

Pyoderma Gangrenosum: Cracking the Code of This Painful Ulcer

PG can be chronic but can often be controlled with treatment.

BY WINDY COLE, DPM

Goals and Objectives

After completing this CME, the reader should be able to:

- 1) Identify wounds caused by Pyoderma Gangrenosum (PG)
- 2) Understand the underlying pathophysiology causing PG wounds
- 3) Explain the use of diagnostic criteria to make the diagnosis of PG
- 4) Describe the various complications related to PG wounds
- 5) Understand evidencebased therapies available for treating atypical wounds

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Following this article, an answer sheet and full set of instructions are provided (pg. 102).—Editor

Introduction

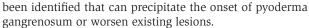
Pyoderma gangrenosum (PG) is a complex and serious condition characterized by the rapid development of painful ulcers on the skin. It falls under the category of autoinflammatory disorders known as neutrophilic dermatoses, which are conditions arising from the dysregulation of the immune system.1 The general incidence of patients diagnosed with PG is 3-10 per million annually. Despite its alarming name, pyoderma gangrenosum is a misnomer; it is important to clarify that it is not caused by an infection, nor does it lead to true gangrene, which involves tissue death due to a lack of blood supply.1

The hallmark of pyoderma gangrenosum is the presence of deep, full-thickness ulcers that have distinctive features (Figure 1). These ulcers often present with undermined borders that are typically blue or purple, making them visually striking and painful.2 The pathogenesis of PG involves a hyperactive immune response to internal antigens, particularly involving neutrophils—an

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essential type of white blood cell responsible for fighting infections.2 This dysfunctional response can lead to excessive inflammation and tissue destruction characteristic of the condition. Research suggests that there is significant involvement of T lymphocytes and a variety of cytokines in the inflammatory process, indicating the condition's complexity.3 Furthermore, genetic predisposition may play a significant role in an individual's susceptibility to developing pyoderma gangrenosum, with certain underlying genetic factors contributing to immune dysregulation.4 Various triggers have



Notably, certain medications have been implicated

Pyoderma gangrenosum is a chronic inflammatory skin condition.

in triggering PG. These include cocaine—a powerful stimulant known to influence vascular responses—and isotretinoin, a medication used primarily for severe acne.5 Other drugs such as propylthiouracil, which is used in the treatment of hyperthyroidism, and sunitinib, a targeted cancer therapy that inhibits protein kinases, have also been recognized as potential triggers.5

Moreover, skin injuries are a significant trigger for the disease; this phenomenon, known as "pathergy," refers to the development of lesions at the site of trauma, even if minimal.⁶ Surgical procedures are particularly relevant in this context, as resultant PG wounds can often be misconstrued as simple post-op wound infections. Such misunderstandings can lead to delays in appropriate treatment, exacerbating the patient's condition and causing further complications.

Understanding these multifaceted triggers, along with the underlying immune mechanisms, is crucial for healthcare professionals in diagnosing pyoderma gangrenosum accurately and devising effective management strategies to mitigate the impact of this challenging condition on patients' quality of life.

Pyoderma gangrenosum is a rare but serious disease that can affect both men and women at any age, though it is seen more frequently in those over 50.7 What makes this condition particularly concerning is its strong association with various internal diseases and medical conditions.7 Recognizing these links is crucial for timely diagnosis and treatment.

Some of the primary associations⁷ include:

• Inflammatory bowel diseases like ulcerative colitis and Crohn's disease



Figure 1: The hallmark of pyoderma gangrenosum is a full-thickness ulcer having distinctive features such as a violaceous border.

- Rheumatoid arthritis
- Myeloid blood disorders, including leukemia
- Monoclonal gammopathy, especially IgA
 - Chronic active hepatitis
 - Granulomatosis with polyangiitis
 - PAPA syndrome
 - Adulterated cocaine

Remarkably, around half of those affected by pyoderma gangrenosum do not exhibit any of these known risk factors.7 This highlights the unpredictability of the disease and reinforces the importance of awareness and early intervention.

Clinical Manifestations

Pyoderma gangrenosum is a severe and often distressing skin condition that typically manifests quite abruptly, frequently occurring at the site of a minor injury, such as a cut or scrape. It may initially be present as a small pustule, a raised red bump, or even a blood blister.8 As the condition progresses, the skin in the affected area begins to deteriorate, resulting in a painful ulcer that can rapidly deepen and widen. The characteristics of the ulcer are particularly telling: the edges are not only purple but also exhibit an undermined quality, indicating that the tissue beneath the surface is losing its integrity. This advanced breakdown of skin can be intensely painful, significantly affecting the quality of life for those impacted.9 Additionally, it's crucial to recognize that multiple ulcers can form

Ulcerative colitis is a common underlying condition associated with pyoderma gangrenosum.

simultaneously or develop sequentially over a span of months to years, often requiring careful medical evaluation and management to prevent further complications.8

The evolution of pyoderma gangrenosum (PG) lesions is a crucial aspect of understanding this condition (Figure 2). Initially, PG often begins as a small, painful bump or pustule that can easily be mistaken for an insect bite or a minor skin infection. As the lesions progress, they typically undergo significant changes. Within a few days to weeks, these bumps can rapidly enlarge and develop into deep, ulcerative wounds with a characteristic necrotic base.8 The borders of the lesions are often raised, and they may be surrounded by an area of erythema, appearing inflamed and warm. In some cases, multiple lesions can develop simultaneously or following trauma to the skin, a phenomenon known as the "pathergy" response, where minor injuries provoke the formation of new lesions.8 As PG continues to evolve, the ulcers may

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exude a purulent discharge and can become increasingly painful, complicating daily activities for those affected.

Forms of Pyoderma Gangrenosum

There are three distinct forms of PG-bullous, pustular and granulomatous. Bullous pyoderma gangrenosum (PG) represents a distinctive superficial variant of pyoderma gangrenosum that typically manifests with the development of inflammatory bullae and superficial ulcers. This presentation is not only painful but may also

Pyoderma gangrenosum lesions are painful and necrotic.

indicate an underlying issue, as it is frequently associated with hematological malignancies such as leukemia or lymphoma. The recognition of this link is essential for timely diagnosis and treatment of potential underlying conditions.

The pustular variant of PG is primarily observed in individuals suffering from inflammatory bowel diseases, including Crohn's disease and ulcerative colitis. ¹⁰ It is characterized by the presence of numerous pustules that arise on an erythematous base, often causing discom-

fort and necessitating a comprehensive treatment approach to manage both the skin symptoms and the underlying inflammatory condition.¹⁰

Granulomatous PG, another variation, is typically recognized for its vegetative appearance and affects the skin with verrucous lesions and superficial ulcerations.11 These lesions are generally found on the face and neck, which can have significant psychosocial implications for affected individuals.11 Although systemic diseases linked to this variant are rare, awareness and thorough clinical evaluation are imperative for correct diagnosis, ensuring that patients receive appropriate care and do not suffer from unnecessary complications.11 Proper management of these variants is crucial for improving patient quality of life and minimizing the impact of these challenging dermatological conditions.

Making the Diagnosis

Pyoderma gangrenosum often presents as a diagnostic challenge owing to the lack of validated laboratory tests or histological markers. Thus, the condition is primarily diagnosed based on its unique clinical presentation and the severe pain it inflicts on patients.

The hallmark of this diagnosis often includes a positive pathergy test, which involves a controlled skin prick that can result in the development of a papule, pustule, or ulcerative lesion. This phenomenon underscores the heightened sensitivity of the skin in individuals with the condition.¹² While it's critical to perform wound swabs and microbial cultures to rule out potential infections, it's important to emphasize that these microorganisms are not the root cause of pyoderma gangrenosum.¹²

The underlying pathology is largely driven by immune-mediated processes. To ensure accurate diagnosis, a skin biopsy may be necessary to exclude other conditions that might present similarly, such as infectious ulcers or vascular issues. In typical presentations, pyoderma gangrenosum features a prominent neutrophilic inflammatory infiltrate.13 However, this characteristic may become less pronounced or even absent in patients undergoing treatment, highlighting the complexities involved in management. Although routine blood tests are often of limited value in providing specific insights, some patients may test positive for ANCA (antineutrophil cytoplasmic antibody), which can indicate a broader systemic involvement and help guide further investigation.13 Understanding these details is crucial for effective diagnosis and tailored treatment strategies for those affected by the disease.

Three frameworks do exist as helpful tools to aid in PG diagnosis. Each framework employs unique diagnos-

tic criteria: Su, PARACELSUS and Delphi. 14-16 A comparison of these criteria is presented in Table 1 on the next page.

Additionally, pyoderma gangrenosum exhibits a unique predilection for certain areas of the body while typically sparing others. The most common sites of involvement are the lower extremities, particularly the legs, where it can lead to painful ulcers that may expand rapidly, limiting patient ambulation or ability to perform activities of daily living.12 In addition to the legs, lesions can also manifest on the trunk and arms, presenting significant challenges in both diagnosis and treatment.12 Notably, this condition largely avoids regions of the head and neck, which is an important consideration for healthcare professionals dealing with suspected cases.12 Understanding these specific patterns of manifestation is essential for effective management and intervention strategies.

When evaluating a suspected case of pyoderma gangrenosum, it is crucial to consider several other ulcerating conditions that can closely resemble it. Differential diagnoses^{12,17} with condition

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Figure 2: The evolution or PG lesions (A) Acute PG lesions with violaceous border (B) Deep ulcerative wounds with surrounding erythema (C) Spreading wounds with a necrotic base (D) Cribriform scarring of resolved wounds

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types and descriptions are included in Table 2 on the next page.

By considering these potential diagnoses, healthcare providers can ensure a more accurate and effective treatment plan for patients.

Complications

Pyoderma gangrenosum can lead to several significant complications that warrant attention. One of the primary concerns is the risk of infection, as open wounds associated with this condition may become susceptible to bacterial invasion, complicating the healing process.¹⁸ Patients may also experience uncontrolled pain, which can severely impact their quality of life and necessitate ongoing pain management strategies.¹⁸

Moreover, after the affected skin has healed, individuals often face changes in skin pigmentation. These chromatic alterations can manifest in two forms: post inflammatory hyperpigmentation, where the skin becomes darker due to an overproduction of melanin, and post inflammatory hypopigmentation, where the skin loses color and can appear lighter than the surrounding tissue. ¹⁸ This is especially relevant for individuals with darker skin *Continued on page 99*

Su 2004 ¹⁴	PARACELSUS 2018 ¹⁵	DELPHI 2018 ¹⁶		
Major Criteria Rapid progression of a painful, necrolytic cutaneous ulcer with an irregular, violaceous and undermining border Other causes of cutaneous ulcer have been excluded	 Major Criteria (3 pts each) Progressive disease Assessment of differential diagnoses Reddish-violaceous wound borders 	Major Criterion • Biopsy with neutrophilic infiltrate		
Minor Criteria (≥2) • History of pathergy or cribriform scarring • Systemic disease(s) associated with PG • Histopathologic findings to include sterile neutrophilia ±mixed inflammation ±lymphocytic vasculitis • Rapid response to systemic steroid treatment	Minor Criteria (2 pts each) • Amelioration by immunosuppressant drugs • Characteristically irregular ulcer shape • Extreme pain (>4/10 VAS score) • Pathergy	Minor Criteria Histology excludes infection Pathergy History of inflammatory bowl disease or inflammatory arthritis History of papule, pustule, or vesical that rapidly ulcerates Peripheral erythema, undermining and tenderness at site of ulceration Multiple ulcers with at least 1 located on the lower leg Cribriform scars at healed ulcer sites Decrease in wound size after 1 month of immunosuppressi treatment		
	 Additional Criteria (1 pt each) Suppurative inflammation in histopathology Associated systemic disease ≥10 pts PG is highly likely, 			

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tones, as they are at a higher risk of experiencing these long-term changes in skin color, which can lead to additional psychosocial challenges. Therefore, it is crucial for patients to be informed about these potential outcomes and to seek appropriate follow-up care to manage both the physical and emotional impacts of the condition.

Treatment

Early intervention is vital to alleviate pain and promote healing, making awareness of this condition essential. If left untreated, ulcers can not only enlarge but may also persist or heal very slowly. It's vital to recognize that effective treatment can successfully halt this progression, though complete healing may require months, especially in cases involving underlying venous disease, which is another common cause of leg ulcers. Deep ulcers often heal with scarring, with some developing a distinctive cribriform pattern or an atrophic appearance. It's important to be aware of the various rarer subtypes of pyoderma gangrenosum that may also arise in these situations. The healing process can be prolonged and often leaves significant scarring. Proper management is critical, as early intervention can help mitigate the severity of the lesions and improve patient outcomes.

The management of pyoderma gangrenosum is predominantly non-surgical, emphasizing gentle care in treatment.¹⁹ Treatment may involve a combination of corticosteroids, immunosuppressive agents, and wound care strategies, tailored to the individual's needs and the severity of their condition.²⁰ Understanding and documenting the evolution of PG lesions is essential for clinicians to provide accurate diagnoses and develop effective treatment plans.

It's imperative to remove necrotic tissue carefully, while avoiding wide surgical debridement during the active phase, as this can lead to ulcer expansion. Conventional antibiotics are often administered initially, even before a clear diagnosis is established. These may be effective if bacteria are identified in the wound or if there's accompanying cellulitis—characterized by inflamed, painful skin.²¹ Antibiotics such as doxycycline or minocycline are particularly useful when there is a concern for secondary bacterial infections, as they provide broad-spectrum coverage and promote healing.²² However, it's essential to note that these antibiotics do not effectively treat uncomplicated pyoderma gangrenosum and should be used judiciously.

Comprehensive wound care and effective pain management are vital components of a successful healing process. Once the disease has reached a stage of stability and is no longer active, various surgical interventions can be considered. These may include advanced techniques such as skin flaps, which involve repositioning healthy skin to cover the wound; skin grafts, where a piece of skin is taken from another area of the body to promote healing; negative pressure wound therapy, which uses a vacuum dressing to draw out fluid and promote new tissue growth; and cellular, acellular and matrix-like products (CAMPs) to aid in tissue regeneration.²¹

Effective management of small ulcers is crucial for promoting healing and minimizing discomfort. A comprehensive treatment plan may include several specialized

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TABLE 2

Other Ulcerating Conditions That Can Closely Resemble Pyoderma Gangrenosum: Differential Diagnoses^{12,17}

CONDITION TYPE	DESCRIPTION
Venous or Arterial Ulcers	Can cause significant discomfort
Medium and Large Vessel Vasculitis	Potentially indicates underlying systemic issues
Occlusive Vasculopathy	Leads to compromised blood flow and tissue damage
Ecthyma and Ecthyma Gangrenosum	Known for their severe ulcerative nature
Ulcerating Infections	Requires urgent attention
Tuberculosis	Can lead to ulcerative lesions, necessitating immediate treatment
Sporotrichosis	Fungal infection that can lead to complicated skin lesions
Cutaneous Amoebiasis	Presents unique diagnostic challenges and results in ulceration
Ulcerating Skin Tumors and Lymphomas	Must not be overlooked; require prompt evaluation
Drug-Induced Ulcers	Includes: Iododerma, Bromoderma, Hydroxycarbamide and Nicorandil

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approaches that include use of potent topical or oral steroids.^{20,22} This medication serves as a cornerstone in ulcer treatment due to its strong anti-inflammatory properties, which help reduce irritation and swelling in the affected area, facilitating faster recovery. Moreover, when it comes to systemic immunosuppressive therapy, it is imperative to implement a careful and gradual tapering process over several months.^{20,22} This approach allows the body to adjust smoothly while minimizing potential side effects and the risk of returning to an active disease state.

Alternatively, Tacrolimus ointment, an immunomodulator, this ointment works by inhibiting the activation of T-cells, thereby decreasing inflammation.^{20,22} It's particularly useful for patients who may not tolerate traditional steroids. More invasive therapy consisting of intralesional steroid injections into the ulcer edge targets delivery allowing for high concentrations of steroids to act directly at the site of inflammation, leading to quicker resolution of the ulcer.^{20,22} Utilizing advanced wound care dressings can cre-

Pyoderma gangrenosum can develop quickly and expand rapidly.

ate an optimal healing environment by maintaining moisture, protecting the ulcer from infections, and allowing for gas exchange.²¹ Oral anti-inflammatory medications can be crucial in managing pain and systemic inflammation, thus improving the patient's quality of life as they heal.^{20,22}

Alternatively, for larger and severe ulcers, intermittent intravenous methylprednisolone may be used for a more aggressive 3-5-day therapy in acute situations. ^{20,22} Ciclosporin can serve as an effective alternative to prednisone, offering a different safety profile and potentially fewer long-term side effects. ^{20,22} There is a growing body of evidence supporting the use of anti-TNF agents such as infliximab, adalimumab, and etanercept illustrating successful outcomes in managing pyoderma gangrenosum. ^{20,22} By understanding and utilizing these diverse treatment strategies, healthcare providers can effectively tailor management plans to meet the specific needs of patients suffering from small ulcers and pyoderma gangrenosum, ensuring optimal care and outcomes.

Conclusions

While the initial occurrence of pyoderma gangrenosum may be preventable, individuals diagnosed with this condition can take significant measures to prevent the development of new sores. A crucial aspect of management is protecting your skin from injury and trauma, which can trigger the formation of new ulcers.²³ This includes being vigilant about everyday activities that could lead to scratches or cuts, along with exercising caution during any medical procedures or surgeries that may pose a risk. Moreover, addressing and effectively managing any underlying medical conditions that are known to be associated with pyoderma gangrenosum, such as inflammatory bowel disease or rheumatoid arthritis, can play an important role in controlling flare-ups.²³ Regular consultations with healthcare professionals, optimal wound care, and a tailored treatment plan can enhance your skin's resilience and overall health. Being proactive and informing the patient about this condition is essential for reducing the likelihood of new ulcers and improving the patient's quality of life.

The prognosis for individuals diagnosed with pyoderma gangrenosum can be quite variable, indicating that the course of the disease can differ significantly from one patient to another. Research indicates that approximately 50% of patients who are treated with systemic medications, particularly prednisone or ciclosporin, will experience considerable wound healing within a one-year timeframe.²² To optimize the chances of recovery and minimize the risk of complications, it is essential for patients to practice heightened caution to avoid any form of trauma to the skin. This is particularly important because even minor injuries, such as a small cut or a scrape, have the potential to trigger the onset of new ulcers, exacerbating the condition. Patients should be aware of their activities and surroundings, employ protective measures such as wearing appropriate clothing, and maintain a vigilant approach toward any situations that could lead to skin injuries. By doing so, they can significantly reduce the likelihood of flare-ups and support their overall healing process. PM

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Dr. Cole is a wound specialist, researcher, principal investigator, medical monitor, medical legal expert, professor, speaker, medical writer, consultant, medical affairs editor, and content creator. She is Director of Global Medical Affairs for Natrox* Wound Care.

CME EXAMINATION

SEE ANSWER SHEET ON PAGE 103.

- 1) What is pyoderma gangrenosum?
 - A) A bacterial infection
 - B) A chronic inflammatory skin condition
 - C) A viral skin disease
 - D) An allergic reaction
- 2) Which of the following is a common underlying condition associated with pyoderma gangrenosum?
 - A) Asthma
 - B) Ulcerative colitis
 - C) Diabetes mellitus
 - D) Eczema
- 3) What is a typical characteristic of pyoderma gangrenosum lesions?
 - A) They are pruritic (itchy).
 - B) They usually occur on the scalp
 - C) They are painful and necrotic.
 - D) They are often filled with pus.

4) Where on the body do pyoderma gangrenosum lesions most commonly develop?

- A) On the arms
- B) On the face
- C) On the legs
- D) On the back
- 5) Which class of medications is often used to treat pyoderma gangrenosum?
 - A) Antihistamines
 - B) Corticosteroids
 - C) Antibiotics
 - D) Antivirals
- 6) What is a hallmark of the diagnosis of pyoderma gangrenosum?
 - A) Positive skin cultures
 - B) Response to steroid therapy
 - C) Increased white blood cell count
 - D) Presence of specific antibodies

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CME EXAMINATION

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- 7) In which age group is pyoderma gangrenosum most commonly diagnosed?
 - A) Children under 5
 - **B)** Teenagers
 - C) Adults aged 20-50
 - D) Elderly over 65
- 8) Which of the following can potentially trigger an outbreak of pyoderma gangrenosum?
 - A) Vaccinations
 - B) Surgery or trauma
 - C) Sun exposure
 - D) Changes in diet
- 9) What distinguishes pyoderma gangrenosum from other skin ulcers?
 - A) It often features a purulent discharge.
- B) It has a clear border and is well-defined.
- C) It can develop quickly and expand rapidly.
 - D) It is typically associated with a fever.
- 10) What is the prognosis for patients with pyoderma gangrenosum?
- A) It is usually self-limiting with no treatment.
- B) It can be chronic but can often be controlled with treatment.
- C) It always resolves without any complications.
 - D) It has a high mortality rate.

SEE ANSWER SHEET ON PAGE 103.

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Mail-In Grading

To receive your CME certificate, complete all information and mail with your credit card information to: **Program Management Services**, 12 Bayberry Street, Hopewell Junction, NY 12533. PLEASE DO NOT SEND WITH SIGNATURE REQUIRED, AS THESE WILL NOT BE ACCEPTED BY THE RECEIVER.

There is **no charge** for the mail-in service if you have already enrolled in the annual exam CME program, and we receive this exam during your current enrollment period. If you are not enrolled, please send \$35.00 per exam, or \$299 to cover all 10 exams (thus saving \$51 over the cost of 10 individual exam fees).

Facsimile Grading

To receive your CME certificate, complete all information and fax 24 hours a day to 1631-532-1964. Your test will be dated upon receipt and a PDF of your certificate of completion will be sent to the Email address on file with us. Please allow 5 business days for the return of your certificate. This service is available for \$2.95 per exam if you are currently enrolled in the 10-exam CME program, and can be charged to your Visa, MasterCard, or American Express.

If you are *not* enrolled in the 10-exam CME program, the fee is \$35 per exam.

Phone-In Grading

You may also complete your exam by using the toll-free service. Call 516-521-4474 from 10 a.m. to 5 p.m. EST, Monday through Friday. Your CME certificate will be dated the same day you call and mailed within 48 hours. There is a \$2.95 charge for this service if you are currently enrolled in the 10-exam CME program, and this fee can be charged to your Visa, Mastercard, American Express, or Discover. If you are not currently enrolled, the fee is \$35 per exam. When you call, please have ready:

- 1. Program number (Month and Year)
- 2. The answers to the test
- 3. Credit card information

In the event you require additional CME information, please contact PMS, Inc., at 516-521-4474.

ENROLLMENT FORM & ANSWER SHEET

Please print clearly...Certificate will be issued from information below.

Name				Email Address				
Please Print:	FIRST	MI	LAST					
Address								
City			State	Zip	<u></u>			
Charge to:	Visa/	MasterCardA	merican Express					
Card #			Exp. Date	<u> </u>	for credit card			
Note: Credit card is the only method of payment. Checks are no longer accepted.								
Signature			_ Email Address	Dayti	me Phone			
State License(s)	ls	this a new address? Ye	s No				
Check one: I am currently enrolled. (If faxing or phoning in your answer form please note that \$2.95 will be charged to your credit card.)								
	I am not enrolled. Enclosed is my credit card information. Please charge my credit card \$35.00 for each exam submitted. (plus \$2.95 for each exam if submitting by fax or phone).							
	I am not enrolled and I wish to enroll for 10 courses at \$299.00 (thus saving me \$51 over the cost of 10 individual exam fees). I understand there will be an additional fee of \$2.95 for any exam I wish to submit via fax or phone.							

ENROLLMENT FORM & ANSWER SHEET (continued)

	EXAM #6/25
F	Pyoderma Gangrenosum:
Crackir	ng the Code of This Painful Ulcer
Circle:	(Cole)

1.	A	В	c	D	6.	Α	В	c	D
2.	Α	В	c	D	7.	A	В	C	D
3.	Α	В	c	D	8.	A	В	C	D
4.	Α	В	C	D	9.	A	В	C	D
5.	Α	В	C	D	10.	Α	В	C	D

Medical Education Lesson Evaluation

Strongly agree [5]	Agree [4]	Neutral [3]	Disagree [2]	Strongly disagree [1]					
1) This CME lesson was helpful to my practice									
2) The educat	2) The educational objectives were accomplished								
3) I will apply	3) I will apply the knowledge I learned from this lesson								
4) I will makes changes in my practice behavior based on this lesson									
5) This lesson presented quality information with adequate current references									
6) What overall grade would you assign this lesson? A B C D									
7) This activity		ed and free		cial bias.					
8) What overall grade would you assign to the overall management of this activity? A B C D									
How long did it take you to complete this lesson?									
hourminutes									
What topics would you like to see in future CME lessons? Please list:									