workers need to be trained on skin testing before giving BPG injection for secondary prophylaxis.”³⁵ Despite this widespread practice, there is no evidence that skin testing with dilute BPG is useful, and it cannot be recommended.

However, formal skin testing of patients who have a history of hypersensitivity to penicillin or allergy to penicillin has a high negative predictive value for anaphylaxis. Formal testing involves subcutaneous injection of

benzylpenicilloyl polylysine (major determinant) penicillin G diluted with normal saline to 10 000 units/mL (minor determinant), positive and negative controls.³⁶ This test is not expected to be readily available in primary or secondary health care settings in limited-resource countries, and, in these settings, clinical history most commonly identifies those labeled as being allergic to penicillin. However, even when formal skin testing is available, it is not recommended as routine for most patients with RHD who have no history of penicillin sensitivity.

RESEARCH PRIORITIES: PATHOGENESIS, IMPACT, AND PREVENTION OF SEVERE BPG REACTIONS

This advisory has been written based on an identified urgent and potentially modifiable clinical situation, BPG-triggered cardiac deaths, with the hopes of saving lives and bolstering confidence in BPG administration for low-risk patients around the globe. However, there is little contemporary evidence on adverse BPG reactions, anaphylactic or otherwise, in patients with RHD. Although there are many studies that could be done on this topic, the priority is research to understand the extent and nature of the problem, and to identify and implement solutions. Table 3 contains a summary of outstanding issues considered to be of high importance with identified research priorities.

CONCLUSIONS

This expert advisory panel continues to advocate that BPG is the most effective form of secondary prophylaxis and should be prescribed to all low-risk patients with RHD who have no contraindication to penicillin. However, we acknowledge with this advisory that there is now a growing body of evidence that patients with RHD who have severe valvular heart disease with or without reduced ventricular function may be dying from cardiovascular compromise following BPG injections. Given this emerging data and the questionable benefit of secondary prophylaxis in severe RHD, we strongly advise the prescription of oral antibiotic prophylaxis, preferably oral penicillin, for patients with RHD at elevated risk, if readily available. Further, when possible, we recommend vasovagal risk reduction for all patients with RHD receiving BPG, in the hopes of saving more lives and avoiding syncope events that, even if reversible, can have devastating effects on patient and clinician confidence in BPG (Table 4).

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if: (1) the individual receives \geq \$10 000 during any 12-month period, or \geq 5% of the individual's gross income; or (2) the individual owns \geq 5% of the voting stock or share of the entity or owns \geq \$10 000 of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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