

## **The PCS Evidence-based Clinical Practice Guidelines on the Diagnosis and Treatment of Chronic Lower Extremity Ulcers**

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The management of chronic lower extremity ulcers (CLU) in our country has not been consistent. It has involved various specialists including general surgeons, orthopedic surgeons, vascular surgeons, plastic surgeons, endocrinologists, internists, dermatologists, and vascular medicine specialists. Because of the involvement of several specialists, the approach to the diagnosis and management of patients with CLU has been varied. The current practice is individualized depending on the primary specialist involved in the case. Only a few hospitals, in our country, employ a multidisciplinary team approach in the diagnosis and treatment.

The need to ensure that a complete assessment and adequate treatment for these patients are performed, prompted the Philippine College of Surgeons to formulate these guidelines. These guidelines are based on the most recent available evidence and opinion of local experts in the field. These recommendations are intended to assist general surgeons and practitioners involved in the care of patients with CLU in decision-making.

The guidelines are divided into three main categories: Assessment, Diagnostics and Wound Management.

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### **Executive Summary**

The Technical Working Group was formed last March 2014 and is composed of practitioners who are considered experts in the field.

### **Technical Working Group**

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The guidelines focus on the diagnosis and treatment of CLU that are relevant to general practice. For this reason, it does not present recommendations on when to perform surgical reconstruction. Guide questions were discussed and developed by the TWG members and the PCS Committee on Surgical Research on April 2014 and were approved by the BOR on May 25, 2014.

Full text articles were searched using Pubmed (Medline) of the US National Library of Medicine. The articles retrieved were appraised from which articles were used to answer the research questions.

The initial draft of recommendations was prepared last November 15, 2014. The group applied the latest version of the Levels of Evidence of the Oxford Center for Evidence-based Medicine, (2011).

**Levels of Evidence**

## Oxford Centre for Evidence based Medicine 2011 Levels of Evidence

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or n-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, n-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or n-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non-randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

\* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

The initial draft was presented to a multidisciplinary panel of experts and members of the BOR during the 70th PCS Annual Clinical Convention on December 2, 2014, for revisions and to determine strength of recommendation.

### Categories of Recommendations

- Category A Recommendations that were approved by consensus (at least 75 % of the multi-sectoral expert panel)
- Category B Recommendations that were somewhat controversial and did not meet consensus
- Category C Recommendations that caused real disagreements among members of the panel

### Panel of Experts

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The final draft was presented in a public forum during the 71st Annual Convention in EDSA Shangri-la Plaza.

### Definition of Terms

Wound: A disruption of the normal continuity of the skin.

Chronic Wound: A wound which does not show any sign of healing after three months of appropriate treatment or still not fully healed at 12 months.<sup>1</sup>

Neglected Chronic Wound: A wound without any professionally prescribed treatment.<sup>2,3</sup>

Adjunct Therapy: Modalities used in addition to the primary treatment in order to aid in the effectiveness of the primary treatment.<sup>4</sup>

### References

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3. Australian Wound Management Association, Inc. and New Zealand Wound Care Society. (October 2011). Australian and New Zealand Clinical Practice Guideline for Prevention and Management of Venous Leg Ulcers. Cambridge Publishing.
4. Dorland's Illustrated Medical Dictionary 32ed 2011.

**List of Clinical Questions**

I. Assessment

- 1. What are the components of a complete initial wound assessment?
- 2. What clinical characteristics of a CLU will point to its etiology?

II. Diagnostic

- 3. What diagnostic tests are recommended for the initial assessment of CLU based on etiology?
  - 3.1 What diagnostic tests are recommended for the initial assessment of CLU suspected to be due to venous insufficiency?
  - 3.2 What diagnostic tests are recommended for the initial assessment of CLU suspected to be due to peripheral arterial occlusive disease?
  - 3.3 What diagnostic tests are recommended for the initial assessment of CLU suspected to be due to diabetes mellitus?

III. Wound Management

- 4. What are the factors critical to promote healing of CLU?
- 5. What are the recommended specific management options?
- 6. What is the role of a multidisciplinary team approach in CLU management?
- 7. What additional treatments are necessary based on the etiology of the wound?
  - 7.1 What are the treatment options to address CLU due to venous insufficiency?
  - 7.2 What are the treatment options to address CLU due to peripheral arterial occlusive disease?

7.3 What are the treatment options to address CLU due to diabetes?

8. What is the role of adjunct treatment?

9. When is amputation recommended?

10. What is the recommended monitoring strategy for CLU?

**Recommendations**

- 1. What are the components of a complete initial wound assessment?

A complete initial wound assessment should include a thorough history and complete physical examination of the patient and the local wound problem with particular emphasis on peripheral vascular assessment. Using the mnemonics ASSESSMENTS provides an extensive tool for serial wound evaluation. This will serve as baseline findings for which future comparison after serial assessments will be made.

**Level 5 Category A**

**Summary of Evidence**

Evaluation of patients with chronic wounds of the lower extremity should include identification of the presence of systemic factors like diabetes, nutrition, and medications that may contribute to the wound problem.

Assessment of the local wound problem involves documentation of observations and evaluations. Evaluation of the wound should be done in a systematic manner. The elements of local wound assessment provide a structured way of thoroughly evaluating the wound. This could be performed using the mnemonics ASSESSMENTS developed by Ayello in 1992 and would include the following:<sup>1</sup>

- Anatomic Location of the wound/Age of the wound
- Size of the wound (length x width x depth)/Shape of the wound/Stage or Grade

Sinus tract/tunneling/undermining  
 Exudate (Color, Amount, Consistency)  
 Sepsis  
 Surrounding skin  
 Margins/Maceration  
 Erythema, Epithelialization  
 Necrotic tissue (Eschar)/Nose (Odor)  
 Tissue bed, Tenderness/Pain, Temperature  
 Status

A diagram of the human body with the wound location should be included in the assessment because the location of the wound needs to be indicated precisely using anatomic terms. All wound characteristics such as location, size, depth, exudate, tissue type and periwound condition should be described during serial assessment. These elements are recorded to evaluate changes in the wound, be it progression or deterioration.

Wound measurement techniques can either be a two dimensional (surface area) or three dimensional (wound volume). Wound size can be accurately measured by the linear method using a paper and a ruler (in centimeter or millimeter).<sup>2</sup> There are also a number of technology assisted methods available to measure wound size and progress.

The wound exudate is fluid accumulation containing serum, cellular debris, bacteria and leukocytes. It may be classified in two ways: by type and amount. When classifying by type, the color and consistency should be noted. Wound exudates can be described as serous/clear, sanguineous/bloody or purulent. When classifying by amount, you should take note of how much exudate has seeped through the dressing surface. It can be described as none, small (detectable discharge covering < 33% of the dressing surface), moderate (covering <67%), and large (covering >67% of the dressing surface).<sup>3</sup>

The wound bed tissue is described based on the color, moisture and presence of granulation. A clean and granulating wound will present with a red or pink wound bed; devitalized tissues may present with yellow color slough; necrotic/dessicated tissues or eschar will appear as brown/black tissue.<sup>4</sup>

The skin surrounding the wound provides clues as to the presence of infection or inflammation in the presence

of periwound erythema or warmth; and allergic reaction in the presence of denudation or erosion at the periwound area.<sup>5</sup>

Wound assessments are observations that are an important part of wound management as a whole. The use of proper terminology in describing the standard elements of wound assessment is essential for wound monitoring and for proper communication between members of the multidisciplinary team.

A sample wound assessment form endorsed by the Philippine Wound Care Society is provided at the appendix section (Appendix 1).

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2. What clinical characteristics of a CLU will point to its etiology?

The location of the wound and local wound characteristics are helpful in determining the cause of the wound.

Venous ulcers are usually located in the gaiter's area or above the medial and lateral malleoli. It presents as a discrete ulcer with a fibrinous ulcer bed with hyperpigmentation, induration, fibrosis and edema. Pain is relieved upon elevation of the involved extremity

Arterial ulcers usually occur over toes, heels and bony prominences. The ulcers appear as "punched out" lesions with well demarcated edges, and a pale, non-granulating often necrotic base. The surrounding skin may show dusky erythema, is cool to touch, hairless, thin and brittle. There is also reduced capillary refill time. Pain is relieved by lowering the involved extremity.

Neuropathic ulcers are characterized by sensory loss. They are usually located along pressure points.

**Level 5 Category A**

**Summary of Evidence**

Ulcers secondary to venous insufficiency constitute 70% of leg ulcer presentations, arterial disease, 10% and ulcer of mixed etiology, 15%.<sup>1</sup> The remaining 5% are due to the less common pathologic causes.<sup>2-4</sup>

The etiology of chronic wounds of the lower extremity can be determined by the location of the wound. Wounds secondary to venous insufficiency usually occur above the medial or lateral malleoli while arterial ulcers usually affect the toes, shin or over pressure points. Neuropathic ulcers tend to occur on the sole of the foot over pressure points.<sup>5</sup>

There are also specific clinical features that may point to wound etiology (Table 1). Venous ulcers present as either a discrete or circumferential ulcer in the gaiter's area. The bed is covered with a fibrinous layer mixed with granulation tissue and surrounded by an irregular gently sloping edge.<sup>6</sup> There is usually pitting edema proximal to the ulcer formation. In long standing venous ulcers, the affected area becomes indurated and fibrosed, a condition called lipodermatosclerosis. The area then becomes hard and woody resembling an "inverted champagne bottle". Venous eczema characterized by erythema, scaling, weeping and itching may also develop.

**Table 1.** Features of venous and arterial ulcers (Grey, 2006).

	Venous	Arterial
History	History of varicose veins, deep vein thrombosis, venous insufficiency or venous incompetence	History suggestive of peripheral arterial disease, intermittent claudication. And/or rest pain
Classic site	Over the medial gaiter region of the leg	Usually over the toes, foot and ankle
Edges	Sloping	Punched out
Wound bed	Often covered with slough	Often covered with varying degrees of slough and necrotic tissue
Exudate level	Usually high	Usually low
Pain	Pain not severe unless associated with excessive edema or infection	Pain, even without infection
Edema	Usually associated with limb edema	Edema not common
Associated features	Venous eczema, lipodermatosclerosis, atrophic blanche, hemosiderosis	Trophic changes; gangrene may be present
Treatment	Compression is mainstay	Appropriate surgery for arterial insufficiency; drugs of limited value

## Comments from the Expert Panel

No data is available for those of mixed etiology.

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3. What diagnostic tests are recommended for the initial assessment of CLU based on etiology?

3.1 What diagnostic tests are recommended for the initial assessment of CLU suspected to be due to venous insufficiency?

The recommended screening test for CLU due to venous insufficiency is a venous duplex scan.

## Level 2 Category A

### Summary of Evidence

Venous duplex scan is a non invasive diagnostic modality that uses high frequency sound waves to capture images of the vein. The doppler ultrasound determines the blood flow through the veins. A venous duplex scan is the study of choice for the evaluation of venous insufficiency syndromes. When used to evaluate patterns of venous reflux, it has a sensitivity of 82% and a specificity of 78%.<sup>1</sup> In the diagnosis of deep venous thrombosis (DVT), it is the initial diagnostic imaging modality of choice, because it has been shown to be superior to contrast venography.<sup>2</sup>

It is recommended as the initial diagnostic tests for the following reasons:

1. It is safe, non-invasive, cost effective and reliable.
2. It has a much better accuracy in the assessment of venous insufficiency.
3. The study can establish presence of infrainguinal venous obstruction. It can differentiate between acute venous thrombosis and chronic venous changes.
4. For patients with advanced venous disease, those with healed or active, or those with recurrent varicose veins after previous intervention, perforator incompetence can be evaluated.<sup>3</sup>

## Comments from the Expert Panel

A clear definition of what a venous duplex scan is should be included in the manuscript. It should be differentiated from a DVT scan and a venous insufficiency scan.

Before recommending a duplex scan, do evaluation for any arterial problem by physical examination. There is no evidence showing any advantage with the use of a handheld doppler except if used in the context of performing an ankle-brachial index.

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1. <http://emedicine.medscape.com/article/1085412-overview#a0104>
3. Mills Sr JL, et al. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: Risk stratification based on wound ischemia and foot infection. *J Vasc Surg* 2014; 59(1): 220-34.
- 3.2 What diagnostic tests are recommended for the initial assessment of CLU suspected to be due to peripheral arterial occlusive disease (PAOD)?

There is no single test that can completely evaluate vascular health. The recommended screening

examination to evaluate PAOD is an ankle brachial index.

## Level 2 Category A

### Summary of Evidence

Peripheral arterial occlusive disease (PAOD) is a condition leading to reduced blood flow due to narrowing or luminal stenosis of the artery. Although majority of patients with PAOD are asymptomatic, it may present with intermittent claudication and in severe cases as persistent rest pain or leg wound.

Vascular evaluation is more complicated. ABI is an indicator of atherosclerosis. Compared to MRA and conventional angiography, ABI was comparable with a reasonably high specificity 83-99% and a lower sensitivity of 69-79%.<sup>1-3</sup> ABI is effective as a screening procedure for the diagnosis of lower extremity PAD because it is simple, inexpensive, objective and reliable.<sup>4</sup>

The toe brachial index (TBI) is less susceptible to false readings due to diabetic arterial calcification. Therefore, TBI should always be performed.

Skin perfusion pressure (SPP) measures capillary pressure in the skin and is very sensitive at uncovering vascular disease in diabetics as well as predicting wound healing. Transcutaneous oximetry (TCPO<sub>2</sub>) can validate referral for hyperbaric oxygen. Vascular imaging tests should be performed by an appropriate specialist if there is reasonable suspicion of underlying vascular disease.

### Comments from the Expert Panel

It must be mentioned what machine is to be used in measuring ABI. If it is a handheld doppler, it would be unreliable because it is operator-dependent.

Blood pressure in the ankles should be measured by a linear ultrasound probe capable of color doppler and spectral doppler if available rather than rely on a standard Doppler ultrasonic probe. The exact vessel being investigated can be seen. It would also be good to get the different ABI for the anterior and posterior tibial arteries and not just one of the two. As for the venous assessment, if the waveforms of the lower extremity veins do not show spontaneous phasic flow but there is no evidence

of LE DVT, a color doppler imaging of the pelvis and iliac veins should be automatically done to rule out extrinsic compression of the IVC or iliac veins.

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3.3 What diagnostic tests are recommended for the complete assessment of CLU extremity suspected to be due to diabetes mellitus?

A comprehensive clinical examination and risk assessment is needed. The examination should include assessment of dermatologic changes, musculoskeletal deformities, neurologic assessment, ulcer evaluation and peripheral vascular examination.

## Level 2 Category A

### Summary of Evidence

The evaluation of CLU due to diabetes mellitus involves neurovascular assessment.

## A. Neurological Assessment

The ankle and first metatarsophalangeal joints is assessed for restriction in dorsiflexion when doing the range of motion examination. Deformities associated with Charcot joint disease should be noted on inspection.<sup>1</sup>

Four simple clinical tests, each with evidence from well-conducted prospective clinical cohort studies,<sup>2-6</sup> are considered useful in the diagnosis of loss of protective sensation (LOPS) in the diabetic foot. Any of these four tests could be used by clinicians to identify LOPS. Ideally two of these should be regularly performed during the screening exam: the 10-g monofilament and one other test. One or more abnormal tests would suggest LOPS, while at least two normal tests (and no abnormal test) would rule out LOPS.<sup>1</sup>

The tests recommended are the following:

### 1. 10-g monofilaments.

Monofilaments, also known as Semmes-Weinstein monofilaments, were originally used for the diagnosis of sensory loss in patients with leprosy. Many prospective studies have confirmed that loss of pressure sensation using the 10-g monofilament is highly predictive of subsequent ulceration.<sup>7-9</sup> Screening for sensory loss with the 10-g monofilament is in widespread use across the world, and its efficacy in this regard has been confirmed in a number of trials, including the recent Seattle Diabetic Foot Study.<sup>10</sup>

### 2. 128-Hz tuning forks

The tuning fork provides an easy and inexpensive test of vibratory sensation. Vibratory sensation should be tested over the tips of both great toes. An abnormal response is defined as loss of vibratory sensation by the patient while the examiner still perceives.<sup>1</sup>

### 3. Pinprick sensation.

Similarly, the inability of a patient to perceive pinprick sensation has been associated with an increased risk of

ulceration. This test is performed by applying enough using a disposable pin applied just proximal to the toenail on the dorsal surface of the hallux. The amount of pressure applied is just enough to deform the skin. The inability to perceive pinprick over either hallux would be regarded as an abnormal test result.<sup>1</sup>

### 4. Ankle reflexes.

The patient is positioned either in a kneeling position or resting on a couch/table. The Achilles tendon is stretched until the ankle is in a neutral position before striking it with the tendon hammer. If a response is initially absent, retesting is done after asking the patient to hook fingers together and pull. Total absence of ankle reflex either at rest or upon reinforcement is regarded as an abnormal result.<sup>1</sup>

## B. Assessment of Peripheral Arterial Disease

Diabetic patients with signs or symptoms of vascular disease or absent pulses on screening foot examination should undergo ankle brachial index (ABI) pressure testing and be considered for a possible referral to a vascular specialist. Palpation of pulses alone cannot be relied upon in this population. The absence of pulses is a good indicator of poor flow, but the presence of pulses cannot rule out arterial insufficiency. Blood pressure at the ankle (dorsalis pedis or posterior tibial arteries) is measured using a standard Doppler ultrasonic probe. The ABI is obtained by dividing the ankle systolic pressure by the higher of the two brachial systolic pressures. Normal values for the ABI is 0.99-1.4. An ABI >0.9 is normal, <0.8 is associated with claudication, and <0.4 is commonly associated with ischemic rest pain and tissue necrosis. The ABI may be falsely elevated in the presence of severe calcifications.<sup>11</sup>

The following table presented by Boulton, et al, can be used to perform risk assessment for patients with chronic wounds of the lower extremity due to diabetes mellitus:<sup>1</sup>

Risk category	Definition	Treatment recommendations	Suggested follow-up
0	No LOPS, no PAD, no deformity	Patient education including advice on appropriate footwear.	Annually (by generalist and/or specialist)
1	LOPS ±deformity	Consider prescriptive or accommodative footwear. Consider prophylactic surgery if deformity is not able to be safely accommodated in shoes. Continue patient education.	Every 3-6 months (by generalist or specialist)
2	PAD ±LOPS	Consider prescriptive or accommodative footwear. Consider vascular consultation for combined follow-up.	Every 2-3 months (by specialist)
3	History of ulcer or amputation	Same as category I. Consider vascular consultation for combined follow-up.	Every 1-2 months (by specialist)

**Comments from the Expert Panel**

**TBI is more accurate than ABI.**

The treatment recommendations in the table above mentions that you should consider vascular consultation for those in risk categories 2 and 3. Following discussions between the TWG and expert panel a strong recommendation for consult with a vascular specialist instead of just considering consult should already be performed.

**References**

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#### 4. What are the factors critical to promote healing of CLU?

The factors critical to promote healing of CLU should be assessed and documented. These factors can be classified into intrinsic and extrinsic. Intrinsic factors include the overall health status, age and nutritional status. Extrinsic factors include mechanical stress, debris, temperature, desiccation, infection, chemical stress and medications.

#### Level 5 Category A

#### Summary of Evidence

There are multiple intrinsic and extrinsic factors that are critical in affecting wound healing. Intrinsic factors include age, health and nutritional status of the patient.

Medical conditions reflect the general health status of each patient with CLU. The presence of diabetes may predispose a patient to have poor inflammatory response and a higher rate of infection. In such conditions, controlling the blood sugar levels improves wound healing. Low levels of hemoglobin cause low oxygen delivery which also impairs wound healing. The nutritional status of a patient with CLU, likewise, contributes to the healing of wounds. Adequate caloric intake is required to help the body establish the normal reparative process of healing.

Extrinsic factors include mechanical stress, debris, temperature, desiccation, infection, chemical stressors and drugs.

Unrelieved pressure to any part of the body contribute to tissue destruction. Patients who are bed-ridden due to illness or paralyzed are vulnerable. Debris and necrotic tissues found in wounds should be removed for proper wound healing. Normal body temperature enhances enzymatic and cellular functions that affect the biological processes of healing. Wounds should be kept moist because cells, enzymes and growth factors cannot function in dry environment. Infection promotes accumulation of purulent material, lymphadenopathies and fever. Gram stain, culture & sensitivity tests ensure that the proper antibiotics will be given to control the

infection. Chemical stressors like antiseptics are cytotoxic and damages cellular element and microcirculation in the wound area. Certain medications, like steroids have adverse effects that interfere with wound healing. A review of the patients drug intake history is essential to detect medications that may impair healing.

Ensuring adequate oxygenation and nutrition, treating any infection that is present, removing foreign bodies, providing a moist environment and giving the proper antibiotic regimen ensures proper wound healing.

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6. get references of the review to strengthen evidence (could still be increased to level 3)
5. What are the recommended specific management options?

The options should be based on the TIME concept, the following are the recommended treatment options:

To promote tissue viability, adequate debridement is required.

To control wound infection/inflammation, appropriate antibiotics based on c/s results should be provided to reduce the microbial burden.

To maintain moisture balance, ensure appropriate dressing materials for each type of wound.

The above mentioned tenets, when followed, will promote epithelialization and wound edge advancement.

## Level 2 Category A

### Summary of Evidence

TIME framework includes four main components of wound bed preparation:

- Tissue management
- Infection and inflammation control
- Moisture imbalance
- Epithelial edge of the wound advancement

### Tissue Management

TIME principles of wound bed preparation has been designed to help clinicians make a systematic interpretation of the observable characteristics of a wound for optimizing the management. It is a practical guide for both the assessment/evaluation and management of these chronic wounds.<sup>1-2</sup>

The key management principle and technique in this area is the debridement of all non-viable or foreign material, including the following: host necrotic tissue; adherent dressing material; multiple organism-related biofilm or slough; exudates; and debris. Debridement is the first step towards stimulating healthy tissue to heal. Debridement may be autolytic, mechanical, surgical or chemical. It may be episodic or continuous. Wound base assessment should be performed after debridement. The aim is to provide a viable wound base for granulation tissue to form.

It is common practice for clinicians to cleanse the wound area with normal saline. There is no strong evidence to support the use of any particular solution or technique for cleansing pressure ulcers.<sup>3</sup>

There is some evidence that using tap, boiled or distilled water to clean a wound may reduce the risk of wound infection and that it is likely to be as safe as sterile water or saline. Caution should be exercised in the use of tap water in immunocompromised patients.<sup>4</sup>

Though widely practiced, the use of non-cytotoxic antiseptic irrigants for wound cleansing is backed up

by a weak evidence base, and requires further research.

**INFECTION/INFLAMMATION** (differentiate colonisation from infection: indicating that there is no need for antibiotics)

Excessive or inappropriate inflammation, often because of the presence of infection would significantly impair wound healing in venous ulcers. Other non-infective causes of inflammation (like autoimmune diseases, SLE, etc.) should be investigated.

Wounds that contain bacteria when not controlled will cause increase bacterial burden or occult infection. The two most useful predictors of infection in chronic wounds are: an increase in pain; and an increase in wound size.<sup>5</sup> This will lead to involvement of the superficial wound bed or may involve the deep compartments and the surrounding tissue/wound margins. Treatment of infection should include optimizing host resistance, promoting healthy eating, encouraging smoking cessation and addressing underlying medical conditions such as diabetes. Appropriate use of antibiotics, guided by culture and sensitivity tests, should be carefully considered, and discriminately used to prevent antimicrobial resistance. Generally the use of topical antibiotics is not recommended. On the other hand, topical antiseptic dressings are recommended for the following reasons: 1) prevention of infection in patients who are considered at an increased risk; 2) treatment of localised wound infection; 3) local treatment of wound infection in cases of local spreading or systemic wound infection, in conjunction with systemic antibiotics.<sup>6</sup> The use of antiseptic dressings should be continued for 14 days.<sup>7</sup> Empirical treatment with broad-spectrum antibiotics may be started following clinical diagnosis, but specific antibiotic regimens should be prescribed once the infecting microorganisms and their antibiotic sensitivities have been identified.

### Moisture Balance

It is stated that appropriate wound moisture is required for optimal wound healing to enhance the action of growth factors, cytokines, and cell migration. Exudate

is produced as part of the body's response to tissue damage and the amount of exudate produced is dependent on the pressure gradient within the tissues.<sup>8</sup> Excessive or insufficient exudate production both adversely affect wound healing. The presence of high levels of proteases in the exudates have an adverse effect on wound healing by slowing down or blocking cell proliferation.<sup>1</sup>

Moisture enhances the natural autolytic process and also acts as a transport medium for essential growth factors during epithelialization. If a wound bed becomes too dry, a scab will form which then impedes healing and wound contraction. The underlying collagen matrix and the surrounding tissue at the wound edge become desiccated.<sup>9</sup>

Occlusive dressing products promote a moist environment at the wound interface. Classic dressing would include: gauze; foam; hydrocolloid; and hydrogels. When compared to traditional moist saline gauze, no dressing or device has yet been proven superior.<sup>10-14</sup> Despite the lack of scientific evidence to substantiate the effectiveness of the various dressings, many of these have proven to be of use to the wound care practitioner. The characteristics of an appropriate dressing are the following:

- 1) Dressing care is patient centered and individualized.
- 2) Dressing removal is atraumatic and minimally painful.
- 3) Dressings ensure a moist wound environment while absorbing excess exudates.
- 4) Dressing choice considers costs including individual price of the dressing along with labor costs associated with having a health care professional change the dressing.

### Edge of Wound

When wound bed preparation is satisfactory after addressing the first 3 elements of the TIME concept, i.e. tissue management, infection/inflammation, moisture balance, other treatment modalities are now available to effect wound closure, aside from the use of split thickness skin grafts or biological skin replacements. Among these, studies have supported improved wound closure with negative pressure wound therapy.<sup>15,16</sup>

### Comments from the Expert Panel

If a scab is present, the arterial supply should be examined to determine what is going on underneath.

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6. What is the role of a multidisciplinary team (MDT) approach in CLU management?

The MDT approach plays a major role by providing a cost-effective method of treating CLU. The approach can decrease the incidence of major limb amputations and provide better quality of life for the patients.

**Level 3 Category A**

**Summary of Evidence**

The MDT approach can provide appropriate wound-related education that lead to improvement in the continuity of care which would eventually lead to a shortened hospital stay and a decrease in the overall cost of treatment.<sup>1</sup>

This approach leads to shorter healing time and reduced overall health care costs for the patients.<sup>2</sup> Two cohort studies reported a decrease in both the number of home visits to patients and types of products used.<sup>3,4</sup>

Several authors reported a significant reduction in the rate of major limb amputations in patients with active disease. Jeffcoate (2012) reported a 70-80% reduction in the incidence of amputations which was collaborated by Gottrup (2003, 2004), reporting a decrease in the incidence by 84%.<sup>3-5</sup>

Gottrup (2001, 2004) also reported an increase in patient satisfaction with this approach. He collected unpublished studies showing an 85%-93% satisfaction with regards to wound treatment and quality of care.<sup>4,6</sup>

Other advantages of using an MDT approach include better communication among members, development of a standardized treatment plan, improved training and access to relevant data leading to improvement in research opportunities.<sup>1,3,7</sup>

It is recognized that no single health care provider is adequately equipped to handle chronic wounds by himself.<sup>8</sup> This belief further reinforces the need to establish a multidisciplinary team for the care of chronic wounds. The success of the team will depend on the dedication of each member because they have different roles in the care of these patients.

The recommended members of the MDT are listed in Table II.

**Table II.** Members of the multidisciplinary clinical team.

Member	Contribution
Plastic surgeon	Soft tissue reconstruction and coverage
Podiatric surgeon	Wound care and surgical biomechanical management
Orthopedic surgeon	Lower extremity skeletal reconstruction
Vascular surgeon	Vascular assessment and open and endovascular intervention
Infection disease specialist	Medical infection management
Endocrinologist	Aggressive glucose management
Hospitalist	Acute inpatient management
Internalist	Medical management of comorbidities
Rheumatologist	Vasculitic and autoimmune processes
Hematologist	Coagulopathy components
Psychiatrist	Behavior modification and psychological assessment
Hyperbarist	HBO therapy
Interventionalist (radiology, cardiovascular)	Assessment and endovascular intervention
Nutritionist	Optimization of healing potential through counseling and supplementation
Physical therapist	Rehabilitation and mobility training
Orthocist/prosthetist	Orthotics, prosthetics, bracing
Wound nurse	Wound care and patient education
Medical assistant	Casting and dressing application
Nurse practitioners/physician assistant	Pre and postoperative care, wound care, discharge planning, and patient education
Anesthesiologist	Anesthesia induction in high risk patients
Surgical technician	Knowledge and equipment/supplies

HBO Hyperbaric oxygen

The specialists in the list are needed for an adequate evaluation and treatment of patients with chronic leg wounds. This should be adjusted for our setting since several specialists are not available in our country. In any case, their contributions can be covered by most practitioners in the list.

Having an MDT will help in the standardization of evaluation and management. This strategy may be facilitated by the formation of wound care center in each institution.

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## 7. What additional treatments are necessary based on the etiology of the wound?

### 7.1 What are the treatment options to address CLU due to venous insufficiency?

Compression therapy is the recommended treatment for all patients with venous ulcers without peripheral arterial disease.

## Level 1 Category A

### Summary of Evidence

Venous hypertension and wounds are treated together. The key to wound care and edema management is immobilization. Conservative means like intermittent elevation, compression bandages, and intermittent pneumatic compression are used to control edema.<sup>1</sup> Studies have demonstrated that moist wound healing combined with compression improves healing rate of venous ulcers.<sup>2</sup> Compression therapy is the mainstay of venous ulcer therapy.<sup>3</sup> Elevation of the legs above the heart is recommended if possible. A compression dressing isn't required when the patient is immobilized with the leg elevated, such as during sleeping hours.

The mainstay for the treatment of venous insufficiency continues to be good external compression. In many patients, this is all that is required. Compression acts both as treatment for various states of venous insufficiency as well as prophylaxis for the development of the adverse sequelae.

Compression is the application of pressure to the limb. It is measured in millimeters of mercury (mm Hg) and is applied by bandages, elastic stockings, and/or intermittent pneumatic compression pumps. The amount of compression prescribed is determined by the diagnosis, comorbid conditions, and the patient's ability or willingness to accept the treatment (Table 1). Compression strength of 30 to 40 mm Hg is recommended to counteract the capillary filling pressures within the leg. Many factors affect bandage pressure. Compression therapy should be performed by an experienced practitioner.

The ambulatory venous patient is best served by semirigid dressings, such as the Unna boot, or by multi-component system compression wraps. Multi-component compression is more effective than single-component compression; both four layer and short-stretch bandages have higher healing rates than paste plus an outer support.

One study found that ulcers treated with the foam dressing under the Unna boot healed twice as fast as ulcers treated without the foam.<sup>5</sup> Bandages may be made of different materials, including elastic and inelastic materials or both. Stiff bandages are made of multiple

**Table 1.** Classification of compression hosiery.

Class	Pressures	Support	Indications for use
I	14-17 mmHg	Light	Varicose veins Mild edema
II	18-24 mmHg	Medium	Severe varicose veins Mild edema Prevention of ulcer recurrence
III	25-35 mmHg	Strong	Severe varicose veins Post-phlebotic limb Prevention of ulcer recurrence Chronic venous insufficiency

Adapted from Scholl 1996<sup>4</sup>

layers of elastic or inelastic material. This type of bandage remains rigid and generates high pressure during exercise, which reduces venous hypertension. Elastic bandages are considered long stretch and capable of stretching to double their size. Because these dressings can be stretched too tight, they are not recommended as a primary dressing for compression.<sup>6</sup> Inelastic bandages are non-stretch bandages, short-stretch bandages, and zinc paste bandages. Compression wraps should be applied starting just below the toes and ending just below (two finger breadths) the popliteal fossa. Extra padding around bony prominences reduces the possibility of creating a pressure ulcer.

Stockings reduce ambulatory venous pressure by decreasing venous reflux and improving calf muscle ejection capacity during use.<sup>7</sup> The benefit derived from stockings is in direct proportion to the fit.

A pneumatic compression pump may be used to reduce lower-extremity edema.<sup>8-13</sup>

A graded exercise program may be used to improve the calf muscle pump in those patients with abnormalities in pump function. One author<sup>13</sup> determined that a structured exercise program to improve muscle function may have a significant positive outcome in patients with venous disease.<sup>14</sup>

In some patients, the use of compression alone is inadequate; for these patients, surgical intervention is usually necessary.

Surgical treatment for venous ulcers is aimed at correcting the cause of the venous hypertension. Patients can have venous reflux without the symptoms of insufficiency. It is when reflux is severe enough that the insufficiency results in dermal venous hypertension and the eventual skin changes with which patients present. Procedures aimed at correcting insufficiency of the deep venous system include vein valve transplantation, direct valve repair, and veno-venous bypass. Outflow obstruction of a limb is addressed with veno-venous bypass, endovascular intervention, or a combination of the two. Varicose veins, the manifestation of superficial venous insufficiency, generally require ablation. Their treatment is usually by excision, ligation, injection, or the more recent method of endovenous ablation, depending on the size of the vein.

In patients with an outflow obstruction, but in whom insufficiency or hypertension is caused by occlusion of the greater saphenous vein, the venous hypertension may be alleviated by isolated partial saphenous vein ligation and stripping.

If, however, the reflux or hypertension is the result of the deep venous system, then ablating the non-pathological greater saphenous vein wouldn't help and actually may be detrimental due to elimination of one of the venous outflow tracts of the extremity.

Two fairly recent publications on neovalve construction and valvular repair highlight the various

techniques employed to restore venous competency of the deep system and their outcomes.<sup>15-16</sup> These are technically challenging operations that are not widely available. When successful, ulcer healing rates exceed 88%.

In patients in whom no suitable vein valve segment can be found or it's deemed an inadequate operation, the development and implantation of a prosthetic valve holds some promise. The appropriate use of adequate compression is necessary in conjunction with all the surgical treatments.

Proper application of compression is required afterward to reduce local venous hypertension. A subfascial ligation of incompetent perforator veins with an endoscope (SEPS) is a significant advancement in the Linton technique.

The reason for ligating incompetent perforators is to eliminate the venous hypertension associated with the reflux of venous blood.<sup>15</sup> In a meta-analysis by Tenbrook, et al. ulcers treated by SEPS with or without additional venous ablation healed in 88% of patients.<sup>17-18</sup>

Others use duplex ultrasound?guided foam sclerotherapy, which scleroses the perforator veins to achieve the same effect.<sup>19</sup>

The use of endovenous ablation has really become widespread in the United States, supplanting traditional vein stripping. In most places, endovenous ablation is an outpatient office-based procedure. It involves ultrasound-guided cannulation of the distal saphenous vein, either lesser or greater, with a catheter whose tip is positioned 2 cm distal to the sapheno-femoral junction.

The energy delivered is either in the form of a laser (endovenous laser therapy, EVLT) or radiofrequency (RF). Proponents of both forms claim superiority. The end result, if successful, is controlled thrombosis and destruction of the vein and thereby prevention of reflux through it. U.S. data show 99.6% successful occlusion initially,<sup>20</sup> falling to 86% to 89% at 4 years. Endovenous ablation has been widely accepted as a tool for the patient seeking removal of mostly asymptomatic varicosities.

Despite compression therapy, typically 30% of ulcers will not have healed at one year. This has led to the evaluation of a number of potential pharmacological agents which may prevent or reduce damage to the

microcirculation which occurs as a result of the underlying venous hypertension, and thus promote healing

Pentoxifylline is believed to increase microcirculatory blood flow although the exact mechanism of action is unknown.<sup>21</sup> A well conducted systematic review identified 11 RCTs comparing pentoxifylline with placebo or no treatment. Treatment with pentoxifylline (400 mg three times daily) improved venous leg ulcer healing rates by 21% (RR 1.56, 95% CI 1.14 to 2.13) when used as an adjuvant to compression or by 23% when used alone where compression is not possible.<sup>22</sup>

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7.2 What are the treatment options to address CLU due to peripheral arterial occlusive disease?

Patients with CLU with established peripheral arterial disease (PAD) should be started on medical management. In the presence of critical limb ischemia, revascularization is recommended.

**Level 1 Category A**

**Summary of Evidence**

There is a strong correlation between ABI, as a measure of the severity of the PAD. A number of studies, using different ABI 'cut-off' points have demonstrated this relationship.<sup>1</sup>

ABI	Interpretation
1.0-1.2	Normal
0.75-0.90	Moderate disease
0.50-0.75	Severe disease
<0.5	Rest pain or gangrene
Unreliable	Diabetes

Treatment of arterial ulcers includes increasing the blood supply to the area. Positioning the extremity in a dependent position may facilitate blood flow by gravity through collateral vessels. Use caution if devices such as a foot cradle are used for protection because an insensate foot is subject to trauma from the cradle's hard wood or metal. Debridement of non-viable tissue should not be performed in the presence of ischemia because the blood flow is insufficient to heal the new surgical wound. Ulcers without adequate arterial inflow must be kept dry-in contrast to the principle of moist wound healing for ulcers with adequate blood supply. Moisture provides a bed for bacterial growth if eschar, slough, or gangrenous tissue is present. This tissue, if kept dry, can be left in place until demarcation or debridement is indicated.

Arterial reconstruction is the treatment of choice to improve the circulation for most patients.<sup>2</sup> Treatment for arterial leg ulcers requires reinstating arterial inflow before any other treatment is established. This is usually preceded by a noninvasive vascular test, an arteriogram (computerized tomography angiogram, magnetic resonance angiogram, digital subtraction angiogram) followed by angioplasty and/or surgery. Simultaneously, local ulcer treatment can be determined.

Surgical treatment should be considered when patients have incapacitating claudication, rest pain, non-healing ulcers, or progressive gangrene and infection that cannot be controlled.

For arterial ulcers, surgical treatment is aimed at restoring tissue perfusion. Bypass grafting may be performed using autologous veins or, when autologous veins are not available, prosthetic grafts, either reversed or in situ. Despite the fact that endovascular techniques are not superior to surgical techniques with regard to vessel patency, wound healing and limb salvage can be attained by using endovascular techniques for patients previously considered ineligible for revascularization. There are poor long-term results from percutaneous balloon angioplasty and stent insertions, atherectomy (percutaneous endoluminal removal of atherosclerotic plaque),<sup>3</sup> and laser ablation of atherosclerotic lesions,<sup>4</sup> except in the common iliac arteries. However, these minimally invasive procedures are very useful in the high-risk patient and expand treatment options. Ulcers

with large skin loss may require skin grafting to close the defect.

The recently published BASIL (Bypass versus Angioplasty in Severe Ischemia of the Leg) trial,<sup>5</sup> which compared bypass surgery and angioplasty, clearly showed that bypass surgery was superior in achieving amputation-free survival. Also, those patients who underwent bypass surgery first fared better than those who underwent angioplasty first. However, this superiority was not significant until after 2 years. The BASIL trial also showed that autologous veins were superior to prosthetic conduits for these bypasses.

It reinforces the long-held concept in limb salvage surgery that being aggressive is usually better for the patient.

The treatment of ulceration due to arterial insufficiency depends on the level that the occlusive disease occurs. Surgeries for arterial insufficiency are generally grouped into three major areas: aortoiliac bypass; femoropopliteal bypass; and distal bypass.

Occlusive disease in many patients is multi-leveled. The rule of thumb is to improve inflow first in these patients and then, if necessary, perform an outflow procedure. Inflow usually involves the aortoiliac segments. The exact surgery is tailored to the individual patient's physiologic status and need.

The development of percutaneous balloon angioplasty, with or without stent placement, has significantly reduced the need for routine aortobifemoral bypass surgery in patients with aortoiliac occlusive disease.<sup>6</sup> Isolated short-segment stenoses can be treated successfully with balloon angioplasty. Short-segment stenoses are generally defined as those less than 10 cm in length, commonly less than 5 cm. With more recent advances in stent development, acute occlusions occurring as a result of atherosclerotic plaque rebound have decreased. The long-term patency rate for stents approaches that for arterial bypass, but only in the aortoiliac segments.<sup>7</sup>

Infra-inguinal balloon angioplasty with or without stent placement is still inferior to surgical intervention. However, this procedure still holds a place in the treatment of high-risk patients.

According to the TASC II Guidelines,<sup>8</sup> arterial reconstruction by means of endovascular techniques

should be considered before more invasive surgical techniques when possible.

Medical treatment of arterial disease may include antiplatelet drugs, such as aspirin or clopidogrel, which inhibit the binding of adenosine triphosphate (ATP). Clopidogrel was shown to be slightly better than aspirin in a comparative study.<sup>9</sup> In addition, cilostazol<sup>10-12</sup> has been used not only to decrease platelet aggregation but also to act as a vasodilator that may facilitate an increase in exercise capacity. However, it cannot be used in patients with heart failure.

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### 7.3 What are the treatment options to address CLU due to diabetes?

The treatment of patients with CLU due to diabetes include optimal diabetes control, effective local wound care, infection control, pressure relieving strategies (offloading) and restoration of pulsatile blood flow.

#### Level 1 Category A

#### Summary of Evidence

Practitioners should identify the underlying cause of the diabetic foot ulcer (DFU) during patient assessment and, where possible, correct or eliminate it. Successful diagnosis and treatment of patients with DFUs involves a holistic approach that includes optimal diabetes control, effective local wound care, infection control, pressure relieving strategies (off-loading) and restoring pulsatile blood flow. This should include a full patient history including medications being taken, the presence of comorbidities and diabetes status. The underlying cause(s) of DFUs will have a significant bearing on the management.

Diabetic wound healing depend greatly on strict control of blood sugar as well as aggressive infection control (as described earlier in the TIME concept). Achieving optimal diabetic control involves tight glycemic control and managing all other risk factors present such as high blood pressure, hyperlipidemia and smoking.<sup>1</sup> Nutritional deficiencies should also be corrected.<sup>2</sup>

The physical cause of the trauma should be addressed. Practitioners should examine the patient's footwear for proper fit, wear and tear and any foreign body that may traumatise the foot. It is important to relieve pressure in identified at-risk areas of the foot in patients with peripheral neuropathy. The goal is to redistribute pressures evenly to prevent tissue damage and ulceration.

Protective footwear and insoles can be prescribed for the patient and then evaluated and monitored for their effectiveness. The primary role of therapeutic footwear is to protect the foot from repetitive injuries and eliminate the shoe as a source of pathology. The combination of a correctly sized shoe and a protective insole can reduce

pressure on the sole, top, and sides of the foot by as much as 20%.<sup>3,4</sup> Custom-molded shoes are individually made from a mold of the patient's foot. For most patients with less severe deformities, there are a number of more affordable athletic, comfort, and therapeutic shoes with multiple sizes and extra depth to accommodate a wide variety of foot deformities.

Use of a total contact cast (TCC) is considered the gold standard for off-loading the foot. This device is a well molded, minimally padded cast encasing both the foot and the lower leg. TCCs reduce pressure at the ulcer site while still allowing the patient to be ambulatory.<sup>5,6</sup> It can distribute pressures evenly over the entire plantar surface of the foot and is one of the most effective ways of treating plantar neuropathic foot ulcers.<sup>6-8</sup> A skilled clinician or technician is required to apply the molded plaster cast to ensure a proper fit.

Numerous studies<sup>7-14</sup> have shown that TCCs can heal ulcers in 6 to 8 weeks. One of the main advantages of using a TCC is that it forces patient compliance with off-loading. The ulcer is protected with every step the patient takes. Using a TCC to facilitate wound healing is analogous to using a cast to heal a fracture- in both cases, healing is facilitated by rest and immobilization. The TCC reduces the patient's activity level,<sup>11</sup> decreases stride length and cadence, and significantly reduces pressure at the ulcer site.<sup>6,8</sup> The main disadvantages for patients are the same as their complaints with a fracture cast-a cast is heavy and hot and makes bathing, walking, and sleeping difficult.

Another device that can be used for these patients are removable cast walkers. The effectiveness of removable cast walkers to reduce pressure at ulcer sites has been shown in several studies to be comparable to that of TCCs.<sup>6,8</sup> Many practitioners consider removable cast walkers to be their preferred off-loading device because they are less time-consuming and easier to apply than TCCs and they are more readily accepted by patients.<sup>8,11,12,15-17</sup> It's also possible to modify removable walkers into non-removable devices by securing the walker with cast material or a non-removable cable tie; this is known as an instant TCC (ITC). If patients can't remove the walker, the element of forced compliance that makes the TCC attractive is maintained and the outcomes for healing improve to the levels seen with the TCC.<sup>18-20</sup>

Acute limb ischemia is a clinical emergency. Treating severe ischemia is important to wound healing.<sup>21</sup> It is recommended that all patients with critical limb ischemia, rest pain, ulceration and tissue loss be referred for possible revascularization<sup>22</sup> in order to achieve and maintain healing and to avoid or delay future amputation.<sup>23</sup>

Armstrong and colleagues validated a four-tier surgery classification that consists of elective, prophylactic, curative, and emergent surgery.<sup>24</sup>

Elective surgery is planned reconstructive surgery in a patient with foot deformity to eliminate pain or to enhance function. Prophylactic surgery is intended to prevent ulcer recurrence. Curative surgery is intended to facilitate wound healing in a patient with an existing foot wound. Emergent surgery is intended to remove infection or devitalized tissue.<sup>24</sup>

There is no evidence that elective surgery reduces the risk of future ulceration. Patients with diabetes should undergo elective foot surgery only if they have severe deformity, pain, or functional limitations that warrant surgery rather than an expectation that surgery will prevent a foot ulcer in the future.

Prophylactic surgery includes toe and bunion deformity correction, Achilles tendon lengthening, and exostectomy.

Regular foot evaluation is essential to identify new risk factors and prevent impending complications.

Education is an essential component of any program designed to reduce the incidence of diabetic foot ulcers. Preventive education usually takes the form of an intensive introduction to the disease and includes practical steps to cope with the manifestations of diabetes over time. However, in a 2004 Cochrane Review<sup>25</sup> of nine RCTs to determine the effectiveness of educational programs in preventing diabetic foot ulceration, the authors concluded that there was only weak evidence to suggest that education reduces foot ulceration and amputations in high-risk patients.

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#### 8. What is the role of adjunct treatment?

Adjuvant strategies may be helpful in situations where the mainstay of treatment, e.g. conventional revascularization methods for arterial ulcers, or compression therapy for venous ulcers, may not be feasible, or in instances where ulcers fail to heal within a prescribed period despite application of adequate wound care principles and correction of the underlying etiopathology.

#### **Level 1 Category A**

Adjuvant strategies are not primary treatment strategies and should not be used in lieu of TIME principles and addressing the main etiopathogenesis of CLU.

#### **Level 1 Category A**

#### **Summary of Evidence**

Adjuvant therapies commonly include but are not limited to wound dressings with active components (defined here as advanced wound dressings), physical energy modalities such as laser, ultrasound and electrical stimulation, positive and negative barometric applications, oxygen supplementation and various molecular and cellular therapies, as well as specific surgical techniques aimed at correcting contributory hemodynamic abnormalities.<sup>1</sup>

If the wound is not 30% smaller at week 4, despite optimal local wound care, then it is unlikely to heal by week 12 and adjuvant therapies should be considered.

The stalled wound is one that has entered a non-healing or intransigent phase.<sup>5</sup> This can occur as a progression of an acute wound to one of chronicity dictated by events within the wound milieu or following alterations in host factors. A stalled wound may occur spontaneously and unexpectedly in the midst of a supposedly successful healing plan.<sup>6</sup> It is imperative that in analyzing the stalled wound, causes related to wound management must be ruled out first, followed by an appraisal of the host factors. Thus, physical factors, as opposed to physiologic factors, should be examined first. These include ruling out infection and vascular complications, ensuring proper off-loading, performing adequate debridement, and facilitating a moist healing environment.

Many advanced wound dressings are founded on the provision of active components thought to be lacking in the wound environment that result in an imbalance between healing and inflammation.<sup>5</sup> Some contain substances with reported antiseptic or antibiotic properties aimed at reducing the wound bacterial load, which results in shifting the balance from inflammation to healing. Other advanced wound dressings offer superior absorbent capacities for highly exudative wounds, and still others claim to provide a continuous moist environment for wounds that tend to desiccate.

There is no specific advanced wound dressing product that is superior and applicable to all CLUs. The selection of advanced dressings should be based on clinical assessment of the ulcer, cost, access and patient tolerance.

There is a wide body of research showing a great variety in the use of advanced wound dressings in the management of CLU. However, there is insufficient evidence to show the superiority of one over another in all types of CLU. It is best to select dressings based on clinical assessment of the ulcer, cost, access and patient/health professional preferences.<sup>7-9</sup>

A list of the common topical antimicrobial agents used is seen in Appendix 2.

Prolonged use of topical antiseptics or antibiotics or dressings containing such should not be used in the

standard care of CLU with no clinical signs of infection, and should be reserved for situations in which concern for bacterial load is higher than that of healability.

Current evidence suggests that topical antiseptics may be beneficial for short term use, particularly when bacterial levels are sufficiently high to cause tissue destruction and the goal of care is the maintenance of the wound.<sup>10</sup> Toxic effects of antimicrobial/antiseptics solutions on fibroblasts and macrophages *in vitro* are well documented.<sup>11</sup> There may be a role for judicious use of topical antimicrobials when there is known or suspected increased microbial burden.

### **Molecular Cellular and Acellular Therapies**

There is insufficient evidence that protein and cellular-based treatments shorten healing times for CLU.

Various strategies have been employed in the constant quest to mimic the healing sequence seen in acute wounds. These strategies usually involve administering a therapeutic stimulus that is reasoned to trigger a healing response (eg, growth factors, cell lines, tissue substitutes).<sup>12</sup> The role of stem cell therapy as an alternative method of limb revascularization is promising but currently undefined.

The evidence on growth factors, cell lines, and tissue substitutes is conflicting. While some trials report significant improvements in healing, others found no significant difference in healing times compared with standard care. Further research is required on these adjuvant strategies.<sup>13-15</sup>

Stem cell therapy is a promising treatment modality for small vessel revascularization with initial success in the TACT trial as well as other small series.<sup>16-18</sup> Recent reports of success have now been documented in small randomized trials.

Additional studies are needed to define the role of this therapy in appropriate populations of patients.<sup>19</sup>

### **Physical and Energy Modalities**

There is insufficient evidence on which to base a recommendation for electromagnetic therapy, laser and infra-red light therapy, ultrasound therapy, negative pressure and hyperbaric oxygen as well as topical

oxygen therapy, and intermittent pneumatic compression and balneotherapy, for the treatment of CVLU.<sup>19-37</sup>

Adjuvant physical energy modalities are those devices that deliver physical and energy effects to the wound in the hope of reducing healing time by tipping the balance into activating the proliferative stage of wound healing. Examples of these modalities are electromagnetic therapy, laser and infrared light therapy, ultrasound therapy, negative pressure and hyperbaric oxygen therapy. Also included under this category are strategies for mimicking or improving calf muscle function such as intermittent pneumatic compression and balneotherapy.<sup>38-39</sup>

### **Pharmacologic Adjuncts**

Despite adequate standard of care, it has been estimated that nearly 30% of ulcers will not have healed at one year.<sup>40</sup> This has led to the evaluation of a number of potential pharmacological agents which may prevent or reduce damage to the microcirculation which occurs as a result of the underlying venous hypertension, and thus promote wound healing.<sup>38</sup> Current adjuvant pharmacologic therapies include the use of aspirin, phlebotonics such as micronized purified flavonoid fraction, mesoglycan, pentoxifylline, cilostazole and zinc.

There is insufficient evidence on which to base a recommendation for aspirin, micronized purified flavonoid fraction, mesoglycan, zinc, and cilostazole for reducing the healing time of CLU. Pentoxifylline (400mg three times daily for up to six months) may be used to improve healing in patients with CVLU. It has not shown to be significantly different from adequate standard of care in patients with CALU.<sup>41-49</sup>

Traditional and folk practices abound consisting of the use of plant and animal extracts as wound healing remedies prescribed by folk healers. Most notable among these are honey, horse chestnut seed extract (HCSE), virgin coconut oil (VCO), *Psidium guajava* (bayabas) leaves extract, and even *Canis sp* (dog) saliva.<sup>50</sup>

Honey offers no benefits over standard care in promoting healing in CLU. There is insufficient evidence to recommend the use of HSCE, VCO, *Psidium guajava*

extracts and *Ca-nis sp* saliva for the treatment of wounds.<sup>50-59</sup>

The result of this document review underscores the need for further research and trials for the validation of adjuvant therapies for wound healing. By no means does this document claim to comprehensively detail all adjuvant therapies. It is recognized that although the lack of evidence does not lend itself to treatment recommendations, it does not presume lack of effectivity especially for certain specific and also as yet unelucidated conditions. Furthermore this document recommends continued responsible use of these modalities under protocolized conditions, that the data gathered may be contributed to the global pool for stronger statistical analysis and more valid recommendations.

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9. When is amputation recommended?
- Limb amputation is considered the last resort when limb salvage is not feasible or when the limb condition endangers the patient's life.
- Level 4 Category A**
- Summary of Evidence**
- Lower limb amputation is performed predominantly for acute and chronic limb ischemia caused by severe vascular disease, poorly controlled diabetes and in some cases, uncontrolled infection and unsuccessful limb

salvage procedures.<sup>1</sup> Most often, patients undergoing amputation present late when limb salvage is not a viable option anymore.<sup>2,3</sup>

The key factors in the decision to undergo an elective amputation are the presence of pain and the desire to improve function.<sup>4</sup>

In selected patients, a below the knee amputation maybe a good salvage procedure for intractable foot and ankle pain that is unresponsive to all medical and local surgical reconstructive techniques.<sup>5</sup>

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10. What is the recommended monitoring strategy for CLU?

Wound monitoring in patients with CLU is performed by measuring wound size reduction. This method involves measuring the length and width of the wound and comparing it with the findings on initial wound assessment.

## Level 3 Category A

### Summary of Evidence

Precise and regular evaluation with documentation of wound healing is one of the most important part of wound management for this would dictate whether further treatment is required.<sup>1,2</sup> Wound appearance changes dynamically therefore repeated systematic assessment is necessary.<sup>2,3</sup>

According to Romanelli, the clinical evaluation of the extent of tissue involvement due to a skin lesion, and the way a lesion evolves over time, should be assessed.<sup>3</sup> Evaluations are performed using the same tool used during the initial assessment to make objective and accurate measurements.

The measurement of perimeter, maximum dimensions of length, width, and depth, surface area, volume, and determination of tissue viability are included in the assessment of CLU.<sup>3</sup> Several criteria are used to determine healing rate. These include the following: wound edge migration; change in wound area; and percentage change in area which are dependent on wound geometry (length, width). Wounds are assessed on a weekly basis for 8 to 12 weeks.<sup>4</sup> Early percent reduction in wound area has been the most reliable in predicting complete ulcer healing.<sup>3</sup>

Biopsy is indicated for all patients with CLU, specifically for those presumed to have venous ulcers which does not heal for more than 3 months despite appropriate treatment, with or without suspicion of malignancy.

Alavi (2011), enumerated the signs and symptoms that may be suggestive of malignancy in a wound:

1. Non-healing despite optimal wound care
2. Friable granulation tissue
3. Easy bleeding
4. Tissue overgrowth and induration
5. Foul-smelling discharge
6. Destruction of underlying tissue

In a study by Miller, et al (2004), it has been documented that even patients with no clinical evidence of malignancy can show a positive result. In another study by Senet (2010), they found out that the overall

skin cancer frequency in CLUs was 10.4%. The recommended biopsy technique is a wedge biopsy at the center of the wound or a punch biopsy.<sup>5,6,7</sup>

**References**

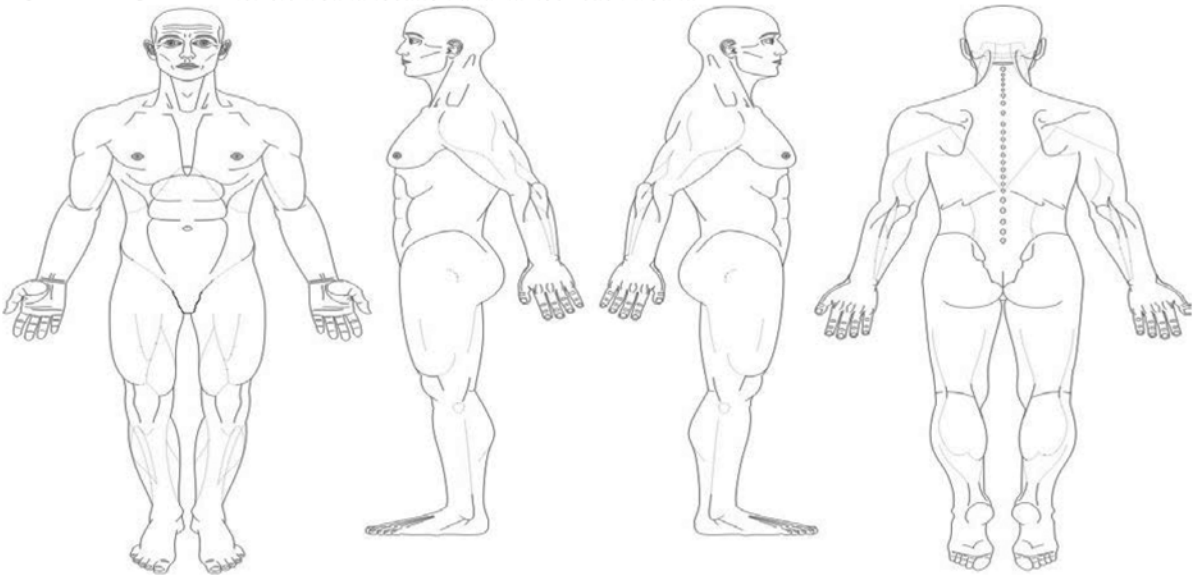
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**Appendices**

- I. WOUND ASSESSMENT FORM DEVELOPED BY THE PHILIPPINE WOUND CARE SOCIETY. This form was created in 2012, through the cooperation of members of seven wound care centers in Metro Manila, Philippines including NKTI, CGH, SLMC, PHC, EAMC, TMC, and JRRMMC under the leadership of Ma. Kristina Simon, RN.

**Wound Assessment Form**

Personal Details						
PATIENT NAME LAST NAME                      FIRST NAME MIDDLE NAME		BIRTHDATE MM / DD / YYYY	AGE	SEX <input type="checkbox"/> Male <input type="checkbox"/> Female	PATIENT ID	HOSPITAL/PIN NO.
BIRTHPLACE	NATIONALITY	RELIGION	ICD CODE			
PRESENT ADDRESS			PERMANENT ADDRESS (if different from Present Address)			
MOBILE NO	TELEPHONE NO		OCCUPATION			
ACCOUNT TYPE <input type="checkbox"/> Personal <input type="checkbox"/> HMO, pls. specify _____ <input type="checkbox"/> Stockholder, pls. specify <input type="checkbox"/> Company, pls. specify _____			<input type="checkbox"/> Service <input type="checkbox"/> Others, pls. specify _____		HMO / COMPANY ID NO:	
			VALIDATION/APPROVAL CODE:			
			VALIDITY DATE:			
IN CASE OF EMERGENCY, PLEASE NOTIFY		RELATIONSHIP			CONTACT NO	
INFORMANT NAME (if any)		RELATIONSHIP			CONTACT NO	
WOUND CARE PHYSICIAN		REFERRING PHYSICIAN Date & Time of Referral: _____		PATIENT CLASSIFICATION <input type="checkbox"/> Outpatient                      Room No: _____ <input type="checkbox"/> Inpatient:                      Date of Admission: _____		
Medical History						
Present Hx:		Social Hx:		VITAL SIGNS:    PR: ____    RR: ____    BP: ____    T: ____		
Past Medical Hx:		Family Hx:		<b>FUNCTIONAL ASSESSMENT</b> Please indicate: I – Independent, D- Dependent, A- Assisted Eating                      Toilet Transfer Grooming                      Tub/Shower Transfer Bathing                      Walk/ Wheelchair Dressing Upper Body                      Stairs Dressing Lower body                      Comprehension Toileting                      Expression Bowel Mx                      Social Interaction Bladder Mx                      Problem Solving Bed/Chair/WC transfer                      Memory		

MEDICATIONS, please specify:	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 70%; padding: 5px;"> <b>LOWER EXTREMITY PULSES: 0 - no pulse, +1 weak, +2 normal</b>                      Femoral:     L: _____, R: _____                      Popliteal:   L: _____, R: _____                      Post.tibialis: L: _____, R: _____                      Dorsalis pedis L: _____, R: _____                 </td> <td style="width: 30%; padding: 5px;"> <b>*For PAD/DM FOOT</b>                      ABPI:   L: _____                                R: _____                      Monofilament:                                L: _____                                R: _____                 </td> </tr> </table>	<b>LOWER EXTREMITY PULSES: 0 - no pulse, +1 weak, +2 normal</b> Femoral:     L: _____, R: _____ Popliteal:   L: _____, R: _____ Post.tibialis: L: _____, R: _____ Dorsalis pedis L: _____, R: _____	<b>*For PAD/DM FOOT</b> ABPI:   L: _____ R: _____ Monofilament: L: _____ R: _____
<b>LOWER EXTREMITY PULSES: 0 - no pulse, +1 weak, +2 normal</b> Femoral:     L: _____, R: _____ Popliteal:   L: _____, R: _____ Post.tibialis: L: _____, R: _____ Dorsalis pedis L: _____, R: _____	<b>*For PAD/DM FOOT</b> ABPI:   L: _____ R: _____ Monofilament: L: _____ R: _____		
IS PATIENT HAS ACCESS TO OTHER WOUND CENTER? <input type="checkbox"/> No <input type="checkbox"/> Yes:			
ALLERGIES: <input type="checkbox"/> None <input type="checkbox"/> Drug, pls. specify: _____ <input type="checkbox"/> Food, pls. specify: _____ <input type="checkbox"/> Others, pls. specify: _____	OTHER INFORMATION RELEVANT TO WOUND HEALING:		
<b>BODY DIAGRAM</b> <i>Encircle wound location and number each wound</i>			
			

FORM CODE

WOUND NO: ____	WOUND NO: ____
----------------	----------------

<p><b>WOUND TYPE &amp; CLASSIFICATION:</b></p> <p><input type="checkbox"/> Pressure Ulcer (NPUAP):</p> <p><input type="checkbox"/> Stage I    <input type="checkbox"/> Stage II    <input type="checkbox"/> Stage III</p> <p><input type="checkbox"/> Stage IV    <input type="checkbox"/> Unstageable    <input type="checkbox"/> Suspected deep tissue injury</p> <p><input type="checkbox"/> Vascular Ulcers:</p> <p><input type="checkbox"/> Venous _____    <input type="checkbox"/> Arterial _____    <input type="checkbox"/> Lymphatic _____</p> <p><input type="checkbox"/> Diabetic Foot:</p> <p><input type="checkbox"/> Grade 0    <input type="checkbox"/> Grade 2a    <input type="checkbox"/> Grade 3a</p> <p><input type="checkbox"/> Grade 4</p> <p><input type="checkbox"/> Grade 1    <input type="checkbox"/> Grade 2 b    <input type="checkbox"/> Grade 3b</p> <p><input type="checkbox"/> Grade 5</p> <p><input type="checkbox"/> Others, pls. specify: _____</p> <p>_____</p>	<p><b>WOUND TYPE &amp; CLASSIFICATION:</b></p> <p><input type="checkbox"/> Pressure Ulcer (NPUAP):</p> <p><input type="checkbox"/> Stage I    <input type="checkbox"/> Stage II    <input type="checkbox"/> Stage III</p> <p><input type="checkbox"/> Stage IV    <input type="checkbox"/> Unstageable    <input type="checkbox"/> Suspected deep tissue injury</p> <p><input type="checkbox"/> Vascular Ulcers:</p> <p><input type="checkbox"/> Venous _____    <input type="checkbox"/> Arterial _____    <input type="checkbox"/> Lymphatic _____</p> <p><input type="checkbox"/> Diabetic Foot:</p> <p><input type="checkbox"/> Grade 0    <input type="checkbox"/> Grade 2a    <input type="checkbox"/> Grade 3a    <input type="checkbox"/></p> <p><input type="checkbox"/> Grade 4</p> <p><input type="checkbox"/> Grade 1    <input type="checkbox"/> Grade 2b    <input type="checkbox"/> Grade 3b    <input type="checkbox"/></p> <p><input type="checkbox"/> Grade 5</p> <p><input type="checkbox"/> Others, pls. specify: _____</p> <p>_____</p>
<p>DATE OF ONSET OF WOUND: ___ / ___ / ___</p>	<p>DATE OF ONSET OF WOUND: ___ / ___ / ___</p>
<p>(INSERT PHOTO)</p>	<p>(INSERT PHOTO)</p>
<p>WOUND SIZE: Length ___cm x Width ___cm</p>	<p>WOUND SIZE: Length ___cm x Width ___cm</p>
<p>WOUND DEPTH: ___ cm</p> <p><input type="checkbox"/> Undermining: ___ cm, location: _____</p> <p><input type="checkbox"/> Tunnelling: ___ cm, location: _____</p>	<p>WOUND DEPTH: ___ cm</p> <p><input type="checkbox"/> Undermining: ___ cm, location: _____</p> <p><input type="checkbox"/> Tunnelling: ___ cm, location: _____</p>
<p>WOUND BED: <i>tick box and indicate percentage</i></p> <p><input type="checkbox"/> Necrotic _____    <input type="checkbox"/> Granulating _____    <input type="checkbox"/></p> <p>Sloughy _____</p> <p><input type="checkbox"/> Epithelialising _____    <input type="checkbox"/> Others, pls. specify: _____</p> <p>_____</p>	<p>WOUND BED: <i>tick box and indicate percentage</i></p> <p><input type="checkbox"/> Necrotic _____    <input type="checkbox"/> Granulating _____    <input type="checkbox"/></p> <p>Sloughy _____</p> <p><input type="checkbox"/> Epithelialising _____    <input type="checkbox"/> Others, pls. specify: _____</p> <p>_____</p>
<p>WOUND EDGES: <i>tick box and indicate location</i></p> <p><input type="checkbox"/> Attached _____    <input type="checkbox"/> Not attached _____    <input type="checkbox"/> Diffuse _____</p> <p><input type="checkbox"/> Rolled _____    <input type="checkbox"/> Callous: _____</p>	<p>WOUND EDGES: <i>tick box and indicate location</i></p> <p><input type="checkbox"/> Attached _____    <input type="checkbox"/> Not attached _____    <input type="checkbox"/> Diffuse _____</p> <p><input type="checkbox"/> Rolled _____    <input type="checkbox"/> Callous: _____</p>
<p>WOUND EXUDATE AMOUNT:</p> <p><input type="checkbox"/> Dry    <input type="checkbox"/> Moist    <input type="checkbox"/> Wet    <input type="checkbox"/> Saturated    <input type="checkbox"/></p> <p>Leaking</p> <p>No. of dressing change per 24hrs: _____</p>	<p>WOUND EXUDATE AMOUNT:</p> <p><input type="checkbox"/> Dry    <input type="checkbox"/> Moist    <input type="checkbox"/> Wet    <input type="checkbox"/> Saturated    <input type="checkbox"/></p> <p>Leaking</p> <p>No. of dressing change per 24hrs: _____</p>
<p>WOUND EXUDATE COLOUR:</p> <p><input type="checkbox"/> Clear, amber    <input type="checkbox"/> Cloudy, milky, creamy    <input type="checkbox"/> Pink, red</p> <p><input type="checkbox"/> Green    <input type="checkbox"/> Yellow or brown    <input type="checkbox"/> Grey or blue</p>	<p>WOUND EXUDATE COLOUR:</p> <p><input type="checkbox"/> Clear, amber    <input type="checkbox"/> Cloudy, milky, creamy    <input type="checkbox"/> Pink, red</p> <p><input type="checkbox"/> Green    <input type="checkbox"/> Yellow or brown    <input type="checkbox"/> Grey or blue</p>

<p>WOUND EXUDATE CONSISTENCY</p> <p><input type="checkbox"/> High viscosity (thick, sometimes sticky)      <input type="checkbox"/> Low viscosity (thin, 'runny')</p>	<p>WOUND EXUDATE CONSISTENCY</p> <p><input type="checkbox"/> High viscosity (thick, sometimes sticky)      <input type="checkbox"/> Low viscosity (thin, 'runny')</p>
<p>WOUND EXUDATE ODOUR</p> <p><input type="checkbox"/> No unpleasant odour      <input type="checkbox"/> With unpleasant odour _____</p>	<p>WOUND EXUDATE ODOUR</p> <p><input type="checkbox"/> No unpleasant odour      <input type="checkbox"/> With unpleasant odour _____</p>
<p>PERIWOUND SKIN APPEARANCE:</p> <p><input type="checkbox"/> Erythema    <input type="checkbox"/> Edema      <input type="checkbox"/> Macerated    <input type="checkbox"/> Dry, scaly  <input type="checkbox"/> Healthy      <input type="checkbox"/> Other: _____</p>	<p>PERIWOUND SKIN APPEARANCE:</p> <p><input type="checkbox"/> Erythema    <input type="checkbox"/> Edema      <input type="checkbox"/> Macerated    <input type="checkbox"/> Dry, scaly  <input type="checkbox"/> Healthy      <input type="checkbox"/> Other: _____</p>
<p>WOUND PAIN: ___ / 10      Frequency: _____</p>	<p>WOUND PAIN: ___ / 10      Frequency: _____</p>
<p>IS INFECTION SUSPECTED?    <input type="checkbox"/> Yes    <input type="checkbox"/> No  WOUND GS/CS TAKEN?        <input type="checkbox"/> Yes    <input type="checkbox"/> No</p>	<p>IS INFECTION SUSPECTED?    <input type="checkbox"/> Yes    <input type="checkbox"/> No  WOUND GS/CS TAKEN?        <input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
<p>DIAGNOSTICS:</p>	<p>DIAGNOSTICS:</p>
<p>THERAPEUTICS:</p>	<p>THERAPEUTICS:</p>
<p>REMARKS/NOTES:</p>	<p>REMARKS/NOTES:</p>
<p>ASSESSOR'S NAME &amp; SIGNATURE:</p>	<p>DATE &amp; TIME:</p>
<p>WOUND PHYSICIAN NAME &amp; SIGNATURE:</p>	<p>DATE &amp; TIME:</p>

## II. Topical Antimicrobials

Topical antimicrobial preparations (antiseptics and antibiotics) can be used as either irrigation agents or designed to remain in contact with the wound for longer periods (as in, until the next time the dressing is changed).

		SA	MRSA	STREP	PS	F	Anaer	VRE	
<b>Safe &amp; Effective</b>	Cadexomer Iodine	/	/	/	/	/	/		Broad spectrum, Effective for fungi and virus. Widely available. Sheet requires wound contact. Caution if on thyroid medication.
	Ionized silver	/	/	/	/	/	/	/	Broad spectrum. Effective for fungi and virus. Sheet requires wound contact.
	Silver Sulfadiazine	/	/	/	/		/		Limited potential for resistance. Available in paste or ointment. Don not use if sulfa sensitive.
	polymyxinB sulfate-bacitracin Zinc	/	/	/	/		/		Sheet requires wound contact.
<b>Selective Use</b>	Metronidazole Gel/cream						/		Reserve for anaerobes and odor control

	Benzyl/Peroxide	/		/	/		/		Reserve for MRSA and other re-sistant gram positive
	Acetic Acid				/				Used in 0.25%
	Mupirucin		/						Good for MRSA Excellent topical penetration
<b>Caution</b>	Gentamycin	/		/	/				Reserve for oral/iv use
	Fusidic Acid	/		/					Sensitize
	PolymyxinB Sulfate- Bacitracin Zinc Neomycin	/	/	/	/		/		Potent Sensitizer
<b>Not recommended</b>	Alcohol Betadine Boric acid Daikens Iodine								Cytotoxic

Legend: (SA = Staphylococcus Aureus), (MRSA = Methicillin Resistant Staph Aureus), (Strep = Streptococci), (PS = Pseudomona), (F = Fungi – Mucor, Aspergillus, Candida Albicans, Candida Tropicalis, Candida Glabrata, & Saccharomyces), (VRE = Vancomycin-Resistant Enterococci)

Reprinted with permission from Dr. Gary Sibbald.

III. WOUND PROGRESS FORM DEVELOPED BY THE PHILIPPINE WOUND CARE SOCIETY. This form was created in 2012, thru the cooperation of seven institutions in Metro Manila, Philippines including NKT, CGH, SLMC, PHC, EAMC, TMC, and JRRMMC under the leadership of Ma. Khrystina Simon, RN

## WOUND PROGRESS FORM

PATIENT NAME: _____ <small>LAST NAME                      FIRST NAME                      MIDDLE NAME</small>			AGE/SEX	PATIENT ID:	HOSPITAL/PIN NUMBER:
DATE: ___/___/___ _____			WOUND NO: _____		DATE: ___/___/___ _____
(INSERT PHOTO)			(INSERT PHOTO)		
WOUND SIZE: Length ___cm x Width ___cm			WOUND SIZE: Length ___cm x Width ___cm		
WOUND DEPTH: ___ cm <input type="checkbox"/> Undermining: ___ cm, location: _____ <input type="checkbox"/> Tunnelling: ___ cm, location: _____			WOUND DEPTH: ___ cm <input type="checkbox"/> Undermining: ___ cm, location: _____ <input type="checkbox"/> Tunnelling: ___ cm, location: _____		
WOUND BED: <i>tick box and indicate percentage</i> <input type="checkbox"/> Necrotic _____ <input type="checkbox"/> Granulating _____ <input type="checkbox"/> Sloughy _____ <input type="checkbox"/> Epithelialising _____ <input type="checkbox"/> Others, pls. specify: _____			WOUND BED: <i>tick box and indicate percentage</i> <input type="checkbox"/> Necrotic _____ <input type="checkbox"/> Granulating _____ <input type="checkbox"/> Sloughy _____ <input type="checkbox"/> Epithelialising _____ <input type="checkbox"/> Others, pls. specify: _____		
WOUND EDGES: <i>tick box and indicate location</i> <input type="checkbox"/> Attached _____ <input type="checkbox"/> Not attached _____ <input type="checkbox"/> Diffuse _____ <input type="checkbox"/> Rolled-under _____ <input type="checkbox"/> Callous: _____			WOUND EDGES: <i>tick box and indicate location</i> <input type="checkbox"/> Attached _____ <input type="checkbox"/> Not attached _____ <input type="checkbox"/> Diffuse _____ <input type="checkbox"/> Rolled-under _____ <input type="checkbox"/> Callous: _____		
WOUND EXUDATE AMOUNT: <input type="checkbox"/> Dry <input type="checkbox"/> Wet <input type="checkbox"/> Moist <input type="checkbox"/> Saturated <input type="checkbox"/> Leaking No. of dressing change per 24hrs: _____			WOUND EXUDATE AMOUNT: <input type="checkbox"/> Dry <input type="checkbox"/> Wet <input type="checkbox"/> Moist <input type="checkbox"/> Saturated <input type="checkbox"/> Leaking No. of dressing change per 24hrs: _____		
WOUND EXUDATE COLOUR: <input type="checkbox"/> Clear, amber <input type="checkbox"/> Cloudy, milky, creamy <input type="checkbox"/> Pink, red <input type="checkbox"/> Green <input type="checkbox"/> Yellow or brown <input type="checkbox"/> Grey or blue			WOUND EXUDATE COLOUR: <input type="checkbox"/> Clear, amber <input type="checkbox"/> Cloudy, milky, creamy <input type="checkbox"/> Pink, red <input type="checkbox"/> Green <input type="checkbox"/> Yellow or brown <input type="checkbox"/> Grey or blue		
WOUND EXUDATE CONSISTENCY <input type="checkbox"/> High viscosity (thick, sometimes sticky) <input type="checkbox"/> Low viscosity (thin, 'runny')			WOUND EXUDATE CONSISTENCY <input type="checkbox"/> High viscosity (thick, sometimes sticky) <input type="checkbox"/> Low viscosity (thin, 'runny')		
WOUND EXUDATE ODOUR <input type="checkbox"/> None <input type="checkbox"/> With unpleasant odour _____			WOUND EXUDATE ODOUR <input type="checkbox"/> None <input type="checkbox"/> With unpleasant odour _____		
PERIWOUND SKIN APPEARANCE: <input type="checkbox"/> Erythema <input type="checkbox"/> Edema <input type="checkbox"/> Macerated <input type="checkbox"/> Dry, scaly <input type="checkbox"/> Healthy <input type="checkbox"/> Other: _____			PERIWOUND SKIN APPEARANCE: <input type="checkbox"/> Erythema <input type="checkbox"/> Edema <input type="checkbox"/> Macerated <input type="checkbox"/> Dry, scaly <input type="checkbox"/> Healthy <input type="checkbox"/> Other: _____		
WOUND PAIN: ___ / 10 Frequency: _____			WOUND PAIN: ___ / 10 Frequency: _____		

IS INFECTION SUSPECTED? <input type="checkbox"/> Yes <input type="checkbox"/> No WOUND GS/CS TAKEN? <input type="checkbox"/> Yes <input type="checkbox"/> No	IS INFECTION SUSPECTED? <input type="checkbox"/> Yes <input type="checkbox"/> No WOUND GS/CS TAKEN? <input type="checkbox"/> Yes <input type="checkbox"/> No
DIAGNOSTICS & THERAPEUTICS:	DIAGNOSTICS & THERAPEUTICS:
REMARKS/NOTES:	REMARKS/NOTES:
ASSESSOR'S SIGNATURE:	ASSESSOR'S SIGNATURE:
WC PHYSICIAN SIGNATURE:	WC PHYSICIAN SIGNATURE:

## **The PSGS Evidence-based Clinical Practice Guidelines on the Diagnosis and Initial Management of Cervical Lymphadenopathy**

**Fernando L. Lopez, MD, FPCS<sup>1,2,3</sup>; Ida Marie Tabangay-Lim, MD, FPCS<sup>1,2,3</sup>;  
Alfred Phillip O. de Dios, MD, FPCS<sup>1,4</sup>; Marwin Emerson V. Matic, MD, FPCS<sup>1,5</sup>;  
Rex Jeffrey P. Montecillo, MD, FPCS<sup>1</sup>; Maria Cheryl L. Cucueco, MD, FPCS<sup>1,3</sup> and  
Ma. Luisa D. Aquino, MD, FPCS<sup>3,4,6</sup>**

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<sup>2</sup>Department of Surgery, Faculty of Medicine & Surgery, University of Santo Tomas

<sup>3</sup>Department of Surgery, UST Hospital

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<sup>5</sup>Department of Surgery, De la Salle University Medical Center

<sup>6</sup>Philippine College of Surgeons

The presence of cervical lymphadenopathy is a common condition presenting to the surgeon. This may be associated with various diseases such as an acute bacterial infection in the head and neck region, tuberculosis, or malignancy. There is significant variability among clinicians in the approach to its diagnosis and management because of the lack of evidence-based guidelines which are can be applicable to our local setting. Recognizing this need, the Philippine Society of General Surgeons (PSGS), through the Head and Neck Study Group decided to formulate evidence-based clinical practice guidelines on the diagnosis and initial management of cervical lymphadenopathy.

These guidelines are based on the most recent available scientific evidence and the views of local experts on current practices. They are intended to guide surgeons (fellows and resident trainees) and general physicians who encounter such clinical condition in their practice and assist them in clinical decision making. They are merely recommendations and may be modified according to patients' preferences, socio cultural and other factors that may affect the management of actual patients. These statements are not to be used as a basis for court litigations, administrative sanctions or similar situations. This project was funded solely by PSGS.

### **Executive Summary**

The Technical Working Group (TWG) composed of fellows of PSGS and who are also active members of the Philippine Academy for Head and Neck Surgery, Inc., held a meeting on March 18, 2015 to establish the basic framework of the CPG. Clinical questions to be tackled were formulated and literature search using Medline and HERDIN was done. Key words used for the search included Mesh terms: "cervical lymph node", "cervical lymphadenopathy", "diagnosis", "clinical evaluation", "clinical history", "benign", "malignant", "ultrasound", "CT scan", "fine needle biopsy", "trial of antibiotic therapy". The search yielded 269 articles. Out of the 47 articles considered relevant, 43 articles were available with full text. Critical appraisal was conducted from April to June 2015. On July 11, 2015, the group together with PSGS Committee on Research Chair Dr. Cheryl Cucueco held a meeting to evaluate the level of evidence using Oxford Center for Evidence Based Medicine, 2011. The TWG held several meetings from August to December 2015 to propose a recommendation for each clinical question. The draft of the clinical practice guidelines was prepared from January to March 2016. To ensure acceptability of the guidelines by the other specialties, a multidisciplinary

Panel of Experts was convened on April 30, 2016 to discuss and finalize the recommendations. Six additional articles were provided by the experts. The recommendations were then presented in a public forum last August 5, 2016 during the Philippine Society of General Surgeons' Annual Surgical Forum. The technical writing and editing was done by the current Chair of the Research Committee Dr. Joseph Quebral.

#### Technical Working Group:

1. Fernando L. Lopez, MD (Chairman)
2. Maria Cheryl L. Cucueco, MD  
(Chair, PSGS Committee on Research , 2015 )
3. Alfred Phillip O. de Dios, MD (PSGS, PAHNSI)
4. Ida Marie Tabangay-Lim, MD (PSGSM, PAHNSI)
5. Marwin Emerson V. Matic, MD (PSGS, PAHNSI)
6. Rex Jeffrey P. Montecillo, MD (PSGS, PAHNSI)
7. Ma. Luisa D. Aquino, MD (PCS)

#### Levels of Evidence

#### Grade of the Recommendations

- A- at least 75 percent agree on the recommendation
- B- less than 75 percent agree on the recommendation
- C- disagreement among the experts regarding the recommendation

#### Members of the Expert Panel

Aristotle Peter T. Lee, MD, FPSP, DPSP  
*Pathologist*

Lino S. Pabillo MD, FPCR, FUSP  
*Radiologist, Past President  
Ultrasound Society of the Philippines, 2012-2014*

Ma. Antonia O. Yamamoto, MD, FPAFP, FPCOM  
*Family Physician*

Samantha S. Castañeda, MD, FAHNOP, FPSO-HNS  
*Otorhinolaryngologist-HNS, PAHNSI*

Jose Hesron D. Morfe, MD, FPCP, FPCCP  
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- o TB Service Delivery Specialist, Innovations and Multisectoral Partnership to Achieve Control of TB project
- o Secretary, Philippine Coalition Against Tuberculosis (PhilCAT)

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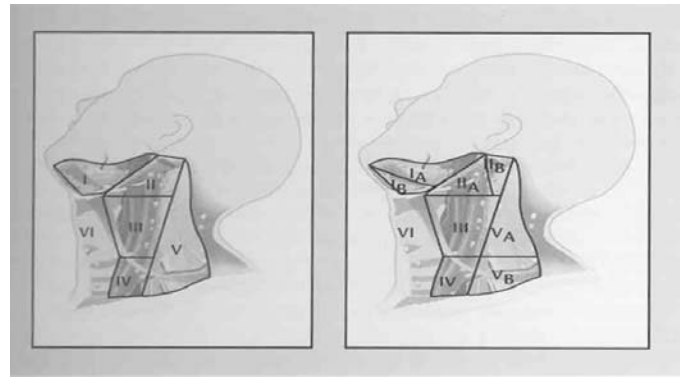
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### Operational Definitions

1. Lymphadenopathy - refers to any condition or disease process involving lymph nodes which are abnormal in size and consistency.
2. Lymphadenitis - lymphadenopathies that are due to inflammatory processes. It is characterized by inflammatory signs: swelling, pain, fever, edema, erythema, and collection of pus.
3. Acute lymphadenitis - 2 weeks in duration
4. Sub-acute lymphadenitis - 2 to 6 weeks duration
5. Chronic lymphadenitis- > 6 weeks duration
6. Non-specific reactive hyperplasia of lymph nodes (NSRH) - a benign reversible enlargement of the lymph node resulting from the proliferation of part or all of its cellular components

The American Head and Neck System for leveling of cervical lymph nodes was utilized.



Source: Shah, JP. Head & Neck Surgery & Oncology, 2003

For the purpose of this guideline, lymphadenopathies were classified according to the duration of its presentation as a guide to its pathology and recommended management approach.

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### Clinical Questions

- I. Among patients with cervical lymphadenopathy, what is the role of history taking and physical examination?
  - Ia. Among patients with cervical lymphadenopathy, what are the clinical manifestations that will support a clinical diagnosis of acute infection?
  - Ib. Among patients with cervical lymphadenopathy what are the clinical manifestations that will support the clinical diagnosis of tuberculous lymphadenopathy?

Ic. Among patients with cervical lymphadenopathy, what are the clinical manifestations that will support the clinical diagnosis of malignancy?

patients presenting with cervical lymphadenopathy. Clinical evaluation is helpful in coming up with a presumptive diagnosis that can guide further management of the lymphadenopathy.

II. Among patients with cervical lymphadenopathy, what is the role of fine needle aspiration cytology (FNAC)?

**Level 5 Category A**

IIa. What is the role of FNAC among patients suspected to have acute lymphadenitis?

The important clinical information to obtain include: patient's age, duration and progression of the lymphadenopathy, symptoms of inflammation and systemic manifestations like fever, malaise, and other associated symptoms like difficulty swallowing, voice change, epistaxis including exposure to an infectious source or known carcinogen.

IIb. What is the role of FNAC among patients suspected to have TB lymphadenitis?

IIc. What is the role of FNAC among patients suspected to have metastatic lymphadenopathy?

**Level 5 Category A**

IId. What is the role of FNAC among patients suspected to have lymphoma?

The important physical findings to take note of include: size, number, consistency, tenderness, location of the lymph nodes; other abnormal findings in the head and neck region like infections, masses and non-healing ulcers among others.

III. Among patients with cervical lymphadenopathy, what is the role of neck ultrasound?

IIIa. What is the role of US among patients suspected to have acute lymphadenitis?

**Level 5 Category A**

IIIb. What is the role of US among patients suspected to have TB lymphadenitis?

A. Among patients with cervical lymphadenopathy, what are the clinical manifestations that will support a clinical diagnosis of acute infection?

IIIc. What is the role of US among patients suspected to have metastatic lymphadenopathy?

Cervical lymphadenopathy of less than two weeks duration, tender, accompanied by fever and symptoms such as nasal discharge or sore throat; dental caries or other infections in the head and neck area point to a septic etiology.

IV. Among patients with cervical lymphadenopathy, what is the role of CT scan of the neck?

**Level 3 Category A**

V. Among patients with cervical lymphadenopathy, what is the role of trial of antibiotic therapy?

B. Among patients with cervical lymphadenopathy, what are the clinical manifestations that will support the clinical diagnosis of tuberculous lymphadenopathy?

Cervical lymphadenopathy that last for more than two weeks, do not resolve with intake of antibiotics, occurring in a patient from a country endemic for TB or with history of TB and/or exposure to TB, possibly

**Summary of Recommendations**

I. Among patients with cervical lymphadenopathy, what is the role of history taking and physical examination?

A comprehensive history and thorough physical examination should be the initial step in evaluating

associated with fever, unintended weight loss, cough with nodes that are usually matted and non-tender, should be suspected as TB lymphadenopathy. In this setting, the presence of a draining sinus is highly suggestive of TB adenitis.

#### Level 4 Category A

- C. Among patients with cervical lymphadenopathy what are the clinical manifestations that will support the clinical diagnosis of malignancy?

Adult patients with risk factors for head and neck cancer, presenting with hard non-tender cervical lymphadenopathy more than 2 cm, more than six weeks duration, should raise the suspicion of malignancy.

#### Level 5 Category A

Among pediatric patients, an increase in size of the lymph nodes over a period of two weeks or non-resolution within six weeks, becoming firm or matted should raise the suspicion of malignancy.

#### Level 5 Category A

- II. Among patients with cervical lymphadenopathy, what is the role of fine needle aspiration cytology (FNAC)?

IIa. What is the role of FNA/FNAC among patients suspected to have acute lymphadenitis

Fine needle aspiration cytology is not indicated in acute lymphadenitis. However, needle aspiration for culture and sensitivity studies is indicated in patients who fail to improve within 48 to 72 hours of antibiotic therapy signifying the possibility of antimicrobial resistance.

#### Level 5 Category A

IIb. What is the role of FNAC among patients suspected to have TB lymphadenitis?

In the absence of evidence of pulmonary TB (PTB) FNAC may be used as a diagnostic procedure in support of TB adenitis.

#### Level 2 Category A

IIc. What is the role of FNAC among patients suspected to have metastatic lymphadenopathy?

FNAC is a useful procedure to confirm metastasis. However, a negative FNAC result warrants further diagnostic procedures.

#### Level 2 Category A

IId. What is the role of FNAC among patients suspected to have lymphoma?

For patients in whom there is a strong clinical consideration of lymphoma, fine needle aspiration cytology is not adequate, hence a tissue biopsy is recommended.

#### Level 3 Category A

III. Among patients with cervical lymphadenopathies, what is the role of neck ultrasound?

Among patients with equivocal clinical findings, high resolution grey scale ultrasound with power Doppler is useful in determining the characteristics of the lymph nodes to help in its diagnosis.

#### Level 2 Category A

IV. Among patients with cervical lymphadenopathies, what is the role of neck CT scan?

Neck CT scan is not recommended as a first line diagnostic test but is useful in staging patients with head and neck cancer.

#### Level 2 Category A

V. Among patients with cervical lymphadenopathies, what is the role of trial of antibiotic therapy?

Trial of antibiotic therapy should be given only to patients suspected of having bacterial cervical lymphadenitis.

Antimicrobials given to patients with bacterial cervical lymphadenitis should cover for gram-positive microorganisms.

Re-assessment is performed if there is no improvement or there is worsening of the symptoms.

#### **Level 4 Category A**

##### **Summary of Evidence**

- I. Among patients with cervical lymphadenopathy, what is the role of history taking and physical examination?

A comprehensive history and thorough physical examination should be the initial step in evaluating patients presenting with cervical lymphadenopathy. Clinical evaluation is helpful in coming up with a presumptive diagnosis that can guide further management of the lymphadenopathy.

#### **Level 5 Category A**

The important clinical information to obtain include: patient's age, duration and progression of the lymphadenopathy, symptoms of inflammation, and systemic manifestations like fever, malaise, and other associated symptoms like difficulty swallowing, voice change, epistaxis including exposure to an infectious source or known carcinogen.

#### **Level 5 Category A**

The important physical finding to take note of include: size, number, consistency, tenderness, location of the lymph nodes; other abnormal findings in the head and neck region like infections, masses and non-healing ulcers among others.

#### **Level 5 Category A**

- A. Among patients with cervical lymphadenopathy, what are the clinical manifestations that will support a clinical diagnosis of acute infection?

#### **Recommendation**

Cervical lymphadenopathy of less than two weeks duration, tender, accompanied by fever and symptoms such as nasal discharge or sore throat; dental caries or other infections in the head and neck area point to an infectious cause.

#### **Level 3 Category A**

- B. Among patients with cervical lymphadenopathy, what are the clinical manifestations that will support the clinical diagnosis of tuberculous lymphadenopathy?

#### **Recommendation**

Cervical lymphadenopathy that last for more than two weeks, do not resolve with intake of antibiotics, occurring in a patient from a country endemic for TB or with history of TB and/or exposure to TB, possibly associated with fever, unintended weight loss, cough with nodes that are usually matted and non-tender, should be suspected as TB lymphadenopathy. In this setting, the presence of a draining sinus is highly suggestive of TB adenitis.

#### **Level 4 Category A**

- C. Among patients with cervical lymphadenopathy what are the clinical manifestations that will support the clinical diagnosis of malignancy?

Adult patients with risk factors for head and neck cancer, presenting with hard non-tender cervical lymphadenopathy more than 2 cm, more than six weeks duration, should raise the suspicion of malignancy.

#### **Level 5 Category A**

Among pediatric patients, an increase in size of the lymph nodes over a period of two weeks or non-resolution within six weeks, becoming firm or matted should raise the suspicion of malignancy.

## Level 5 Category A

### Summary of Evidence

The etiology of cervical lymphadenopathy is varied. It may be an acute infection in the head and neck area, tuberculosis or metastasis either from a known or unknown primary in the head and neck region. It can be categorized as inflammatory/reactive or neoplastic. A thorough history and comprehensive physical examination should always be the first step to help the clinician obtain relevant data to determine the possible etiology and thereby assist in the decision-making regarding the use of diagnostic tests or treatment options to offer.<sup>1-5</sup>

Among the information which can be gathered, the age of the patient, duration of the symptoms, progression of the lymphadenopathy, as well as symptoms of either inflammation with or without systemic manifestations like fever, malaise, or other associated symptoms like difficulty swallowing, voice change, epistaxis can point to its possible cause.

History of environmental exposures can also strengthen one's clinical suspicion like living in an endemic area for TB or exposure to person with TB or exposure to risk factors for head and neck cancer such as smoking and alcohol and provide a good starting point to help the physician in the step by step work-up when required, including laboratory tests, imaging modalities, and tissue diagnosis to reach an appropriate diagnosis.

Physical examination findings which include the size, number, consistency, location of the lymph nodes; and other abnormal findings in the head and neck area like dental caries, inflamed tonsillopharyngeal area or the presence of a mass or non-healing ulcer are also useful in determining the etiology of the lymphadenopathy.

### Age

Malignancy as a cause of lymphadenopathy is not common among children but increases with age.<sup>6</sup> Among the benign causes, only 39% can be attributed to a specific etiology while 61% are of unknown origin.<sup>7</sup> In a review by Mohsen, the prevalence of malignancy

was 0.4% in patients under 40 years old and 4% in those over 40 years old in the primary care setting, with increasing prevalence to 17% in referral centers and further increases to 40-60% in highly suspicious patients.

### Duration of Symptoms

A lymph node which is only less than two weeks in duration or already a year long but with a stable size has a low probability of being malignant.<sup>6</sup> Acute lymphadenopathy in the pediatric age group are usually benign (98.2%). Malignancy and tuberculosis usually present as chronic lymphadenopathy.<sup>7</sup>

### Related Symptoms and Signs

A recent upper respiratory tract infection, fever, or pharyngitis points to an infectious cause of the lymphadenopathy. Significant fever, night sweats, and unexplained weight loss are the "B" symptoms of lymphomas but may also be associated with TB or collagen vascular diseases.<sup>6,7</sup> Patients with a known diagnosis of head and neck cancer or those with dysphagia, change in voice quality or hoarseness should increase the suspicion of metastatic lymphadenopathy.

### Exposure

TB is a common cause of lymphadenopathy in adults and children living in tropical and endemic areas.<sup>8-10</sup> A history of exposure to tobacco, alcohol and ultraviolet radiation should make the clinician suspect the possibility of head and neck, and skin cancer.<sup>6</sup>

### Location

Lymphadenopathy in the supraclavicular area has been noted to be associated with a higher risk for malignancy<sup>6,11</sup> especially in older age groups: 90% in patients more than 40 years old and 25% in those under 40 years old.<sup>2</sup> The same high association between a supraclavicular location of a node and malignancy has been noted in pediatric patients ( $p = 0.008$ ).<sup>7,12</sup>

**Size**

Based on several studies, there is no uniform nodal size at which one should suspect malignancy but there are some useful guides. A lymph node larger than 1 cm is considered a lymphadenopathy although this varies by lymphatic region. Cervical nodes more than 1.5 cm in diameter are considered abnormal except if they are in the submental or submandibular area.<sup>2,13</sup> Palpable supraclavicular nodes of any size are considered abnormal. Maximum diameters of more than 1.5 cm to 2 cm, has been recommended by Bazemore as an appropriate starting point for high suspicion of malignant or granulomatous disease. However, a more important basis to consider malignancy is the increase in size or persistence over time rather than a specific degree of nodal enlargement.<sup>6</sup> In the series by Oguz, the size associated with malignancy was more than 3 cm (p=0.001).<sup>7</sup>

**Tuberculous Lymphadenopathy**

Tuberculous lymphadenopathy should be among the considerations in a cervical node which has been present for more than two weeks in duration and especially if it happens in an endemic region.<sup>9,10,14</sup> In the study by Jha, the 11-30 year old age group was commonly involved. Majority of the patients were from the lower socioeconomic group. For the physical finding, most of the patients had matted nodes. The nodal groups commonly involved were the upper deep jugular, jugulodigastric and jugulo-omohyoid groups.<sup>10</sup>

**Cervical Lymphadenopathy Due to Malignancy**

Even when there are no other clinical signs of malignancy, the possibility of malignancy can be as high as 38%. In a review of 95 patients who underwent open lymph node biopsy clinical factors such as age, sex, history of alcohol and tobacco use, location of the mass, number, size and duration of the mass were analyzed on their ability to predict the presence of neoplasia and malignancy using logistic regression analysis. There were 30 cases of new growth (31.6%) and 12 cases of cancer (12.6%).<sup>15</sup> Statistically significant predictors for

neoplasia were patient age, duration and size of the mass with estimated odds ratios as follows: an increase in odds of 1.42 (95% CI 1.05-1.90) for each 10-year increase in age, 1.08 (95% CI, 0.99-1.17) for each 10-week increase in duration, and 1.50 (95% CI 1.11-2.02) for each centimeter increase in size.

The overall model for neoplasia had positive and negative predictive values of 63.6% and 78.1%, respectively, and an overall accuracy of 74.7%. However, for prediction of malignancy, age turned out to be the only statistically significant factor. Logistic regression analysis for malignancy of the neck mass found only patient age and a constant to be significant (p < 0.05 for significance of log-rank model improvement).

The estimated odds ratio increased by 1.66 (95% CI 1.15-2.41) times for each 10-year increase in age.

**Table 1.** Descriptive statistics for independent variables.

Clinical Variable	Finding	Univariate Significance* for Neoplasia	Univariate Significance* for Malignant Neoplasm
Categorical, No. (%)			
Sex†		.38	.82
Male	29 (30.5)		
Female	66 (69.5)		
Ever smoked†	29 (30.5)	.58	.66
Never smoked	66 (69.5)		
Smoking at time of biopsy	16 (16.8)		
Heavy alcohol use	4 (4.2)		
Location†		.14	.76
Regions II-IV and VI	52 (54.7)		
Region V	10 (10.5)		
Region I	33 (34.7)		
Bilateral masses	14 (14.7)		
Continuous, mean (range)			
Age, y†	42.2 (2.0-85.0)	.002	.01
Duration of mass, wk†	38.4 (0.5-572.0)	.06	.63
No. of masses†	1.45 (1.0-5.0)	.53	.52
Size, cm†	2.81 (0.5-10.0)	<.001	.04

\*For categorical variables, significance corresponds to significance of Pearson  $\chi^2$  statistics; for continuous variables, to significance of Student t test.

†Variable analyzed in the regression model.

Reference: Bhattacharyya N. , 1999

In another retrospective study by Aribas using ultrasound guided FNAC result as the reference standard, associated predictors for the presence of malignancy in

lymph nodes include the presence of primary malignancy ( $p < 0.001$ ), mid neck and lower neck localizations as Level 3-6 ( $p = 0.001$ ), and markedly hypoechoic lymph nodes ( $p < 0.001$ ). Age, gender, microcalcification, cystic feature, minimum size, and index value seem to be poor predictors in malignancy.<sup>16</sup> Another study among pediatric patients identified these factors predictive of malignancy: lymph node size greater than 2cm, multiple levels of adenopathy and supraclavicular location. In these cases, biopsy should be performed.<sup>17</sup>

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II. Among patients with cervical lymphadenopathy, what is the role of FNAC?

IIa. What is the role of FNA/FNAC among patients suspected to have acute lymphadenitis?

Fine needle aspiration cytology is not indicated in acute lymphadenitis. However, needle aspiration for culture and sensitivity studies is indicated in patients who fail to improve within 48 to 72 hours of antibiotic therapy signifying the possibility of antimicrobial resistance.

## Level 5 Category A

IIb. What is the role of FNAC among patients suspected to have TB lymphadenitis?

In the absence of pulmonary TB (PTB) FNAC may be used as a diagnostic procedure in support of TB adenitis.

## Level 2 Category A

IIc. What is the role of FNAC among patients suspected to have metastatic lymphadenopathy?

FNAC is a useful procedure to confirm metastasis. However, a negative FNAC result warrants further diagnostic procedures.

## Level 2 Category A

IId. What is the role of FNAC among patients suspected to have lymphoma?

For patients in whom there is a strong clinical consideration of lymphoma, fine needle aspiration cytology is not adequate, hence a tissue biopsy is recommended.

### Level 3 Category A

#### Summary of Evidence

An empiric antimicrobial therapy is usually initiated for patients suspected to have acute lymphadenitis. Needle aspiration for culture and sensitivity studies is indicated for patients who have failed to improve within 48 to 72 hours, which may signify a resistant organism.<sup>1</sup> Needle aspiration may also be an effective and safe method of draining suppurative cervical lymphadenitis and avoid open drainage.<sup>2</sup>

Fine needle aspiration cytology (FNAC) may be used as an initial diagnostic procedure in detecting tuberculosis. Although it has a high specificity, its disadvantage is the variable sensitivity in different studies. Studies have shown statistically significant differences in the sensitivity when compared to core needle and excision biopsies ( $p = 0.0003$  and  $p < 0.0001$ , respectively).<sup>4</sup> Performing different stains, such as the Romanowsky's method (Wright's stain) for cytological diagnosis and Ziehl Nielsen (hot method) for the identification of acid-fast bacilli increases the diagnostic accuracy. Submitting some material for culture can further increase the diagnostic accuracy.<sup>5</sup>

In cases where FNAC results are non-diagnostic, excision biopsy should be performed.<sup>6,7</sup>

Fine needle aspiration cytology (FNAC) is very specific, but sensitivity varies in among different studies to the extent such that it cannot yet be relied upon to exclude malignancy. The overall diagnostic sensitivity, specificity, positive predictive value and negative predictive value of FNAC of cervical lymph nodes were 90.9%, 67.2%, 82.6% and 81.3%, respectively. If any of the clinical, radiological or laboratory findings is suspicious, then further investigation is justified.<sup>8</sup> In case of malignancies, the histopathologic correlation is 100%.<sup>9</sup> Due to its high specificity, FNAC has proven to be a good first line method in identifying malignancy in lymph nodes. However, a negative result may not automatically exclude malignancy and may warrant further investigation, such as excision biopsy. For patients in whom there is a strong clinical consideration of lymphoma, fine needle aspiration cytology alone is not sufficient in classifying the different subtypes of lymphoma and

significantly delays obtaining the definitive diagnosis as compared to doing an excision biopsy at the onset.<sup>10</sup>

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### III. Among patients with cervical lymphadenopathy, what is the role of neck ultrasound?

Among patients with equivocal clinical findings, high resolution grey scale ultrasound with power Doppler is useful in determining the characteristics of the lymph nodes to help in its diagnosis.

### Level 2 Category A

#### Summary of Evidence

Conventional ultrasound is presently being used as an adjunct in the evaluation of patient's presenting with cervical lymphadenopathy. This is especially useful when the clinical findings are expected to result in a definitive

diagnosis. Although the use of ultrasonography is now accepted as one of the techniques in the routine evaluation of cervical lymph nodes one drawback is that reporting is not usually standardized and the results are dependent on the user's experience.<sup>1</sup>

A cross-sectional study involving 50 patients who underwent CT examination and subsequent extended field-of-view (EFOV-US) showed that this technique of ultrasonography is comparable to CT scan in detecting the presence of cervical lymphadenopathy. The sensitivity increases the more caudal to the carotid bifurcation (Tables 1 & 2) and there is a strong linear correlation between rates of detection of CT and EFOV-US (Pearson's coefficient = 0.98,  $p < 0.001$ ).<sup>1</sup>

**Table 1.** Detection rate of enlarged cervical lymph node by CT and parallel scanned EFOV-US sequences (Beissert, 2000).

	CT	EFOV-US
Caudal to carotid bifurcation	79	78
Cranial to carotid bifurcation	166	160
Total	245	238

\* data is about number of lymph nodes

**Table 2.** False positive and false negative lymph nodes in parallel scanned EFOV-US sequences (Beissert, 2000).

	CT	EFOV-US
Caudal to carotid bifurcation	1	2
Cranial to carotid bifurcation	9	15
Total	10	17

\* data is about number of lymph nodes

Compared to palpation, ultrasonography has a higher sensitivity (97% to 73%) as shown in one non-systematic review.<sup>2,3</sup> Shown below are the different features differentiating a benign from a malignant lymph node as presented in this non-systematic review.<sup>2</sup>

Several considerations were emphasized by the review. No consensus on the cut-off point for size has been established. The articles advocated the use of comparative increase in size during serial examination. This however, would become a problem if an immediate diagnosis is needed. Shape should not be used as a single criterion since normal submandibular and parotid nodes are round. Half of metastatic nodes may have an echogenic hilus.<sup>2</sup> The evaluation of the vascular pattern

**Table 3.** Sonographic features of benign and malignant neck nodes (Ying, 2013).

Sonographic features	Benign nodes	Malignant nodes
Size	Persistent or slight changes in serial examinations	Increase in serial examinations
Shape	Elliptical (S/L <0.5)	Round (S/L >0.5)
Nodal border	Unsharp	Sharp, Proven malignant nodes with unsharp borders indicate extracapsular spread
Echogenic hilus	Present	Absent
Echogenicity	Hypoechoic	Hyperechoic in metastatic nodes from papillary thyroid carcinoma. Other malignant nodes tend to be hypoechoic
Intranodal reticulation	Absent	Common in lymphomatous nodes
Intranodal calcification	Absent	Punctate and peripherally located calcification is common in metastatic nodes from papillary thyroid carcinoma
Intranodal cystic necrosis	Common in tuberculous nodes	Common in metastatic nodes from papillary thyroid carcinoma and squamous cell
Matting	Common in tuberculous nodes	May be found in patients with previous neck radiation therapy
Adjacent soft tissue edema	Common in tuberculous nodes	May be found in patients with previous neck radiation therapy. May be found in malignant nodes with extracapsular spread
Intranodal vascular pattern	Hilar vascularity or apparently avascular	Peripheral or mixed vascularity
Stiffness	Soft	Hard

can help differentiate metastatic from reactive nodes (sensitivity: 83-89%; specificity: 87-100%). It is also effective in differentiating lymphomatous and reactive nodes (sensitivity: 67%; specificity: 100%). This then could increase the diagnostic accuracy for those with equivocal ultrasound findings.<sup>2</sup>

A cross-sectional study, involving 158 neck masses in 100 patients, evaluated six ultrasound features and correlated each individually and in combination to the histopathological report. Features included the following: 1) echogenicity; 2) border; 3) size; 4) necrosis; 5) shape; and 6) vascular pattern. Hypoechoic echogenicity, a sharply demarcated border, size > 1 cm, round contour, presence of necrosis and abnormal vascular pattern were considered features of a malignant cervical lymph node.<sup>3</sup>

Assessed individually, each feature was found to give significant results in differentiating between a benign and malignant cervical nodes as seen in Table 4 below. Their combination increases the sensitivity, specificity, PPV and NPV significantly.

Another cross-sectional study (4) involving 192 patients undergoing ultrasound examination and subsequent confirmation by fine needle aspiration cytology further enumerated features that could help establish the diagnosis (TB, metastatic, lymphoma and reactive). This is shown in Table 5.

Although average L/S ratio showed significant difference, the use of this feature may not be that accurate as seen from the range of findings that one could obtain. As can be seen from the table the absence of fusion tendency, peripheral halo and internal echoes can help in ruling out a reactive node. Aside from this the following features have also been shown to have low incidence in reactive nodes: irregular margins, hypoechoic center, and absent hilus.

To differentiate lymphoma from TB or metastatic nodes, the following features can be used: presence of a peripheral halo and internal echoes. As can be seen from the table, the incidence of these findings in lymphoma is less than 10%.

**Table 4.** Morphological characteristics compared to pathologic results/biopsy (Genes, 2014).

%	Echogenicity	Border	Shape	Size	Necrosis	Vascular pattern	Six features
Sensitivity	78.07	39.47	84.21	73.68	35.96	97.37	95.24
Specificity	77.27	54.47	52.47	68.88	100	47.73	100
PPV	69.9	82.05	82.05	85.71	100	82.84	100
NPV	57.63	56.1	56.1	50	37.61	87.5	95.24

PPV – Positive predictive value; NPV – Negative predictive value.

**Table 5.** Ultrasonographic findings correlated with tissue diagnosis in cervical lymph Nodes of 192 patients (Khanna, 2011).

Characteristics	Tubercular (n = 62)	Metastatic (n = 18)	Lymphoma (n = 14)	Reactive (n = 98)	p value
L/S Ratio	1.8 ± 0.6	1.2 ± 0.3	1.5 ± 0.4	2.2 ± 0.9	<0.01
Irregular margins	41 (66%)	10 (55%)	3 (21%)	7(7%)	>0.01
Hypoechoic center	48 (77%)	1 (61%)	3 (21%)	8(8%)	>0.01
Fusion tendency	>0 (81%)	12 (66%)	2 (14%)	Nil	>0.01
Peripheral halo	52 (84%)	10 (55%)	1 (7%)	Nil	<0.01
Internal echoe	52 (84%)	2 (11%)	Nil	Nil	<0.001
Absent hilus	16 (26%)	15 (83%)	4 (28%)	9(9%)	<0.01

The 'p values' compare the significance of difference between metastatic and lymphomatous nodes considered together versus the tubercular lymph nodes.

**References**

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IV. Among patients with cervical lymphadenopathies, what is the role of neck CT scan?

Neck CT scan is not recommended as a first line diagnostic test but is useful in staging patients with head and neck cancer.

**Level 2 Category A**

**Summary of Evidence**

Most of the articles which came out in the search utilized CT scan in the management of diagnosed cases of head and neck cancer to evaluate the extent of the tumor and regional nodes which is quite different from our scenario of a clinical presentation of lymphadenopathy and diagnosis is not certain yet. One cross sectional study by Sarvanan involving patients with head and neck malignancy and palpable lymph nodes (N = 26 (neck sides) set the following criteria to label the node as metastatic: 1) size- 11mm or greater in transverse plane; 2) central hypodensity with peripheral rim enhancement; 3) conglomeration of nodes in the drainage of the primary; and 4) loss of fat plane between nodes and carotid artery was considered as carotid artery invasion.

The results of the study by Sarvanan showed that clinical examination had a comparable sensitivity of 92.3% compared to ultrasound (94.44%) and CT scan (94.11 %) in determining whether a lymph node is metastatic. The specificity of clinical exam is slightly better at 79.17% compared with CT (66.66%) but less

specific than ultrasound (100%). Based on these results, clinical examination should still be the primary method of evaluating the possible presence of metastatic nodes.

**Table 6.** Sensitivity and specificity of CT scan criteria for metastatic lymph node. (Sarvanan, 2002)

Criteria	Sensitivity	Specificity
Size 11 mm or greater	88.3	66.67
Presence of lymph node mass/ conglomeration	100	100
Central necrosis	94.11	100
Carotid artery invasion	75	100

**References**

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V. Among patients with cervical lymphadenopathies, what is the role of trial of antibiotic treatment?

Trial of antibiotic therapy should be given only to patients suspected of having bacterial cervical lymphadenitis.

Antimicrobials given to patients with bacterial cervical lymphadenitis should cover for gram-positive microorganisms.

Re-assessment is performed if there is no improvement or there is worsening of the symptoms.

**Level 4 Category A**

**Summary of Evidence**

Fifteen papers were appraised and reviewed for this section. These included two systematic reviews, one

cohort study, three cross-sectional studies, two case series and seven non-systematic reviews. Several of the papers had patients less than 18 years of age as their subjects. These included both systematic reviews, one cross-sectional study, one case series and three non-systematic reviews.

Generally, the initial management of cervical lymphadenitis is based on an accurate clinical diagnosis. All the articles reviewed stated that the treatment of cervical lymphadenitis varies depending on the etiology and clinical presentation of the patients.

In one review involving subjects of all ages that were seen by a primary care physician, most patients presenting with a neck mass were caused by inflammatory disorders. These masses usually resolved by themselves or disappeared following a course of antibiotics.<sup>1</sup>

It is therefore important to determine the underlying cause. This was supported by two reviews, one involving patient of all ages and other involving children.<sup>2,3</sup> A viral etiology is considered in patients presenting with bilateral cervical lymphadenitis. This is usually associated with an upper respiratory infection.<sup>4</sup> This is especially true in children as shown in the review of Brook<sup>5</sup> and Gosche.<sup>2,5</sup> In such conditions specific therapy is not indicated as most of these cases are self-limited and resolve with no treatment.<sup>2,3,5,6</sup> Most of these cases can be safely monitored but require close observation.<sup>1,7</sup> Treatment is supportive, directed at relieving the symptoms associated with the viral illness.

If the presenting symptom is a unilateral cervical lymphadenitis, the primary cause is a gram-positive bacterium. Most authors agree that this is the only condition where initial empiric antimicrobial therapy is acceptable.<sup>2-6,8-11</sup> Giving empiric antibiotic therapy will prevent abscess formation.<sup>2</sup> The most common organisms involved in bacterial cervical lymphadenitis without any known primary source are *Staphylococcus aureus* and group A beta-hemolytic *Streptococci*. For this reason, empiric antibiotic therapy for these patients should provide adequate coverage for gram-positive microorganisms. In one systematic review, a single antimicrobial agent given orally should be sufficient in immunocompetent patients.<sup>7</sup> Treatment is administered for a minimum of 10 days to a maximum of 14 days.<sup>5-7,11</sup> In most observed cases, symptomatic improvement was noted 2 to 3 days

after the initiation of treatment. It is then recommended that patients are followed up within 48 to 72 hours to assess clinical response. Immediate resolution of nodal enlargement is not expected until 4 to 6 weeks after treatment.<sup>5,11</sup>

When a primary source of infection has been identified, empiric antimicrobial therapy has to be adjusted.<sup>2,3</sup> Cultures from the primary site should be obtained and antimicrobial treatment adjusted according to the results of the culture and sensitivity test.<sup>2,5,11</sup> If the primary site is in the oral cavity, specifically, periodontal disease, coverage should include anaerobes. A referral to a dental specialist is warranted.<sup>3-5,11</sup> For patients presenting with moderate or severe symptoms, empiric antibiotic treatment is given parenterally and adjusted once culture and sensitivity results are in.<sup>2,5,6,8</sup>

Lack of clinical improvement or worsening of the patient's condition after initial evaluation should prompt re-assessment.<sup>3,5,6</sup> Several ancillary tests should be considered, including aspiration and culture of the node or a diagnostic biopsy.<sup>3,5,6,11</sup> Failure to improve may indicate infection with a resistant or a rare organism and possible noninfectious cause of cervical lymphadenitis.<sup>11</sup> For general practitioners or primary care physicians it is recommended that a referral to an appropriate specialist be made.<sup>1</sup>

In patients where tuberculous cervical lymphadenitis is suspected there is no role for empiric therapy. All the papers reviewed recommend confirmation of the diagnosis before starting definitive treatment.<sup>12-14</sup>

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