Case Study: Treating Hypertension in Patients With Diabetes

Evan M. Benjamin, MD, FACP

Presentation
L.N. is a 49-year-old white woman with a history of type 2 diabetes, obesity, hypertension, and migraine headaches. The patient was diagnosed with type 2 diabetes 9 years ago when she presented with mild polyuria and polydipsia. L.N. is 5’4” and has always been on the large side, with her weight fluctuating between 165 and 185 lb.

Initial treatment for her diabetes consisted of an oral sulfonylurea with the rapid addition of metformin. Her diabetes has been under fair control with a most recent hemoglobin A1c of 7.4%.

Hypertension was diagnosed 5 years ago when blood pressure (BP) measured in the office was noted to be consistently elevated in the range of 160/90 mmHg on three occasions. L.N. was initially treated with lisinopril, starting at 10 mg daily and increasing to 20 mg daily, yet her BP control has fluctuated.

One year ago, microalbuminuria was detected on an annual urine screen, with 1,943 mg/dl of microalbumin identified on a spot urine sample. L.N. comes into the office today for her usual follow-up visit for diabetes. Physical examination reveals an obese woman with a BP of 154/86 mmHg and a pulse of 78 bpm.

Questions
1. What are the effects of controlling BP in people with diabetes?
2. What is the target BP for patients with diabetes and hypertension?
3. Which antihypertensive agents are recommended for patients with diabetes?

Commentary
Diabetes mellitus is a major risk factor for cardiovascular disease (CVD). Approximately two-thirds of people with diabetes die from complications of CVD. Nearly half of middle-aged people with diabetes have evidence of coronary artery disease (CAD), compared with only one-fourth of people without diabetes in similar populations.

Patients with diabetes are prone to a number of cardiovascular risk factors beyond hyperglycemia. These risk factors, including hypertension, dyslipidemia, and a sedentary lifestyle, are particularly prevalent among patients with diabetes. To reduce the mortality and morbidity from CVD among patients with diabetes, aggressive treatment of glycemic control as well as other cardiovascular risk factors must be initiated.

Studies that have compared antihypertensive treatment in patients with diabetes versus placebo have shown reduced cardiovascular events. The United Kingdom Prospective Diabetes Study (UKPDS), which followed patients with diabetes for an average of 8.5 years, found that patients with tight BP control (< 150/< 85 mmHg) versus less tight control (< 180/< 105 mmHg) had lower rates of myocardial infarction (MI), stroke, and peripheral vascular events. In the UKPDS, each 10-mmHg decrease in mean systolic BP was associated with a 12% reduction in risk for any complication related to diabetes, a 15% reduction for death related to diabetes, and an 11% reduction for MI. Another trial followed patients for 2 years and compared calcium-channel blockers and angiotensin-converting enzyme (ACE) inhibitors, with or without hydrochlorothiazide against placebo and found a significant reduction in acute MI, congestive heart failure, and sudden cardiac death in the intervention group compared to placebo.

The Hypertension Optimal Treatment (HOT) trial has shown that patients assigned to lower BP targets have improved outcomes. In the HOT trial, patients who achieved a diastolic BP of < 80 mmHg benefited the most in terms of reduction of cardiovascular events. Other epidemiological studies have shown that BPs > 120/70 mmHg are associated with increased cardiovascular morbidity and mortality in people with diabetes. The American Diabetes Association has recommended a target BP goal of < 130/80 mmHg. Studies have shown that there is no lower threshold value for BP and that the risk of morbidity and mortality will continue to decrease well into the normal range.

Many classes of drugs have been used in numerous trials to treat patients with hypertension. All classes of drugs have been shown to be superior to placebo in terms of reducing morbidity and mortality. Often, numerous agents (three or more) are needed to achieve specific target levels of BP. Use of almost any drug therapy to reduce hypertension in patients with diabetes has been shown to be effective in decreasing cardiovascular risk. Keeping in mind that numerous agents are often required to achieve the target level of BP control, recommending specific agents becomes a not-so-simple task. The literature continues to evolve, and individual patient conditions and preferences also must come into play.
While lowering BP by any means will help to reduce cardiovascular morbidity, there is evidence that may help guide the selection of an antihypertensive regimen. The UKPDS showed no significant differences in outcomes for treatment for hypertension using an ACE inhibitor or a β-blocker. In addition, both ACE inhibitors and angiotensin II receptor blockers (ARBs) have been shown to slow the development and progression of diabetic nephropathy. In the Heart Outcomes Prevention Evaluation (HOPE) trial, ACE inhibitors were found to have a favorable effect in reducing cardiovascular morbidity and mortality, whereas recent trials have shown a renal protective benefit from both ACE inhibitors and ARBs. ACE inhibitors and β-blockers seem to be better than dihydropyridine calcium-channel blockers to reduce MI and heart failure. However, trials using dihydropyridine calcium-channel blockers in combination with ACE inhibitors and β-blockers do not appear to show any increased morbidity or mortality in CVD, as has been implicated in the past for dihydropyridine calcium-channel blockers alone. Recently, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) in high-risk hypertensive patients, including those with diabetes, demonstrated that chlorthalidone, a thiazide-type diuretic, was superior to an ACE inhibitor, lisinopril, in preventing one or more forms of CVD.

L.N. is a typical patient with obesity, diabetes, and hypertension. Her BP control can be improved. To achieve the target BP goal of < 130/80 mmHg, it may be necessary to maximize the dose of the ACE inhibitor and to add a second and perhaps even a third agent.

Diuretics have been shown to have synergistic effects with ACE inhibitors, and one could be added. Because L.N. has migraine headaches as well as diabetic nephropathy, it may be necessary to individualize her treatment. Adding a β-blocker to the ACE inhibitor will certainly help lower her BP and is associated with good evidence to reduce cardiovascular morbidity. The β-blocker may also help to reduce the burden caused by her migraine headaches. Because of the presence of microalbuminuria, the combination of ARBs and ACE inhibitors could also be considered to help reduce BP as well as retard the progression of diabetic nephropathy. Overall, more aggressive treatment to control L.N.’s hypertension will be necessary. Information obtained from recent trials and emerging new pharmacological agents now make it easier to achieve BP control targets.

**Clinical Pearls**

- Hypertension is a risk factor for cardiovascular complications of diabetes.
- Clinical trials demonstrate that drug therapy versus placebo will reduce cardiovascular events when treating patients with hypertension and diabetes.
- A target BP goal of < 130/80 mmHg is recommended.
- Pharmacological therapy needs to be individualized to fit patients’ needs.
- ACE inhibitors, ARBs, diuretics, and β-blockers have all been documented to be effective pharmacological treatment.
- Combinations of drugs are often necessary to achieve target levels of BP control.
- ACE inhibitors and ARBs are agents best suited to retard progression of nephropathy.

**SUGGESTED READINGS**

ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel-blocker vs. diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. *JAMA* 288:2981–2997, 2002


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Case Study: Atropine Ophthalmic Administration
Unmasking Undiagnosed Diabetic Gastroparesis

Roger Kenneth Eagan, MD, and Pninit Varol, MD

Presentation
R.R. is a 62-year-old white man with glaucoma and long-standing type 2 diabetes complicated by peripheral neuropathy and retinopathy. He presented to the emergency room with persistent nausea and vomiting. The patient was admitted with presumed symptomatic glaucoma. Three months earlier, he had undergone pars plana vitrectomy surgery for a vitreal hemorrhage secondary to a diabetic tractional retinal detachment. The patient had developed subsequent neovascular glaucoma and had been instructed to use his ophthalmic medications to control symptoms.

Several weeks before his emergency room visit, he began to experience left eye pain. The patient was seen by his ophthalmologist, who diagnosed increasing intraocular pressure (IOP). The ophthalmologist intensified his regimen and encouraged the patient to carefully follow the provided regimen. Soon after, R.R. began to suffer from progressive nausea and vomiting.

At the time of presentation, the patient had been unable to keep solids or liquids down for several days. He was admitted and treated with intravenous fluids and promethazine, then discharged after 24 hours with arrangements for surgery the following week. The following day, he returned with ongoing intractable nausea and vomiting with opthalmalgia. He underwent a successful shunt placement to relieve his IOP, which relieved his ophthalmalgia. However, he continued to have severe nausea and vomiting. The ophthalmology service requested a medicine consult for further evaluation of the nausea and vomiting.

The internal medicine consultant found R.R. to be in significant distress with intractable vomiting. His vital signs showed a temperature of 98.6°F, heart rate 88 bpm, respiratory rate 14, and blood pressure of 189/82 mmHg. Per ophthalmology, the eye appeared well with ongoing normal IOP. Heart and lungs were unremarkable. His abdominal exam was unremarkable. Neurological exam demonstrated decreased sensation in the feet in a stocking pattern with no other appreciable defects. A work-up for common causes of intractable nausea and vomiting using laboratory and radiological evaluation was unremarkable.

The diagnosis of gastroparesis was entertained. His atropine ophthalmic solution was discontinued. The patient’s symptoms improved such that he was again able to take food by mouth. Ophthalmology, however, felt that for the long-term benefit of his eyes, it was imperative that the patient be restarted on the atropine ophthalmic solution. Following reinstitution of the ophthalmic atropine, his nausea and vomiting returned.

A gastric emptying study using Tc-99m sulfur colloid was obtained. It showed gastric emptying delay of 43.9% (normal range 8–28%). To optimize symptom management and maintain the necessary ophthalmic regimen, metoclopramide and erythromycin were begun with good symptomatic relief.

Epilogue. Upon further questioning, R.R. and his wife reported a gradual decrease in his meal sizes and increase in meal frequency over the past year. He most likely had been self-managing his progressive diabetic gastroparesis. With the addition of the anticholinergic medication, his underlying diabetic gastroparesis became clinically apparent, leading to his admission and subsequent work-up and diagnosis.

R.R. was eventually taken off the atropine ophthalmic drops, but continued to have mild symptoms of diabetic gastroparesis. Therefore, he was continued on metoclopramide with success.

Questions
1. Can atropine ophthalmic solutions be absorbed in clinically significant amounts?
2. Is systemic absorption of other ophthalmic drugs known to be clinically significant?
3. What is a reasonable approach to use with patients on ophthalmic agents?

Commentary
Patients with diabetes are known to develop autonomic regulatory problems. Because of this, they can be especially susceptible to medications that have effects on the autonomic nervous system. Oral preparations of β-blockers and tricyclic antidepressants have been well described. However, we rarely think of ophthalmic agents in this light. It would make intuitive sense that if systemic absorption of ophthalmic agents can attain sufficient serological levels, there would be an expected clinical effect.1,2 From our review of the basic science literature, we have determined that the atropine ophthalmic solutions are readily absorbed from the nasal and gastric mucosa.3,4 One study that measured biologically active atropine
(1-hyoscyamine) in sera following ocular and intravenous administration noted surprisingly similar concentrations.3

We performed a Medline literature search and found only a few references to the clinical systemic effects that can ensue from the ophthalmic use of atropine.4 We were unable to find any cases of diabetic gastroparesis unmasked by atropine ophthalmic solutions. We also contacted the pharmaceutical makers of the atropine preparation and were informed that no similar event had been reported. It is our assertion that given the above bioavailability information, undiagnosed clinical side effects are more prevalent than the literature reflects.

One of the challenges of primary care physicians is to monitor patients’ medication lists. With our sub-specialist colleagues adding medications appropriate to the conditions they are managing, sometimes side effects and interactions will occur. The ophthalmic drops sometimes are overlooked in this process. There can be significant systemic absorption of these ophthalmic drops. The effects of β-blocker ophthalmic solutions on the cardiovascular and respiratory systems have been widely discussed. However, all of the following ophthalmic agents have consistent data showing systemic effects: prostaglandin analogs, adrenergic agonists, carbonic anhydrase inhibitors, and cholinergic agonists.6

The following is our approach to patients on these ophthalmic medications.

• To minimize the systemic absorption of all ophthalmic agents, patients should be directed to strictly instill the prescribed dosage only.
• They should be further instructed to compress the lacrimal sac for 2–3 minutes after installation of the eye drops.
• Patients and clinicians need to be aware of the possible systemic side effects and be diligent in monitoring for them. It is therefore recommended that, at the follow-up visits, a brief, focused history and physical exam should be performed targeted towards these side effects.
• If side effects are noted, patient education should be reviewed.
• If clinically significant symptoms remain, a dialogue among primary care physician, sub-specialist, and patient should be undertaken weighing the risk and benefits of ongoing administration.

Clinical Pearls

• All medications with autonomic modulating properties should be given with caution to patients with diabetes.
• All ophthalmic agents should be monitored for symptoms of systemic absorption.
• Proper patient education can help minimize the amount of ophthalmic drug absorbed systemically.

REFERENCES


Roger Kenneth Eagan, MD, was a chief resident in internal medicine at Indiana University in Indianapolis at the time this article was written. Pninit Varol, MD, is an internal medicine and pediatric primary care physician for Health Net, Inc., in Indianapolis, Ind.
Case Study: Potential Pitfalls of Using Hemoglobin A1c as the Sole Measure of Glycemic Control
Huy A. Tran, FACE, FRACP, FRCPA; Diego Silva, MD; and Nikolai Petrovsky, FRACP, PhD

Presentation

Case 1
A 55-year-old man of Southeast Asian descent presented with abnormal renal function for investigation. He had a 6-month history of gradual but progressive lethargy, tiredness, and poor concentration. There was no history of inherited or acquired kidney disease, and he had been fit and healthy before recent onset of symptoms. He had a strong family history of type 2 diabetes with an affected father, aunt, and brother. He was a nonsmoker and consumed ~ 0.35 oz of alcohol daily.

Clinically, he appeared well, with a blood pressure of 160/105 mmHg and regular pulse of 88 bpm. His weight was 222 lb (110 kg) and height 5’8” (1.72 m) (BMI ~37 kg/m2). Fundoscopy showed evidence of early nonproliferative retinal disease with macula sparing. His general examination was otherwise normal, with no evidence of nephromegaly, renal bruit, or microvascular disease.

Urinalysis revealed the presence of proteinuria, confirmed to be 1.8 g/day with no hematuria. He had a blood urea nitrogen (BUN) level of 99.7 mg/dl and creatinine of 6.1 mg/dl with sodium of 136 mmol/l and potassium of 5.4 mmol/l. His fasting glucose level was 122.5 mg/dl.

A follow-up oral glucose tolerance test (OGTT) confirmed the presence of impaired fasting glycemia and impaired glucose tolerance, with a fasting glucose level of 117.1 mg/dl (6.5 mmol/l) and a 2-hour post-OGTT glucose level of 160.4 mg/dl (8.9 mmol/l). His hemoglobin A1c (A1C) levels (performed by high-performance liquid chromatography) were 4.5 and 4.2% on two separate occasions with abnormal chromatograms (Figure 1). Follow-up electrophoresis revealed the presence of hemoglobin E. Further investigation of his renal abnormality, including biopsy, confirmed the presence of diabetic nephropathy, with no other causes for chronic renal failure being apparent. On follow-up, his diabetes control was excellent with dietary and lifestyle management.

Case 2
A 60-year-old woman with long-standing obesity and hypertension presented concerned about the possibility of type 2 diabetes given her strong family history of the disease. Clinical examination was otherwise normal, with no evidence of nephromegaly, renal bruit, or microvascular disease.

A review of her hemoglobin chromatogram (Figure 2) showed an abnormal E pattern hemoglobinopathy interfering with the analysis of A1C value.

Figure 1. E pattern hemoglobinopathy interfering with the analysis of A1C value.
mal peak interfering with the isolation of the glycated hemoglobin. This was confirmed with the repeat measurement. Her hemoglobin electrophoresis study showed an abnormal hemoglobin component. This was further confirmed to be hemoglobin British Columbia.

Questions
1. What is A1C, and how relevant is it to the control of diabetes?
2. What are the potential confounders of A1C use in the assessment of patients with diabetes?
3. What are the available alternatives to A1C as markers of glycemic control?
4. Are A1C values diagnostic of diabetes?

Commentary
A1C is the nonenzymatic glycated product of the hemoglobin beta-chain at the valine terminal residue. The number 1c following HbA represents the order in which this hemoglobin is detected on chromatography. Hence, other hemoglobin peaks are referred to as HbA1a1, HbA1a2, HbA1b, and so forth.

The A1C constitutes about 60–80% of total glycated hemoglobin. It is normally present, albeit at low levels, in circulating red cells because of the glycosylation reaction between hemoglobin and circulating glucose. In the presence of excess plasma glucose, the hemoglobin beta-chain becomes increasingly glycosylated, making the A1C a useful index of glycemic control. The importance of A1C as an index of diabetes control was reinforced by the Diabetes Control and Complications Trial (DCCT). This study demonstrated a direct correlation between glycemic control as indicated by A1C and the likelihood of developing long-term diabetes-related complications.

Because A1C is based on hemoglobin, both qualitative and quantitative variations in hemoglobin can affect the A1C value. These factors need to be considered when interpreting A1C results and serve to limit the use of A1C as a diagnostic test for diabetes.

Clinicians should also appreciate the differences in assay methods for A1C, which have relevance to the possibility of interference. In the case of reduced total hemoglobin or increased turnover of red blood cells (RBCs), the level of A1C will be reduced even in the presence of high ambient plasma glucose, thereby falsely lowering the A1C and limiting its usefulness as a measure of glycemia. In situations where the A1C is low, contrary to high day-to-day glucose levels, attention should be paid to the hemoglobin concentration, the blood smear, and possibly hemolytic parameters to rule out the presence of anemia or hemolysis.

The other pathophysiological process that can affect the A1C value is the structure of hemoglobin itself. Qualitatively, any disorder that affects hemoglobin production, particularly the beta-chain, will affect the A1C results. In the case of patients with beta-thalassemia, the absence of beta-hemoglobin chains for glycosylation invalidates the use of A1C. In other hemoglobinopathies, there is often the combination of abnormal hemoglobin plus associated excessive intramedullary hemolysis. These, in turn, will lead to a falsely low A1C.

Case 1 illustrates this well. The abnormality in hemoglobin E is a point substitution of glutamine for lysine at position 26 on the beta-chain (B26 glu → lys). Patients with this kind of hemoglobinopathy are likely to form glycated hemoglobin E1c instead of A1C, leading to a low A1C level. In Case 2, the abnormality in the hemoglobin British Columbia was found to be at codon number 101 [Glu (GAG) → Lys (AAG)] on the beta-chain, which interferes with glycosylation and hence falsely lowers the A1C level. Any suspicion of a discordant A1C level should be followed up with a review of the hemoglobin chromatogram for any abnormal peaks and hemoglobin electrophoresis, if indicated.

The immunooassay technique used is another potential interference with the measurement of A1C. This method employs various antibodies to detect the A1C fraction. If the antibodies recognize specifically the N-terminus of the beta-chain, this assay will deliver falsely low results in situations where the number of beta-chains is either abnormal or reduced as demonstrated in our two cases. If not suspected, patients may be thought to have better glycemic control than is actually the case due to falsely low A1C results.
In the presence of renal failure, the clinical utility of A1C is even more questionable. The hemoglobin in renal disease gets carbamylated due to condensation of urea-derived cyanate with the N-terminal amino groups. This can subsequently lead to a high A1C result when detected by common methods such as ion-exchange chromatography. The A1C level in renal failure thus represents a balance between the anemia associated with renal disease and hemoglobin adducts in renal failure. These two factors often balance each other out with the eventual outcome being that the A1C value is unchanged. Therefore, A1C could be employed usefully as a marker for diabetes-related complications in patients with uremia. The combination of anemia and hemoglobinopathy resulted in a falsely low A1C level in Case 1.

Other useful markers for diabetes control include total glycohemoglobin, which does not take into account the hemoglobin beta-chain and other blood-based glycated proteins such as fructoseamine. The latter is also readily available in most laboratories and is reflective of mean glycemia but over a shorter time of 15–30 days compared with 60–120 days of A1C. While useful, these tests have not been as well validated as A1C. Although they have not been proven to reliably predict diabetes complications, extrapolation of the DCCT data would suggest they should also be useful for monitoring diabetes.

The Australian and New Zealand position statement regarding new classification and criteria for diagnosis of diabetes makes no reference to the use of A1C. Although it can be falsely low, there are other conditions that can lead to a falsely elevated A1C, including alcoholism, lead poisoning, opiate addiction, excessive use of salicylate (due to interference), and pregnancy. The increase is often small and is not of clinical relevance, leaving diabetes in the majority of cases as the primary cause of A1C elevation.

**Clinical Pearls**
- A1C is an important marker of glycemic control in patients with diabetes.
- A1C is subjected to interference in the presence of associated comorbidities including hemoglobinopathies, hemolysis, renal failure, and alcoholism.
- Its use in the diagnosis of diabetes is controversial and not recommended.

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Case Study: Skin Infection in a Diabetic Patient Related to Contamination of an Insulin Bottle

Irma Gazeroglu, MD; Michael Borenstein, MD, PhD; and Maria P. Solano, MD

Presentation
D.P. is a 59-year-old white Hispanic woman with a 12-year history of type 2 diabetes treated with a thiazolidinedione and multiple daily injections of insulin. She presented to the outpatient clinic with a 10-week history of painful skin lesions on her abdomen that had been increasing in size. The lesions developed at the site of insulin injections. She was injecting in the abdomen, using a new needle each time. She had received a 14-day course of levofloxacin 7 weeks before the clinic visit and had been instructed to change the insulin bottles and to use her arms for injection. The skin lesions did not seem to improve, but she did not develop new lesions. She denied fever or other constitutional symptoms.

Her medical history was significant for severe asthma requiring chronic oral steroids and hypertension. Her medications included rosiglitazone; irbesartan; prednisone, 20 mg daily; bronchodilators; and glargine and aspart insulins. Her glycemic control was poor, with a hemoglobin A1c result of 13.2%.

On physical examination, she had Cushingoid features and did not appear ill. Her blood pressure was 120/60 mmHg, heart rate 84 bpm, respiratory rate 16 rpm, and temperature 98.4° F. On her abdomen, she had multiple tender, red, indurated, hemorrhagic crusted papules and nodules, 0.5–2 cm in size in the periumbilical region bilaterally (Figure 1). There was no peripheral edema, and there were no lesions elsewhere on her body.

Routine laboratory tests, including leukocyte count with differential, platelets, electrolytes, creatinine, and liver enzymes, were within normal ranges.

A skin biopsy was performed from one of the nodules and was sent for histopathology and culture.

Questions
1. What is the microorganism involved in this patient’s skin infection?
2. How was the insulin bottle contaminated with the etiologic agent?

Commentary
The biopsy demonstrated numerous acid fast bacilli in the inflamed dermis (Figure 2). Unfortunately, due to lab error, a culture was not performed.

In this patient, the insulin bottle was the culprit. After she changed it, she did not develop new lesions. Upon further questioning, she admitted that there was water dripping in the refrigerator where she kept the insulin bottle, as a possible explanation of how the bottle was contaminated with the environmental pathogen.

D.P. was treated with clarithromycin for 3 months with resolution of the lesions and only mild residual hyperpigmentation in the area.

Occasionally, mycobacteria are isolated from nodular skin lesions of immunosuppressed patients. Many cases are linked to injections, and diabetic patients are at especially high risk. The skin infections are usually due to M. abscessus, M. chelonea, M. fortuitum, and M. kansasii.

Nontuberculous mycobacteria grow slowly. Even the rapid growers may take 3–7 days to form visible colonies on media, whereas slow-growing mycobacteria take weeks or do not grow at all. The slow growth complicates antibiotic susceptibility testing. Antibiotics may be degraded during prolonged incubation.

These mycobacteria are notoriously resistant to most antituberculosis drugs. Debridement is best combined with two or three antibiotic drugs. Most commonly used antibiotics are clarithromycin, clofazimine, amikacin, rifabutin, and sulfonamide.

Figure 1. Pink nodules and pink, crusted, scaly papules coalescing into plaques on the right mid-abdomen.

Figure 2. Multiple acid fast bacilli in the dermis (original magnification 100×)
It is important to consider the possibility of mycobacterial infection in cases that do not respond to standard antibiotic therapy. It is essential to perform skin biopsy and cultures to evaluate the lesions in order to guide therapy.

Clinical Pearls
- It is important to keep in mind the rare but potential skin infection with atypical mycobacteria in diabetic patients who do not respond to antibiotic therapy for common skin pathogens.
- When suspected, it is imperative to inform the lab technician to use special media for atypical mycobacterium isolation. Skin biopsy and cultures are essential to guide the therapy.

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