GUIDELINES

Guidelines to aid healing of acute wounds by decreasing impediments of healing

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Achieving uniformity in the care rendered to patients with wounds has been a major desire of clinicians, government regulators, and third-party payers.[1] One of the goals of the founders of the Wound Healing Society (WHS) in 1991 was to establish guidelines for wound treatment. One of the first tasks of the WHS Board of Directors following the first annual meeting in Galveston, TX, was to appoint a committee to develop treatment guidelines.[1] This committee, under the direction of Gerald S. Lazarus, MD, realized that uniform care guidelines could not be developed because there was no uniformity in the definitions of wounds, wound healing, or wound attributes. The committee developed the necessary definitions and after several public hearings, the article "Definitions and guidelines for assessment of wounds and evaluation of healing" was published in 1994.[2]

That publication defined an acute wound as one that proceeds through an orderly and timely reparative process to establish sustained anatomic and functional integrity, and defined a chronic wound as one that has failed to proceed through an orderly and timely reparative process to produce anatomic and functional integrity or has proceeded through the repair process without establishing a sustained anatomic and functional result.[2] Simply stated, wounds may be classified as those that can repair themselves or can be repaired in an orderly and timely process (acute wounds) and those that cannot (chronic wounds).

In 2006, the WHS published "Guidelines for the best care of chronic wounds."[1] The chronic wounds chosen for treatment guideline development were venous, diabetic, arterial, and pressure ulcers. Because chronic wounds have impaired healing, evidence-based guidelines were developed to maximize healing trajectories and accelerate healing where possible. However, acute wounds are much more numerous than chronic wounds. There are 50,000,000 elective surgical incisions made each year in the United States, and another 50,000,000 traumatic wounds.[3] Add to this 1 million burn injuries and the scope of the problem becomes clear. As opposed to the chronic wound, healing in the acute wound is taken for granted.[4] It is assumed that if one debrides a wound of nonviable tissue and repairs it in a physiologic manner, the normal phases of wound healing—reaction, regeneration, remodeling—should proceed without difficulty.[3,4,5]

Acute wounds are expected to heal with a "normal" wound healing trajectory[3]; hence, accelerating healing has not been the goal in their treatment. Rather, the goal has been to remove detriments or deterrents to normal healing and eliminate the complications that may prevent an orderly and timely reparative process that could convert the acute wound into a chronic wound.

A panel was appointed to develop guidelines to "aid healing of acute wounds by decreasing impediments to healing." The panel consisted of general, vascular, plastic, trauma, burn, and cancer surgeons, nurse clinicians, and researchers drawn from academic, governmental, private practice, and industrial settings. These panel members represented most scientific, medical, and nursing societies/associations that have wound care as a major scope of interest. The panel limited the scope of acute wound healing to integument and soft tissue, and did not address bone, cartilage, neural tissue, or internal organs.

REFERENCES

1. Robson MC, Barbul A. Guidelines for the best care of chronic wounds. *Wound Rep Regen* 2006; 14: 647–8.
2. Lazarus GS, Cooper DM, Knighton DR, Margolis DJ, Pecoraro RE, Rodeheaver G, Robson MC. Definitions and guidelines for the assessment of wounds and evaluation of healing. *Arch Dermatol* 1997; 130: 489–93.
3. Franz MG, Steed DL, Robson MC. Optimizing healing of the acute wound by minimizing complications. *Curr Prob Surg* 2007; 44: 679–766.

4. Robson MC. Wound infection: a failure of wound healing caused by an imbalance of bacteria. *Surg Clin North Am* 1997; 77: 637–50.
5. Robson MC. Disturbances in wound healing. *Ann Emerg Med* 1988; 17: 1274–8.

METHODS

Previous guidelines, meta-analyses, PubMed, MEDLINE, EMBASE, The Cochrane Database of Systematic Reviews, recent review articles of management of acute wounds and their complications were all searched and reviewed for evidence. Guidelines were formulated, the underlying principle(s) enumerated, and evidence references listed and coded. The code abbreviations for the evidence citations are as follows:

STAT	Statistical analysis, meta-analysis, consensus statement by commissioned panel of experts
RCT	Randomized clinical trial
LIT REV	Literature review
CLIN S	Clinical case series
RETRO S	Retrospective series review
EXP	Laboratory or animal study
TECH	Technique or methodology description
PATH S	Pathological series review

The approach used for evidence citations was the same as for the chronic wound guidelines. Major differences exist between this approach to evidence citations compared with past approaches to evidence-based guidelines. Most past approaches relied only on publications regarding clinical human studies. Laboratory or animal studies were not cited. The approach used here and in the previously published guidelines for treatment of chronic wounds used well-controlled animal studies that present proof of principle, especially when a clinical series corroborated the laboratory results. Because of these variations, a different system was used to grade the evidence weight supporting a given guideline. The level strength of evidence supporting a guideline is listed as Level I, Level II, or Level III. The guideline criteria for the levels are:

- *Level I*: Meta-analysis of multiple RCTs or at least two RCTs support the intervention of the guideline. Another route would be multiple laboratory or animal experiments with at least two clinical series supporting the laboratory results.
- *Level II*: Less than Level I, but at least one RCT and at least two significant clinical series or expert opinion papers with literature analysis, RCT, or multiple clinical series.
- *Level III*: Suggestive data of proof of principle, but lacking sufficient data such as meta-analysis, RCT, or multiple clinical series.
- *NB*: The suggestion in the guideline can be positive or negative at the proposed level (e.g., meta-analysis and two RCTs stating intervention is not an aid for decreasing impediments to healing).

RESULTS

Guidelines have been formulated in 11 categories of impediments to acute wound healing reported to lead to significant complications to normal tissue repair. The categories have been separated into five impediments that are *local* to the wound environment and six that are *systemic* conditions affecting the healing of acute wounds. These categories are:

Local:

- Wound perfusion
- Tissue viability
- Hematoma and/or seroma
- Infection
- Mechanical factors

Systemic:

- Immunology
- Oncology
- Miscellaneous systemic conditions
- Thermal injuries
- External agents
- Excessive scarring

Each of the guidelines underwent a DELPHI consensus among the panel members. Each set was critically evaluated by all panel members. There was a consensus of at least 10 of 11 panel members on each individual guideline. The majority of the guidelines had unanimous concurrence. The resultant draft, ''Guidelines to aid healing of acute wounds by decreasing impediments to healing,'' was then reviewed by the WHS Board of Directors and posted on its website for public review and comment. All comments received by these two review processes were evaluated and modifications were made in the final document. The final document is presented as follows:

- #1: Guidelines to decrease the impediment to acute wound healing caused by inadequate wound perfusion
- #2: Guidelines to decrease the impediment to acute wound healing caused by nonviable tissue
- #3: Guidelines to decrease the impediment to acute wound healing caused by wound hematoma or seroma
- #4: Guidelines to decrease the impediment to acute wound healing caused by infection or an increased tissue bioburden
- #5: Guidelines to decrease the impediment to acute wound healing caused by mechanical factors during wound repair
- #6: Guidelines to decrease the impediment to acute wound healing caused by systemic immune deficiencies
- #7: Guidelines to decrease the impediment to acute wound healing caused by cancer and its treatment
- #8: Guidelines to decrease the impediment to acute wound healing caused by systemic conditions such as diabetes mellitus, obesity, malnutrition, etc
- #9: Guidelines to decrease the impediment to acute wound healing caused by burn injuries
- #10: Guidelines to decrease the impediment to acute wound healing caused by external agents such as tobacco, drugs, etc.

- #11: Guidelines to decrease the impediment to acute wound healing caused by excessive scar formation

#1: GUIDELINES TO DECREASE THE IMPEDIMENT TO ACUTE WOUND HEALING CAUSED BY INADEQUATE WOUND PERFUSION

Preamble: Adequate blood supply is a *sine qua non* to normal wound healing and tissue repair. Inadequate wound perfusion can occur from systemic causes, regional causes, and local causes.

Guideline #1.1: Clinically significant arterial disease should be ruled out, preferably before wounding. In the lower extremity, this can be done by establishing that pedal pulses are clearly palpable or that the ankle–brachial index (ABI) is > 0.9. An ABI > 1.3 suggests noncompressible arteries. In elderly patients or patients with an ABI > 1.2, a normal Doppler-derived wave form, a toe–brachial index of > 0.7 or a transcutaneous oxygen pressure of > 40 mmHg may help to suggest adequate arterial flow. Color duplex ultrasound scanning provides anatomic and physiologic data confirming an ischemic etiology for the leg wound.

Level of evidence: I

Principle: Ischemia hinders healing and increases the risk of infection. Although clinical history and physical examination can be very suggestive of ischemia, a definitive diagnosis must be established before undertaking a course of treatment. Successful healing requires that arterial insufficiency be addressed.

Evidence:

1. Hirsch A, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, Hiratzka LF, Murphy WRC, Olin JW, Puschett JB, Rosenfield KA, Sacks D, Stanley JC, Taylor LM, White CJ, White J, White RA, Antman EM, Smith SC, Adams CD, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA Guidelines for the Management of Patients with Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic): A Collaborative Report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society for Vascular Medicine and Biology, and the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease). American College of Cardiology Web Site. Available at: http://www.acc.org/clinical/guidelines/pad/index.pdf. (STAT)
2. Sahli D, Eliasson B, Svensson M, Blohmé G, Eliasson M, Samuelsson P, Ojbrandt K, Eriksson JW. Assessment of toe blood pressure is an effective screening method to identify diabetes patients with lower extremity arterial disease. *Angiology* 2004; 55: 641–51. (CLIN S)
3. Teodorescu V, Chen C, Morrissey N, Faries PL, Marin ML, Hollier LH. Detailed protocol of ischemia and the use of noninvasive vascular laboratory testing in diabetic foot ulcers. *Am J Surg* 2004; 187: 75S–80S. (LIT REV)
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6. Padberg FT, Back TL, Thompson PN, Hobson RW. Transcutaneous oxygen ($TcPO_2$) estimates probability of healing in the ischemic extremity. *J Surg Res* 1996; 60: 365–9. (CLIN S)
7. Butler CM, Ham RO, Lafferty K, Cotton LT, Roberts VC. The effect of adjuvant oxygen therapy on transcutaneous pO_2 and healing in the below-knee amputee. *Prosthet Orthot Int* 1987; 11: 10–6. (RCT)
8. Bercelli SA, Chan AK, Pomposelli FB Jr, Gibbons GW, Campbell DR, Akbari CM, Brophy DT, LoGerfo FW. Efficacy of dorsal pedal artery bypass in limb salvage for ischemic heel ulcer. *J Vasc Surg* 1999; 30: 499–508. (RETRO S)
9. Lopantalo M, Biancari F, Tukiainen E. Never amputate without consultation of a vascular surgeon. *Diabetes Metab Res Rev* 2000; 16 (Suppl. l): S27–32. (LIT REV)
10. Attinger CE, Ducic I, Neville RF, Abbruzzese MR, Gomes M, Sidawy AN. The relative roles of aggressive wound care versus revascularization in salvage of the threatened lower extremity in the renal failure diabetic patient. *Plast Reconstr Surg* 2002; 109: 1281–90. (CLIN S)
11. Moosa HH, Makaroun MS, Peitzman AB, Steed DL, Webster MW. $TcPO_2$ values in limb ischemia: effects of blood flow and arterial oxygen tension. *J Surg Res* 1986; 40: 482–7. (EXP)

Guideline #1.2: Hypotension and skin hypoperfusion should be corrected as soon as possible to improve cutaneous wound healing.

Level of evidence: I

Principle: Skin blood flow is reduced in multiple medical conditions, including shock and hypotension, hypovolemia, cold, connective tissue disease, arterial and venous impairment, advanced age, pain, smoking, diabetes mellitus, and cold. Conversely, warming can increase perfusion.

Evidence:

1. Kumar S, Wong PF, Melling AC, Leaper DJ. Effects of perioperative hypothermia and warming in surgical practice. *Int Wound J* 2005; 2: 193–204. (STAT)
2. Worthley LI. Shock: a review of pathophysiology and management. Part I. *Crit Care Resusc* 2000; 2: 55–65. (LIT REV)

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4. Kamler M, Goedeke J, Pizanis N, Milekhin V, Schade FU, Jakob H. In vivo effects of hypothermia on the microcirculation during extracorporeal circulation. *Eur J Cardiothorac Surg* 2005; 28: 259–65. (EXP)
5. Kanetaka T, Komiyama T, Onozuka A, Miyata T, Shigematsu H. Laser Doppler skin perfusion pressure in the assessment of Raynaud's phenomenon. *Eur J Vasc Endovasc Surg* 2004; 27: 414–6. (RCT)
6. Kenney WI, Munce TA. Invited review: aging and human temperature regulation. *J Appl Physiol* 2003; 95: 2598–603. (LIT REV)
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11. Rendell M, Bamisedun O. Diabetic cutaneous microangiopathy. *Am J Med* 1992; 93: 611–8. (CLIN S)
12. Schubert V. Hypotension as a risk factor for the development of pressure sores in elderly subjects. *Age Ageing* 1991; 20: 255–61. (CLIN S)
13. LoGerfo FW, Coffman S. Vascular and microvascular disease in the foot in diabetes: implications for foot care. *N Engl J Med* 1984; 311: 1615–9. (LIT REV)
14. Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. *N Engl J Med* 1996; 334: 1209–15. (RCT)
15. Melling AC, Baqar A, Scott EM, Leaper DJ. Effects of preoperative warming on the incidence of wound infection after clean surgery. *Lancet* 2001; 358: 876–80. (RCT)

Guideline #1.3: There are not enough clinical data to recommend hyperbaric oxygen for improving healing of acute wounds.

Level of evidence: II

Principle: Although increased oxygen delivered at increased pressures could theoretically augment healing, there are insufficient data to support its use in acute wound healing.

Evidence:

1. Friedman HI, Fitzmaurice M, Lefaivre JF, Vecchiolla T, Clarke D. An evidence-based appraisal of the use of hyperbaric oxygen on flaps and grafts. *Plast Reconstr Surg* 2006; 117 (Suppl.): 175S–92S. (STAT)
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3. Tai YJ, Birely BC, Im MJ, Hoopes JE, Manson PN. The use of hyperbaric oxygen for preservation of free flaps. *Ann Plast Surg* 1992; 28: 284–7. (EXP)
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6. Sheffield P. Tissue oxygen measurements with respect to soft tissue wound healing with normobaric and hyperbaric oxygen. *HBO Rev* 1985; 6: 18–46. (LIT REV)
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#2: GUIDELINES TO DECREASE THE IMPEDIMENT TO ACUTE WOUND HEALING CAUSED BY NONVIABLE TISSUE

Preamble: None of the processes of wound healing can occur unless the tissues within the wound are viable. Attempting to close a wound by edge coaptation, with a skin graft, with a pedicled flap, or even allowing it to heal spontaneously, will be unsuccessful when nonviable tissue is present. Removing nonviable tissue is paramount to successful tissue repair.

Guideline #2.1: Debridement is required to remove necrotic tissue and excessive bacterial burden. The health care provider can choose from a number of debridement methods, including surgical, enzymatic, mechanical, biological, or autolytic. More than one debridement method may be appropriate. (Sharp surgical debridement is preferred.)

If an alternative form of debridement is unsuccessful in removing the nonviable tissue, surgical debridement is mandated.

Level of evidence: I

Principle: Necrotic tissue, excessive bacterial burden, and foreign debris can all inhibit wound healing. The method of debridement chosen may depend on the status of the wound, the capability of the health care provider, the overall condition of the patient, and professional licensing restrictions.

Evidence:

1. Steed DL, Donohoe D, Webster MW, Lindsley L. Effect of extensive debridement on the healing of diabetic foot ulcers. *J Am Coll Surg* 1996; 183: 61–4. (RCT)
2. Saap LJ, Falanga V. Debridement performance index and its correlation with complete closure of diabetic foot ulcers. *Wound Rep Regen* 2002; 10: 354–9. (RCT)

3. Mulder GD. Cost-effective managed care: gel versus wet-to-dry for debridement. *Ostomy Wound Manage* 1995; 41: 68–70. (RCT)
4. Alvarez OM, Fernandez-Obregon A, Rogers RS, Bergamo L, Masso J, Black M. A prospective, randomized, comparative study of collagenase and papain-urea for pressure ulcer debridement. *Wounds* 2002; 14: 293–301. (RCT)
5. Steed DL. Debridement. *Am J Surg* 2004; 187 (Suppl.): 71S–4S. (LIT REV)
6. Ayello EA, Cuddigan JE. Debridement: controlling the necrotic/cellular burden. *Adv Skin Wound Care* 2004; 17: 66–75. (LIT REV)
7. Sieggreen MY, Maklebust J. Debridement: choices and challenges. *Adv Wound Care* 1997; 10: 32–7. (LIT REV)
8. Sibbald RG, Williamson D, Orsted HL, Campbell K, Keast D, Krasner D, Sibbald D. Preparing the wound bed—debridement, bacterial balance, and moisture balance. *Ostomy Wound Manage* 2000; 46: 14–35. (LIT REV)
9. Mosher BA, Cuddigan J, Thomas DR, Boudreau DM. Outcomes of 4 methods of debridement using a decision analysis methodology. *Adv Wound Care* 1999; 12: 81–8. (TECH)
10. Bradley M, Cullum N, Sheldon T. The debridement of chronic wounds: a systematic review. *Health Technol Assess* 1999; 3 (Part 1): (STAT)
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17. Hamer ML, Robson MC, Krizek TJ, Southwick WO. Quantitative bacterial analysis of comparative wound irrigations. *Ann Surg* 1975; 181: 819–22. (EXP)
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20. Draeger RW, Dahners LE. Traumatic wound debridement: a comparison of irrigation *Methods* 2006; 20: 83–8. (EXP)
21. Mumcuoglu KY. Clinical application of maggots in wound care. *Am J Clin Dermatol* 2001; 2: 219–27. (LIT REV)

#3: GUIDELINES TO DECREASE THE IMPEDIMENT TO ACUTE WOUND HEALING CAUSED BY WOUND HEMATOMA OR SEROMA

Preamble: Acute wound fluid collections most often are the result of bleeding (hematomas), inflammation (seromas), or lymph fluid. Acute wound hematomas or seromas can impair and delay acute wound healing. Acute wound fluid collections can mechanically disrupt a wound, cause wound ischemia due to pressure exceeding capillary perfusion, be a nutrient nidus for wound infection, or cause increased dead space. Wound hematomas are increasingly common due to the increased use of prophylactic and therapeutic anticoagulation and antiplatelet therapy in surgical patients. Wound seromas are increasingly common due to the increased use of foreign material soft tissue implants, such as meshes used in hernia repair.

Guideline #3.1: Coagulation should preferentially be normalized preoperatively; correction should continue intraoperatively and for 24 hours following a surgical procedure. Primary coagulopathies such as vitamin K deficiency or hemophilia should be diagnosed and treated before elective operations. Therapeutic anticoagulation, as with warfarin, can be temporarily discontinued and ''bridged'' with shorter-acting anticoagulants. Prophylactic heparins to prevent venous thromboembolism (VTE) are indicated, but will increase the risk of hematomas and other bleeding complications. Antiplatelet agents may be continued during general surgical procedures.

Level of evidence: I

Principle: Bleeding complications, including hematoma formation, are significantly increased when a primary or pharmacological coagulopathy exists. The most common mechanism for coagulopathy is impaired or reduced protein-clotting factors and impaired or reduced platelets. Patients at high risk for a hypercoagulable complication such as stroke, myocardial ischemia, or VTE may be ''bridged'' with a heparin formulation that can be held during the 24-hour period surrounding an operation. Heparin prophylaxis against VTE is indicated in general surgery, but will increase the incidence of hematoma and bleeding complications. There is no evidence that prophylactic or therapeutic antiplatelet therapy increases the risk of acute wound hematomas.

Evidence:

1. Geerts WH, Heit JA, Clagett GP, Pineo GF, Colwell CW, Anderson FA Jr, Wheeler HB. Prevention of venous thromboembolism. *Chest* 2001; 119 (Suppl.): 132S–75S. (STAT)
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thrombosis with either unfractionated or low molecular weight heparin. *Br J Surg* 1996; 83: 1548–52. (RCT)
3. Wille-Jorgensen P, Rasmussen MS, Andersen BR, Borly L. Heparins and mechanical methods for thromboprophylaxis in colorectal surgery. Cochrane Colorectal Cancer Group. *Cochrane Database Syst Rev* 2007; 4. (STAT)
4. Best WR, Khuri SF, Phelan M, Hur K, Henderson WG, Demakis JG, Daley J. Identifying patient preoperative risk factors and postoperative adverse events in administrative databases: results from the Department of Veterans Affairs National Surgical Quality Improvement Program. *J Am Coll Surg* 2002; 194: 257–66. (STAT)
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6. Cruse PJ, Foord R. A five-year prospective study of 23,649 surgical wounds. *Arch Surg* 1973; 107: 206–10. (STAT)
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11. Chlan LL, Sabo J, Savik K. Effects of three groin compression methods on patient discomfort, distress, and vascular complications following a percutaneous coronary intervention procedure. *Nurs Res* 2005; 54: 391–8. (RCT)
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14. Kargi E, Babuccu O, Hosnuter M, Babuccu B, Altinyazar C. Complications of minor cutaneous surgery in patients under anticoagulant treatment. *Aesthetic Plast Surg* 2002; 26: 483–5. (RCT)
15. Warkentin TE, Crowther MA. Reversing anticoagulants both old and new. *Can J Anaesth* 2002; 49: S11–5. (LIT REV)
16. Brophy MT, Flore LD, Deykin D. Low-dose vitamin K therapy in excessively anticoagulated patients: a dose-finding study. *J Thromb Thrombolysis* 1997; 4: 289–92. (CLIN S)
17. Spotnitz WD, Dalton MS, Baker JW, Nolan SP. Reduction of perioperative hemorrhage by anterior mediastinal spray application of fibrin glue during cardiac operations. *Ann Thorac Surg* 1987; 44: 529–31. (RCT)

Guideline #3.2: Meticulous surgical hemostasis by ligature or electrocautery reduces the incidence of wound hematoma formation and improves wound healing.

Level of evidence: I

Principle: Surgical hemostasis prevents hematoma formation. Larger bleeding vessels in a wound should be clamped and tied with an absorbable suture. Electrocautery is an option for wound hemostasis, as are topical chemical hemostatic agents. Primary layered anatomic closure of an incision results in most efficient hemostasis, wound healing, and an optimized anatomic result. By achieving complete hemostasis, hematoma formation is minimized and "dead space" is eliminated, reducing the added risk of localized bacteria utilizing the hematoma as a nutrient media.

Evidence:

1. Patterson ML, Nathanson SD, Havstad S. Hematomas following excisional breast biopsies for invasive breast carcinoma: the influence of deep suture approximation of breast parenchyma. *Am Surg* 1994; 60: 845–8. (CLIN S)
2. Brown SR, Goodfellow PB. Transverse versus midline incisions for abdominal surgery. Cochrane Colorectal Cancer Group. *Cochrane Database Syst Rev* 2007; 4. (STAT)
3. Rappaport WD, Hunter GC, Allen R, Lick S, Halldorsson A, Chvapil T, Holcomb M, Chvapil M. Effect of electrocautery on wound healing in midline laparotomy incisions. *Am J Surg* 1990; 160: 618–20. (CLIN S)
4. Cruse PJ, Foord R. The epidemiology of wound infection: a 10-year prospective study of 62,939 wounds. *Surg Clin North Am* 1980; 60: 27–40. (STAT)
5. Johnson CD, Serpell J. Wound infection after abdominal incision with scalpel or diathermy. *Br J Surg* 1990; 77: 626–7. (RCT)
6. Kearns SR, Connolly EM, McNally S, McNamara DA, Deasy J. Randomized clinical trial of diathermy versus scalpel incision in elective midline laparotomy. *Br J Surg* 2001; 88: 41–4. (RCT)
7. Kumagai SG, Rosales RF, Hunter GC, Rappaport WD, Witzke DB, Chvapil TA, Chvapil M, Sutherland JC. Effects of electrocautery on midline laparotomy wound infection. *Am J Surg* 1991; 162: 620–3. (CLIN S)
8. Lawrenson KB, Stephens FO. The use of electro-cutting and electro-coagulation in surgery. *Austral NZ J Surg* 1970; 39: 417–21. (LIT REV)
9. Keenan KM, Rodeheaver GT, Kenney JG, Edlich RF. Surgical cautery revisited. *Am J Surg* 1984; 147: 818–21. (LIT REV)
10. Groot G, Chappell EW. Electrocautery used to create incisions does not increase wound infection rates. *Am J Surg* 1994; 167: 601–3. (CLIN S)

11. Naumann RW, Hauth JC, Owen J, Hodgkins PM, Lincoln T. Subcutaneous tissue approximation in relation to wound disruption after cesarean delivery in obese women. *Obstet Gynecol* 1995; 85: 412–6. (RCT)
12. Dubay DA, Franz MG. Acute wound healing: the biology of acute wound failure. *Surg Clin North Am* 2003; 83: 463–81. (LIT REV)

Guideline #3.3: Primarily closed, large surface area wounds with skin flaps such as after mastectomy or abdominal wall component separation should be prophylactically drained. Primary incisions or incisions associated with vascular implants do not benefit from closed suction drainage.

Level of evidence: I

Principle: The necessary ''dead-space'' created during flap elevation or the resection of a lymph node chain, for example, may allow significant fluid collection. This fluid may collect to the point that capillary perfusion pressure to the surrounding tissue is exceeded, causing ischemia and even necrosis. Fluid collections also may mechanically disrupt healing tissue layers. Chronically, wound fluid collections are at risk for becoming infected and forming an abscess. All phases along this continuum delay wound healing.

Evidence:

1. de Vries Reilingh TS, van Goor H, Rosman C, Bemelmans MH, de Jong D, van Nieuwenhoven EJ, van Engeland MI, Bleichrodt RP. ''Components separation technique'' for the repair of large abdominal wall hernias. *J Am Coll Surg* 2003; 196: 32–7. (CLIN S)
2. DiBello JN, Moore JH. Sliding myofascial flap of the rectus abdominus muscles for the closure of recurrent ventral hernias. *Plast Reconstr Surg* 1996; 98: 464–9. (CLIN S)
3. Schumpelick V, Conze J, Klinge U. Preperitoneal mesh repair of incisional hernias: a comparative retrospective study. *Chirurg* 1996; 67: 1028–35. (RETRO S)
4. Sugarman HJ. Surgery for morbid obesity. *Surgery* 1993; 114: 865–7. (LIT REV)
5. Pogson CJ, Adwani A, Ebbs SR. Seroma following breast cancer surgery. *Eur J Surg Onc* 2003; 29: 711–7. (CLIN S)
6. Cameron AE, Ebbs SR, Wylie F. Suction drainage of the axilla: a prospective randomized trial. *Br J Surg* 1988; 75: 1211 (RCT)
7. Somers R, Jablon L, Kaplan M. The use of closed suction drainage after lumpectomy and axillary dissection for breast cancer: a prospective randomized trial. *Ann Surg* 1992; 215: 146–9. (RCT)
8. Schultz I, Barrholm M, Grondal S. Delayed shoulder exercises in reducing seroma frequency after modified radical mastectomy: a prospective, randomized trial. *Ann Surg Onc* 1997; 4: 292–7. (RCT)
9. Shaffer D, Benotti PN, Bothe A Jr, Jenkins RL, Blackburn GL. A prospective, randomized trial of abdominal wound drainage in gastric bypass surgery. *Ann Surg* 1987; 206: 134–7. (RCT)
10. Healy DA, Keyser J III, Holcomb GW III, Dean RH, Smith BM. Prophylactic closed suction drainage of femoral wounds in patients undergoing vascular reconstruction. *J Vasc Surg* 1989; 10: 166–8. (RCT)
11. Higson RH, Kettlewell MG. Parietal wound drainage in abdominal surgery. *Br J Surg* 1978; 65: 326–9. (CLIN S)
12. Fraser I, Everson NW, Nash JR. A randomised prospective trial of two drainage methods after cholecystectomy. *Ann R Coll Surg Engl* 1982; 64: 183–5. (RCT)

Guideline #3.4: Large postoperative hematomas or seromas with evidence of wound ischemia or infection should be therapeutically drained or evacuated.

Level of evidence: I

Principle: Wound hematomas or seromas may reach a pressure at which capillary perfusion pressure to the surrounding wound tissue is exceeded. The resulting wound ischemia may lead to acute wound failure or wound infection. Chronically, a wound hematoma may act as a nidus for a wound infection and abscess. Opening a surgical wound and evacuating the fluid or hematoma should correct both of these complications. In the patient who receives a minimally invasive surgical procedure where there are minimal skin incisions, such as following laparoscopic hernia repair, percutaneous aspiration may be attempted.

Evidence:

1. Irvin TT, Goligher JC. A controlled clinical trial of three different methods of perineal wound management following excision of the rectum. *Br J Surg* 1975; 62: 287–91. (RCT)
2. Byrne DJ, Lynch W, Napier A, Davey P, Malek M, Cuschieri A. Wound infection rates: the importance of definition and post-discharge wound surveillance. *J Hosp Infect* 1994; 26: 37–43. (RCT)
3. Purushotham AD, McLatchie E, Young D, George WD, Stallard S, Doughty J, Brown DC, Farish C, Walker A, Millar K, Murray G. Randomized clinical trial of no wound drains and early discharge in the treatment of women with breast cancer. *Br J Surg* 2002; 89: 286–92. (RCT)
4. Youssef F, Jenkins MP, Dawson KJ, Berger L, Myint F, Hamilton G. The value of suction wound drain after carotid and femoral artery surgery: a randomised trial using duplex assessment of the volume of post-operative haematoma. *Eur J Vasc Endovasc Surg* 2005; 29: 162–6. (RCT)
5. Rice DC, Morris SM, Sarr MG, Farnell MB, van Heerden JA, Grant CS, Rowland CM, Ilstrup DM, Donohue JH. Intraoperative topical tetracycline sclero-therapy following mastectomy: a prospective, randomized trial. *J Surg Oncol* 2000; 73: 224–7. (RCT)
6. Knight CD Jr, Griffen FD, Knight CD Sr. Prevention of seromas in mastectomy wounds. The effect of shoulder immobilization. *Arch Surg* 1995; 130: 99–101. (CLIN S)
7. DeMaria, EJ, Moss JM, Sugerman, HJ. Laparoscopic intraperitoneal polytetrafluoroethylene (PTFE) prosthetic patch repair of ventral hernia: prospective comparison to open prefascial polypropylene mesh repair. *Surg Endosc* 2000; 14: 326–9. (CLIN S)

#4: GUIDELINES TO DECREASE THE IMPEDIMENTS TO ACUTE WOUND HEALING CAUSED BY INFECTION OR AN INCREASED TISSUE BACTERIAL BIOBURDEN

Preamble: Infection results in a wound when the bacteria–host defense equilibrium is upset in favor of the bacteria. When an imbalance in this quantitative equilibrium results in infection, a delay in wound healing occurs. Therefore, prevention and treatment of wound infection involves maintenance or reestablishment of the balanced equilibrium.

Guideline #4.1: Do not attempt to close wounds containing $> 10^5$ bacteria/g of tissue or any tissue level of beta hemolytic streptococci by direct wound edge approximation, skin graft, or pedicled or free flap.

Level of evidence: I
Principle: "A wound containing contaminated foci with greater than 10^5 bacteria per gram of tissue cannot be readily closed, as the incidence of wound infection that follows is 50 to 100 percent" (Tobin, 1984).

Evidence:

1. Edlich RF, Rodeheaver GT, Thacker JG, Winn HR, Edgerton MT. Management of soft tissue injury. *Clin Plast Surg* 1977; 4: 191–8. (LIT REV)
2. Robson MC, Duke WF, Krizek TJ. Rapid bacterial screening in the treatment of civilian wounds. *J Surg Res* 1973; 14: 426–30. (RCT)
3. Liedburg NC, Reiss E, Artz CP. The effect of bacteria on the take of split-thickness skin grafts in rabbits. *Ann Surg* 1955; 142: 92–6. (EXP)
4. Krizek TJ, Robson MC, Kho E. Bacterial growth and skin graft survival. *Surg Forum* 1967; 18: 518–9. (RCT)
5. Murphy RC, Robson MC, Heggers JP, Kadowaki M. The effect of microbial contamination on musculocutaneous and random flaps. *J Surg Res* 1986; 41: 75–80. (EXP)
6. Tobin GR. Closure of contaminated wounds: biologic and technical considerations. *Surg Clin North Am* 1984; 64: 639–52. (LIT REV)
7. Robson MC, Lea CE, Dalton JB, Heggers JP. Quantitative bacteriology and delayed wound closure. *Surg Forum* 1968; 19: 501–2. (RCT)
8. Robson MC, Stenberg BD, Heggers JP. Wound healing alterations caused by infection. *Clin Plast Surg* 1990; 17: 485–92. (LIT REV)

Guideline #4.2: When wounds are considered at risk for having a significant bacterial bioburden (clean-contaminated or contaminated cases), prophylactic antibiotics are indicated. Clean cases with negligible bacterial bioburden do not benefit from prophylactic antibiotics except when implanted prosthetic materials are used.

Level of evidence: I
Principle: Clean-contaminated and contaminated wounds result in higher rates of postoperative infection. Clean-refined and clean cases have infection rates that are low enough to make it difficult to demonstrate statistical improvement with prophylactic antibiotic usage.

Evidence:

1. Bratzler DW, Houk PM. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. *Clin Infect Dis* 2004; 38: 1706–15. (STAT)
2. Dellinger EP, Gross PA, Barrett TL, Krause PJ, Martone WJ, McGowan JE Jr., Sweet RL, Wenzel RP. Quality standard for antimicrobial prophylaxis in surgical procedures. *Clin Infect Dis* 1994; 18: 422–7. (STAT)
3. Page CP, Bohner JM, Fletcher JR, McManus AT, Solomkin JS, Wittmann DH. Antimicrobial prophylaxis for surgical wounds: guidelines for clinical care. *Arch Surg* 1993; 128: 79–88. (STAT)
4. Waddell TK, Rotstein OD. Antimicrobial prophylaxis in surgery: Committee on Antimicrobial Agents, Canadian Infectious Disease Society. *Canad Med Assoc J* 1994; 151: 925–31. (STAT)
5. Sanchez-Manuel FJ, Lozano-Garcia J, Seco-Gil JL. Antibiotic prophylaxis for hernia repair. *Cochrane Database Syst Rev* 2007; 3: CD003769. (STAT)
6. Sanabria A, Dominguez LC, Valdivieso E, Gomez G. Prophylactic antibiotics for mesh hernioplasty: a meta-analysis. *Ann Surg* 2007; 246: 904–5. (STAT)
7. Hauser CJ, Adams CA, Eachempati SR, Council of the Surgical Infection Society. Surgical Infection Society guideline: prophylactic antibiotic use in open fractures: an evidence-based guideline. *Surg Infect* 2006; 7: 379–405. (STAT)
8. Whittaker JP, Nancarrow JD, Sterne GD. The role of antibiotic prophylaxis in clean incised hand injuries: a prospective randomized placebo controlled double blind trial. *J Hand Surg* 2005; 30: 162–7. (RCT)
9. Cummings P, DelBeccaro MA. Antibiotics to prevent infection of simple wounds: a meta-analysis of randomized studies. *Am J Emerg Med* 1995; 13: 396–400. (STAT)
10. Platt R. Methodologic aspects of clinical studies of perioperative antibiotic prophylaxis. *Rev Infect Dis* 1991; 13 (Suppl. 10): S810–4. (LIT REV)
11. Leaper DJ, van Goor H, Reilly J, Petrosillo N, Geiss HK, Torres AJ, Berger A. Surgical site infection—a European perspective of incidence and economic burden. *Int Wound J* 2004; 1: 247–3. (STAT)
12. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. *Infect Control Hosp Epidemiol* 1999; 20: 247–78. (STAT)

Guideline #4.3: When prophylactic antibiotics are to be used, they must be started preoperatively so as to obtain an adequate serum and, preferably, a tissue antimicrobial level before incision or wounding.

Level of evidence: I
Principle: Antibiotics begun after bacterial tissue lodgment has occurred cannot favorably affect the bacterial–host defense balance.

Evidence:

1. Burke JF. The effective period of preventive antibiotic action in experimental incisions and dermal lesions. *Surgery* 1961; 50: 161–8. (EXP)
2. Classen DC, Evans RS, Pestotnik SL, Horn SD, Menlove RL, Burke JP. The timing of prophylactic

administration of antibiotics and the risk of surgical infection. *N Engl J Med* 1992; 326: 281–6. (RCT)
3. Bratzler DW, Houk PM. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. *Clin Infect Dis* 2004; 38: 1706–15. (STAT)
4. Dellinger EP, Gross PA, Barrett TL, Krause PJ, Martone WJ, McGowan JE Jr, Sweet RL, Wenzel RP. Quality standard for antimicrobial prophylaxis in surgical procedures. *Clin Infect Dis* 1994; 18: 422–7. (STAT)
5. Page CP, Bohnen JM, Fletcher JR, McManus AT, Solomkin JS, Wittmann DH. Antimicrobial prophylaxis for surgical wounds: guidelines for clinical care. *Arch Surg* 1993; 128: 79–88. (STAT)
6. Polk HC, Lopez-Mayor JF. Postoperative wound infection: a prospective study of determinant factors and prevention. *Surgery* 1969; 66: 97–103. (RCT)
7. Meakins JL. *Surgical infections: diagnosis and treatment*. New York: Scientific American, 1994. (LIT REV)

Guideline #4.4: When prophylactic antibiotics are indicated, a single dose is often sufficient. If multiple doses are used, they should be confined to a 24-hour period and not of prolonged duration.

Level of evidence: I
Principle: A single dose of the proper antibiotic, delivered at the proper time, will usually be effective at maintaining or reestablishing the bacteria–host defense equilibrium.

Evidence:

1. MacDonald M, Grabsel E, Marshall C, Forbes A. Single- versus multiple-dose antimicrobial prophylaxis for major surgery: a systematic review. *Aust NZ J Surg* 1998; 68: 388–96. (STAT)
2. Bratzler DW, Houk PM. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. *Clin Infect Dis* 2004; 38: 1706–15. (STAT)
3. Cornwell EE III, Dougherty WR, Berne TV, Velmahos G, Murray JA, Chahwan S, Belzberg H, Falabella A, Morales IR, Asensio J, Demetriades D. Duration of antibiotic prophylaxis in high risk patients with penetrating abdominal trauma: a prospective randomized trial. *J Gastrointest Surg* 1999; 3: 648–53. (RCT)
4. Mohri Y, Tonouchi H, Kobayashi M, Nakai K, Kusunoki M, Mie Surgical Infection Research Group. Randomized clinical trial of single- versus multiple-dose antimicrobial prophylaxis in gastric cancer surgery. *Br J Surg* 2007; 94: 683–9. (RCT)
5. Fugita S, Saito N, Yamada T, Takii Y, Kondo K, Ohue M, Ikeda E, Moriya Y. Randomized multicenter trial of antibiotic prophylaxis in elective colorectal surgery: single dose vs 3 doses of a second-generation cephalosporin without metronidazole and oral antibiotics. *Arch Surg* 2007; 142: 657–61. (RCT)

Guideline #4.5: In minor superficial, nonbite injuries, prophylactic antibiotics are not indicated.

Level of evidence: I
Principle: Minor superficial lacerations rarely contain a significant bacterial bioburden and do not benefit from prophylactic antibiotics. Bite injuries from animals and humans usually have significant contamination.

Evidence:

1. Whittaker JP, Nancarrow JD, Sterne GD. The role of antibiotic prophylaxis in clean incised hand injuries: a prospective randomized placebo controlled double blind study. *J Hand Surg* 2005; 30: 162–7. (RCT)
2. Cassell OC, Ion L. Are antibiotics necessary in the surgical management of upper limb lacerations? *Br J Plast Surg* 1997; 50: 523–9. (RCT)
3. Cummings P. Antibiotics to prevent infection in patients with dogbite wounds: a meta-analysis of randomized trials. *Ann Emerg Med* 1994; 23: 577–9. (STAT)
4. Hendrick TL, Smith PW, Gazoni LM, Sawyer RG. The appropriate use of antibiotics in surgery: a review of surgical infection. *Curr Prob Surg* 2007; 44: 635–75. (LIT REV)
5. Robson MC, Duke WF, Krizek TJ. Rapid bacterial screening in the treatment of civilian wounds. *J Surg Res* 1973; 14: 426–30. (RCT)

Guideline #4.6: Assuring adequate patient temperature and oxygenation during surgery and in the perioperative period decreases surgical site infections.

Level of evidence: I
Principle: Normothermia and absence of hypoxia increase tissue perfusion and aid healing as well as decreasing surgical site infections.

Evidence:

1. Melling AC, Ali B, Scott EM, Leaper DJ. Effects of preoperative warming on incidence of wound infection after clean surgery: a randomized controlled trial. *Lancet* 2001; 358: 876–80. (RCT)
2. Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. *N Engl J Med* 1996; 334: 1209–15. (RCT)
3. Ueno C, Hunt TK, Hopf HW. Using physiology to improve surgical wound outcomes. *Plast Reconstr Surg* 2006; 117 (Suppl.): 59S–71S. (LIT REV)
4. Greif R, Akça O, Horn EP, Kurz A, Sessler DI. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. *N Engl J Med* 2000; 342: 161–7. (RCT)
5. Belda FJ, Aguilera L, García de la Asunción J, Alberti J, Vicente R, Ferrándiz L, Rodríguez R, Company R, Sessler DI, Aguilar G, Botello SG, Ortí R, Spanish Reduccion de la Tasa de Infeccion Quirurgica Group. Supplemental perioperative oxygen and the risk of surgical wound infection. A randomized controlled trial. *JAMA* 2005; 294: 2035–42. (RCT)
6. Pryor KO, Fahey TJ, Lien CA, Goldstein PA. Surgical site infection and the routine use of perioperative hyperoxia in a general surgical population. A randomized controlled trial. *JAMA* 2004; 291: 79–87. (RCT)
7. Myles PS, Leslie K, Chan MTV, Forbes A, Paech MJ, Peyton P, Silbert BS, Pascoe E, ENIGMA Trial Group. Avoidance of nitrous oxide for patients undergoing major surgery. *Anesthesiology* 2007; 107: 221–31. (RCT)

Guideline #4.7: Preoperative surgical site or wound preparation such as shaving of hair or scrubbing of the skin is not indicated as a means of decreasing incisional wound infection.

Level of evidence: I
Principle: The known resident bacterial flora of skin is 10^3 bacteria/g of tissue, less than the bioburden required to cause infection.

Evidence:

1. Niel-Weise BS, Willie JC, van den Broek PJ. Hair removal policies in clean surgery: a systematic review of randomized, controlled trials. *Inf Control Hosp Epidemiol* 2005; 26: 923–8. (STAT)
2. Tanner J, Woodings D, Moncaster K. Preoperative hair removal to reduce surgical site infection. *Cochrane Database Syst Rev* 2006; 3: CD004122. (STAT)
3. Webster J, Osbourne S. Meta-analysis of preoperative antiseptic bathing in prevention of surgical site infection. *Br J Surg* 2006; 11: 13335–41. (STAT)
4. Ellenhorn JD, Smith DD, Schwarz RE, Kawachi MH, Wilson TG, McGonigle KF, Wagman LD, Paz IB. Paint-only is equivalent to scrub-and-paint in preoperative preparation of abdominal surgery sites. *J Am Coll Surg* 2005; 201: 737–41. (RCT)
5. Edwards PS, Lipp A, Holmes A. Preoperative skin antiseptics for preventing surgical wound infections after clean surgery. *Cochrane Database Syst Rev* 2004; 3: CD003949. (STAT)
6. Shirahatti RG, Joshi RM, Vishwanath YK, Shinkre N, Rao S, Sankpal JS, Govindrajulu NK. Effect of preoperative skin preparation on post-operative wound infection. *J Postgrad Med* 1993; 39: 134–6. (RCT)
7. Robson MC, Duke WF, Krizek TJ. Rapid bacterial screening in the treatment of civilian wounds. *J Surg Res* 1973; 14: 426–30. (RCT)
8. Lammers RL, Fourre M, Callaham ML, Boone T. Effect of povidone-iodine and saline soaking on bacterial counts in acute, traumatic, contaminated wounds. *Ann Emerg Med* 1990; 19: 709–14. (RCT)

#5: GUIDELINES TO DECREASE IMPEDIMENTS TO ACUTE WOUND HEALING CAUSED BY MECHANICAL FACTORS DURING WOUND REPAIR

Preamble: Mechanical factors play an important and often underappreciated role in acute wound healing. Primary closure of an incision stabilizes distractive forces to allow wound healing and an optimized anatomic result. Cellular studies confirm that mechanical load forces are an important signal for acute wound repair. When anatomic stability of a wound is achieved, a particular suture material or suturing technique is of secondary importance. The increased use of foreign material implants, such as meshes for hernia repair, are suggested to manipulate the mechanical environment of the acute wound, even to the point of promoting ''tension-free'' wound healing. Negative pressure wound therapy is increasingly applied to stabilize acute wounds and to support acute wound healing. Mechanical micro-deformation of repair cells in the wound bed is thought to stimulate acute wound healing.

Guideline #5.1: Primarily repaired wounds heal faster than wounds left open to heal by secondary intent. Healing following delayed primary closure also is faster than in wounds left open to heal by secondary intent.

Level of evidence: I
Principle: Primarily closed wounds are of a smaller volume and heal mainly by the synthesis of a new matrix. Wound contraction and epithelialization, as in an open wound healing by secondary intent, contribute a small part to primary wound healing. An open wound, healing by secondary intent, must synthesize granulation tissue to fill in the wound bed, contract at the wound periphery, and cover the surface area with epithelial cells. Wounds heal faster following delayed primary closure than by secondary intent, as well. The mechanical load forces transmitted through a primarily reconstructed wound will stimulate repair. Successful delayed primary closure requires that the acute wound be in bacterial balance. Primary repair should approximate, but not strangulate the incision. The type of suture material used does not matter, as long as the primary repair is anatomic and perfused.

Evidence:

1. Robson MC, Shaw RC, Heggers JP. The re-closure of postoperative incisional abscesses based on bacterial quantification of the wound. *Ann Surg* 1970; 171: 279–82. (CLIN S)
2. Coulthard P, Worthington H, Esposito M, Elst M, Waes OJ. Tissue adhesives for closure of surgical incisions. Cochrane Wounds Group. *Cochrane Database Syst Rev* 2007; 4. (STAT)
3. Robson MC, Heggers JP. Delayed wound closures based on bacterial counts. *J Surg Oncol* 1970; 2: 379–83. (CLIN S)
4. Santora TA, Rosylyn JJ. Incisional hernia. *Surg Clin North Am* 1993; 73: 557–70. (LIT REV)
5. McCallum I, King PM, Bruce J. Healing by primary versus secondary intention after surgical treatment for pilonidal sinus. Cochrane Wounds Group. *Cochrane Database Syst Rev* 2007; 4, (STAT)
6. Zafar M, John A, Khan Z, Allen SM, Marchbank AJ, Lewis CT, Dalrymple-Hay MJ, Kuo J, Unsworth-White J. Single-layer versus multiple-layer closure of leg wounds after long saphenous vein harvest: a prospective randomized trial. *Ann Thorac Surg* 2005; 80: 2162–5. (RCT)
7. Handschel JG, Depprich RA, Dirksen D, Runte C, Zimmermann A, Kübler NR. A prospective comparison of octyl-2-cyanoacrylate and suture in standardized facial wounds. *Int J Oral Maxillofac Surg* 2006; 35: 318–23. (RCT)
8. Murtha AP, Kaplan AL, Paglia MJ, Mills BB, Feldstein ML, Ruff GL. Evaluation of a novel technique for wound closure using a barbed suture. *Plast Reconstr Surg* 2006; 117: 1769–80. (RCT)
9. Ridgway DM, Mahmood F, Moore L, Bramley D, Moore PJ. A blinded, randomised, controlled trial of stapled versus tissue glue closure of neck surgery incisions. *Ann R Coll Surg Eng* 2007; 89: 242–6. (RCT)

10. Henry MC, Moss RL. Primary versus delayed wound closure in complicated appendicitis: an international systematic review and meta-analysis. *Ped Surg Int* 2005; 21: 625–30. (STAT)
11. Nichols RL, Smith JW, Robertson GD, Muzik AC, Pearce P, Ozmen V, McSwain NE Jr, Flint LM. Prospective alterations in therapy for penetrating abdominal trauma. *Arch Surg* 1993; 128: 55–63. (RCT)

Guideline #5.2: Laparotomy fascial incisions heal best when repaired as a mass closure using a continuous suture placed at a suture-length-to-wound-length ratio of 4 : 1.

Level of evidence: I

Principle: All incisions are placed under a strain following repair. An abdominal wall laparotomy incision extends 10% in length following repair. A continuous suture line placed at a suture-length-to-wound-length ratio of 4 : 1 allows the suture line to physiologically extend with the incision. This prevents suture "pull through," which is the most common mechanism of suture failure. A 4 : 1 ratio also minimizes the amount of suture material required, reducing the foreign material inflammatory response in the healing wound. The appropriate suture-length-to-wound-length ratio also optimizes tension on the suture line, minimizing wound ischemia.

Evidence:

1. Cruse PJ, Foord R. A five-year prospective study of 23,649 surgical wounds. *Arch Surg* 1973; 107: 206–10. (STAT)
2. Weiland DE, Bay RC, Del Sordi S. Choosing the best abdominal closure by meta analysis. *Am J Surg* 1998; 176: 666–70. (STAT)
3. Jenkins TPN. The burst abdominal wound: a mechanical approach. *Br J Surg* 1976; 63: 873–6. (CLIN S)
4. Pollock AV, Evans M. Early prediction of late incisional hernias. *Br J Surg* 1989; 76: 953–4. (CLIN S)
5. Carlson MA. Acute wound failure. Wound healing. *Surg Clin North Am* 2001; 77: 607–35. (LIT REV)
6. Poole GV Jr. Mechanical factors in abdominal wound closure: the prevention of fascial dehiscence. *Surgery* 1985; 97: 631–9. (EXP)
7. Mudge M, Hughes LE. Incisional hernia: a 10 year prospective study of incidence and attitudes. *Br J Surg* 1985; 72: 70–1. (CLIN S)
8. Webster C, Neumayer L, Smout R, Horn S, Daley J, Henderson W, Khuri S. National Veterans Affairs Surgical Quality Improvement Program. Prognostic models of abdominal wound dehiscence after laparotomy. *J Surg Res* 2003; 109: 130–7. (STAT)
9. van't Riet M, Steyerberg EW, Nellensteyn J, Bonjer HJ, Jeekel J. Meta-analysis of techniques for closure of midline abdominal incisions. *Br J Surg* 2002; 89: 1350–6. (STAT)
10. Niggebrugge AH, Trimbos JB, Hermans J, Steup WH, Van De Velde CJ. Influence of abdominal-wound closure technique on complications after surgery: a randomised study. *Lancet* 1999; 353: 1563–7. (RCT)

Guideline #5.3: The type of suture material used does not affect laparotomy wound healing. Permanent sutures may result in chronic wound sinus or fistula formation.

Level of evidence: I

Principle: As long as the suture is present until adequate wound breaking or tensile strength is obtained, the type of suture material used does not affect acute wound healing. Permanent sutures increase the risk of chronic wound complications such as fistula and sinus track formation. Braided, permanent suture is at highest risk for an acute wound complication.

Evidence:

1. Hopkinson GB, Bullen BR. Removable subcuticular skin suture in acute appendicitis: a prospective comparative clinical trial. *Br Med J* 1982; 284: 869. (RCT)
2. Houck JP, Rypins EB, Sarfeh IJ, Juler GL, Shimoda KJ. Repair of incisional hernia. *Surg Gyn Obstet* 1989; 169: 397–9. (RCT)
3. Carlson MA. Acute wound failure. Wound healing. *Surg Clin North Am* 2001; 77: 607–35. (LIT REV)
4. Myers MB, Cherry G, Heimburger S. Augmentation of wound tensile strength by early removal of sutures. *Am J Surg* 1969; 117: 338–41. (CLIN S)
5. Pickford IR, Brennan SS, Evans M, Pollock AV. Two methods of skin closure in abdominal operations: a controlled clinical trial. *Br J Surg* 1983; 70: 226–8. (CLIN S)
6. Larsen PN, Nielsen K, Schultz A, Mejdahl S, Larsen T, Moesgaard F. Closure of the abdominal fascia after clean and clean-contaminated laparotomy. *Acta Chir Scand* 1989; 155: 461–4. (RCT)
7. Savolainen H, Ristkari S, Mokka R. Early laparotomy wound dehiscence: a randomized comparison of three suture materials and two methods of fascial closure. *Ann Chir Gyn* 1988; 77: 111–3. (RCT)
8. Derzie AJ, Silvestri F, Liriano E, Benotti P. Wound closure technique and acute wound complications in gastric surgery for morbid obesity: a prospective randomized trial. *J Am Coll Surg* 2000; 191: 238–43. (RCT)
9. Ullrich F, Henningsen B, Bottcher W. Fascial closure of median laparotomy incisions with synthetic reabsorbable sutures (polyglycolic acid). *Chirurg* 1981; 52: 777–9. (RCT)
10. Bresler L, Courbey PJ, Feldman L, Bilweiss J, Tortuyaux JM, Rauch P, Boissel P, Grosdidier J. Results of a controlled trial comparing 3 suture threads at slow resorption for the closure of supra-umbilical midline laparotomies. *Ann Chir* 1995; 49: 544–8. (RCT)

Guideline #5.4: Soft tissue prostheses reduce the incidence of wound failure and recurrence following hernia repair.

Level of evidence: I

Principle: The recurrence rate following inguinal hernia repairs using autologous tissues ranges from 5 to 25% in most series. The recurrence rate following primary incisional hernia repair using autologous tissues is even worse, ranging from 20 to 60%. The introduction of synthetic soft tissue prostheses to inguinal and incisional hernia repair has significantly reduced recurrence rates across general surgery. The prevailing view is that the mechanism for the reduced hernia recurrence rates is the reduction of tension along suture lines when using a soft-tissue prosthesis (mesh).

Evidence:

1. Luijendijk RW, Hop WCJ, van den Tol MP, de Lange DC, Braaksma MM, Ijzermans JN, Boelhouwer RU, de Vries BC, Salu MK, Wereldsma JC, Bruijninckx CM, Jeekel J. A comparison of suture repair with mesh repair for incisional hernia. *N Engl J Med* 2000; 343: 392–8. (RCT)
2. Burger WA, Luijendijk, RW, Hop Wim CJ, Halm JA, Verdaasdonk EG, Jeekel J. Long-term follow-up of a randomized controlled trial of suture versus mesh repair of incisional hernia. *Ann Surg* 2004; 24: 578–85. (RCT)
3. Flum DR, Horvath K, Koepsell T. Have outcomes of incisional hernia repair improved with time? A population based analysis. *Ann Surg* 2003; 237: 129–35. (STAT)
4. Korenkov M, Sauerland S, Arndt M, Bograd L, Neugebauer EA, Troidl H. Randomized clinical trial of suture repair, polypropylene mesh or autodermal hernioplasty for incisional hernia. *Br J Surg* 2002; 89: 50–6. (CLIN S)
5. van Veen RN, Wijsmuller AR, Vrijland WW, Hop WC, Lange JF, Jeekel J. Long-term follow-up of a randomized clinical trial of non-mesh versus mesh repair of primary inguinal hernia. *Br J Surg* 2007; 94: 506–10. (RCT)

Guideline #5.5: Negative pressure therapy mechanically stabilizes the distractive forces of an open acute wound and supports healing. Negative pressure therapy can also stabilize an open abdomen (laparostomy), minimizing wound size and supporting closure of the abdominal wall.

Level of evidence: II

Principle: Distractive tissue forces may act to keep a wound open, with vectors that oppose contraction, thereby delaying healing. This phenomenon is especially true with the therapeutic laparostomy, or "open abdomen." Distractive force from the rectus muscle components and lateral oblique muscles act to keep the laparostomy open, leading to incisional hernia formation and potential loss of abdominal, peritoneal volume (domain). Negative pressure dressings can oppose these distractive soft tissue vectors and stabilize an acute wound.

Evidence:

1. Armstrong DG, Lavery LA, Diabetic Foot Study Consortium. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. *Lancet* 2005; 366: 1704–10. (RCT)
2. Perez D, Wildi S, Demartines N, Bramkamp M, Koehler C, Clavien PA. Prospective evaluation of vacuum-assisted closure in abdominal compartment syndrome and severe abdominal sepsis. *J Am Coll Surg* 2007; 205: 586–92. (CLIN S)
3. Dakin J, Thompson S. Use of topical negative pressure therapy with an abdominal dressing in management of a laparostomy. *J Wound Care* 2006; 15: 386–8. (RETRO S)
4. Quah HM, Maw A, Young T, Hay DJ. Vacuum-assisted closure in the management of the open abdomen: a report of a case and initial experiences. *J Tissue Viabil* 2004; 14: 59–62. (RETRO S)
5. Steenvoorde P, van Engeland A, Bonsing B, Bonsing B, da Costa SA, Oskam J. Combining topical negative pressure and a Bogota bag for managing a difficult laparostomy. *J Wound Care* 2004; 13: 142–3. (RETRO S)
6. Chorbadjian M, Bown M, Graham C, Sayers R. Laparostomy healing by secondary intention after ruptured abdominal aortic aneurysm repair. *J Tissue Viabil* 2004; 14: 24–7. (RETRO S)

Guideline #5.6: External or internal retention sutures do not prevent dehiscence or incisional hernia formation. Retention sutures do not improve laparotomy wound outcomes.

Level of evidence: I

Principle: The incidence of clinically recognized acute laparotomy wound failure and dehiscence is at least 1%, with a mortality of $> 50\%$. The incidence of unrecognized acute laparotomy wound failure and primary incisional hernia formation is at least 11%. Comorbidities such as multiple trauma and wound contamination increase the risk of acute laparotomy wound failure. Purely mechanical efforts to stabilize abdominal wall repairs during primary closure are generally unsuccessful.

Evidence:

1. Wittmann DH, Aprahamian C, Bergstein JM. Etappenlavage: advanced diffuse peritonitis managed by planned multiple laparotomies utilizing zippers, slide fastener, and Velcro analogue for temporary abdominal closure. *World J Surg* 1990; 14: 218–26. (RETRO S)
2. Irvin TT, Stoddard CJ, Greaney MG, Duthie HL. Abdominal wound healing: a prospective clinical study. *Br Med J* 1977; 2: 351–2. (RCT)
3. Hubbard TB, Rever WB. Retention sutures in the closure of abdominal incisions. *Am J Surg* 1972; 124: 378–80. (RCT)
4. Rink AD, Goldschmidt D, Dietrich J, Nagelschmidt M, Vestweber KH. Negative side-effects of retention sutures for abdominal wound closure. A prospective randomised study. *Eur J Surg—Acta Chir* 2000; 166: 932–7. (RCT)

Guideline #5.7: Transverse laparotomy incisions do not form fewer incisional hernias than midline laparotomy incisions.

Level of evidence: I

Principle: The predominant, load-bearing collagen fibers of the abdominal wall are transversely oriented. Incisions parallel to these fibers are least destructive in terms of loss of mechanical integrity. Transverse laparotomy closures encircle these same load-bearing fibers, maximizing mechanical integrity. Although theoretically the mechanical integrity is maximized in the transverse incision, laparotomy incisional herniation occurs at similar rates regardless of incisional orientation.

Evidence:

1. DuBay D, Franz MG. Acute wound healing: the biology of acute wound failure. *Surg Clin North Am* 2003; 83: 463–81. (LIT REV)
2. Carlson M. Acute wound failure. Wound healing. *Surg Clin North Am* 2001; 77: 607–35. (LIT REV)

3. Gislason H, Gronbech JE, Soreide O. Burst abdomen and incisional hernia after major gastrointestinal operations: comparison of 3 closure techniques. *Eur J Surg* 1995; 161: 349–54. (CLIN S)
4. Brown SR, Goodfellow PB. Transverse verses midline incisions for abdominal surgery. Cochrane Colorectal Cancer Group. *Cochrane Database Syst Rev* 2007; 4. (STAT)
5. Halasz NA. Dehiscence of laparotomy wounds. *Am J Surg* 1968; 116: 210–4. (CLIN S)
6. Del Junco T, Lange HJ. Abdominal wound disruption with eventration: report of forty cases. *Am J Surg* 1956; 92: 271–86. (CLIN S)
7. Mäkelä JT, Kiviniemi H, Juvonen T, Laitinen S. Factors influencing wound dehiscence after midline laparotomy. *Am J Surg* 1995; 170: 387–90. (CLIN S)
8. Poole GV Jr. Mechanical factors in abdominal wound closure: the prevention of fascial dehiscence. *Surgery* 1985; 97: 631–40. (CLIN S)
9. Riou JP, Cohen JR, Johnson H Jr. Factors influencing wound dehiscence. *Am J Surg* 1992; 163: 324–30. (CLIN S)
10. Ellis H, Coleridge-Smith PD, Joyce AD. Abdominal incisions—vertical or transverse? *Postgrad Med J* 1984; 60: 407–10. (RCT)
11. Greenall MJ, Evans M, Pollock AV. Midline or transverse laparotomy? A random controlled clinical trial. Part I: Influence on healing. *Br J Surg* 1980; 67: 188–90. (RCT)

#6: GUIDELINES TO DECREASE THE IMPEDIMENT TO ACUTE WOUND HEALING CAUSED BY SYSTEMIC IMMUNE DEFICIENCIES

Preamble: The cellular and humoral inflammatory immune response is a vital part of the mechanism of normal wound healing. Systemic immune deficiency diseases such as HIV infection or the acquired immunodeficiency syndrome (AIDS) and hypogammaglobulinemia have been associated with acute wound healing defects. The increased volume of solid organ and bone marrow transplantation has led to a widespread use of immunosuppressant drugs. Leukopenia may be the result of hematologic diseases or iatrogenic bone marrow suppression. Pathological or iatrogenic immunosuppression impairs acute wound healing.

Guideline #6.1: HIV seropositive patients, especially those with AIDS, should be maximally medically treated for that disease whenever possible before elective operations. Antiretroviral therapy should be initiated, viral load minimized, and absolute lymphocyte count maximized. Effective prophylaxis against wound infection should be used.

Level of evidence: I

Principle: The effect of HIV infection on acute wound healing is multifactorial. Normal cellular immunity is required for normal acute wound healing. A complicating wound infection or associated systemic infection will impair acute wound healing. Finally, progressive malnutrition or hypoalbuminemia is an impediment to acute wound healing.

Evidence:

1. Davis PA, Corless DJ, Gazzard BG, Wastell C. Increased risk of wound complications and poor healing following laparotomy in HIV-seropositive and AIDS patients. *Dig Surg* 1999; 16: 60–7. (CLIN S)
2. Nadal SR, Manzione CR, Galvao VM, Salim VR, Speranzini MB. Healing after anal fistulotomy: a comparative study between HIV+ and HIV− patients. *Dis Colon Rectum* 1998; 41: 177–9. (CLIN S)
3. Lord RV. Anorectal surgery in patients infected with human immunodeficiency virus: factors associated with delayed wound healing. *Ann Surg* 1997; 226: 92–9. (CLIN S)
4. Luck JV. Orthopaedic surgery in the HIV positive patient: complications and outcome. *Instr Course Lect* 1994; 43: 543–9. (CLIN S)
5. Davis PA, Wastell D. A comparison of biomechanical properties of excised mature scars from HIV patients and non-HIV controls. *Am J Surg* 2000; 180: 217–22. (EXP)
6. Pankhurst CL, Lewis DA, Clark DT. Prophylactic application of an intra-alveolar socket medicament to reduce postextraction complications in HIV-seropositive patients. *Oral Surg Oral Med Oral Path* 1994; 77: 33133–4. (RCT)
7. Harrison WJ, Lewis CP, Lavy CB. Wound healing after implant surgery in HIV-positive patients. *J Bone Jt Surg* 2002; 84: 802–6. (CLIN S)
8. Morandi E, Merlini D, Salvaggio A, Foschi D, Trabucchi E. Prospective study of healing time after hemorrhoidectomy: influence of HIV infection, acquired immunodeficiency syndrome, and anal wound infection. *Dis Colon Rectum* 1999; 42: 1140–4. (CLIN S)
9. Ortega KL, Rezende NP, Araujo NS, Magalhaes MH. Effect of topical antimicrobial paste on healing after extraction of molars in HIV positive patients. *Br J Oral Maxillofac Surg* 2007; 45: 27–9. (RCT)

Guideline #6.2: Immunosuppressant drug activity (level) should be minimized whenever possible during surgical procedures and until the acute wound is healed. In particular, steroid doses should be minimized before wounding and during wound healing. However, if an emergency procedure is necessary for a patient on steroids, the steroids must be supported throughout the procedure and weaned postoperatively.

Level of evidence: I

Principle: The humoral and cellular inflammatory response is a fundamental part of the mechanism of acute wound healing. Defects in the early humoral and cellular immune response will increase the risk for both wound infection and acute, mechanical wound failure.

Evidence:

1. Hunt T. Disorders of wound healing. *World J Surg* 1980; 4: 271–7. (LIT REV)
2. Stephens FO, Dunphy JE, Hunt TK. Effect of delayed administration of corticosteroids on wound contraction. *Ann Surg* 1971; 173: 21421–8. (EXP)

3. Gupta A, Jain GK, Raghubir R. A time course study for the development for an immunocompromised wound model using hydrocortisone. *J Pharmacol Toxicol Methods* 1999; 41: 183–7. (EXP)
4. Karatas GU, Yakupoglu U, Yakupoglu YK, Kocak H, Yavuz A, Dinckan A, Tuncer M, Demirbas A, Yakupoglu G, Ersoy FF, Gurkan A. Sirolimus as primary immunosuppression agent in kidney transplant recipients: Akdeniz University experience. *Transplant Proc* 2005; 37: 3006–8. (CLIN S)
5. Anil Kumar MS, Heifets M, Fyfe B, Saaed MI, Moritz MJ, Parikh MH, Kumar A. Comparison of steroid avoidance in tacrolimus/mycophenolate mofetil and tacrolimus/sirolimus combination in kidney transplantation monitored by surveillance biopsy. *Transplantation* 2005; 80: 807–14. (CLIN S)
6. Lo A, Egidi MF, Gaber LW, Gaber AO. Observations on the use of sirolimus and tacrolimus in high-risk renal transplant recipients. *Transplant Proc* 2003; 35 (Suppl.): 105S–8S. (CLIN S)
7. Kuypers DR. Benefit-risk assessment of sirolimus in renal transplantation. *Drug Safety* 2005; 28: 153–81. (LIT REV)

Guideline #6.3: Leukopenia should be corrected whenever possible before an elective surgical procedure. Granulocyte-monocyte colony-stimulating growth factors or blood transfusion may be considered.

Level of evidence: II

Principle: Wound infection delays acute wound healing. White blood cells are also sources for tissue growth factors. Clinically and experimentally, macrophages are required for normal wound healing. Abnormal wound healing occurs in the setting of leukopenia.

Evidence:

1. Elihu A, Gollin G. Complications of implanted central venous catheters in neutropenic children. *Am Surg* 2007; 73: 1079–82. (CLIN S)
2. Shirafuji T, Oka T, Sawada T, Tamura K, Kishimoto K, Yamamoto S, Nagayasu T, Takahashi T, Ayabe H. The importance of peripheral blood leukocytes and macrophage infiltration on bronchial wall wound healing in rats treated preoperatively with anticancer agents. *Surg Today* 2001; 31: 308–16. (EXP)
3. Li Z, Burns AR, Smith CW. Two waves of neutrophil emigration in response to corneal epithelial abrasion: distinct adhesion molecule requirements. *Invest Ophthal Visual Sci* 2006; 47: 1947–55. (EXP)
4. Borregaard N, Theilgaard-Monch K, Cowland JB, Ståhle M, Sørensen OE. Neutrophils and keratinocytes in innate immunity—cooperative actions to provide antimicrobial defense at the right time and place. *J Leukoc Biol* 2005; 77: 439–43. (EXP)
5. Vettenranta K, Hovi L, Makipernaa A, Jalanko H, Saarinen-Pihkala UM. Neutrophil regeneration precedes healing of tissue destruction, as indicated by serum C-reactive protein, in children with cancer recovering from neutropenic fever. *Acta Paediatr* 2002; 91: 915–9. (CLIN S)
6. Cody DT II, Funk GF, Wagner D, Gidley PW, Graham SM, Hoffman HT. The use of granulocyte colony stimulating factor to promote wound healing in a neutropenic patient after head and neck surgery. *Head Neck* 1999; 21: 172–5. (RETRO S)
7. Mayer B, Rösken F, Lepper A, Wanner GA, Menger MD. rG-CSF improves tissue regeneration in neutropenia-induced disorders of wound healing. *Langenbecks Arch Chir* 1998; 115 (Suppl. I): 469–70. (EXP)
8. Masucci G. New clinical applications of granulocyte-macrophage colony-stimulating factor. *Med Oncol* 1996; 13: 149–54. (LIT REV)
9. Jyung RW, Wu L, Pierce GF, Mustoe TA. Granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor: differential action on incisional wound healing. *Surgery* 1994; 115: 325–34. (EXP)
10. Besner GE, Glick PL, Karp MP, Wang WC, Lobe TE, White CR, Cooney DR. Recombinant human granulocyte colony-stimulating factor promotes wound healing in a patient with congenital neutropenia. *J Pediatr Surg* 1992; 27: 288–91. (RETRO S)
11. Schaffer MR, Barbul A. Lymphocyte function in wound healing and following injury. *Br J Surg* 1998; 85: 444–60. (LIT REV)

Guideline #6.4: Blood transfusions have an immunosuppressant effect and can delay wound healing. Blood transfusions should be minimized before and following wounding.

Level of evidence: I

Principle: Tolerance of blood transfusions requires a relative immunosuppressed response on the part of the host (transfusion recipient). Perioperative blood transfusions are associated with worse outcomes in surgical oncology and trauma. The minimum tissue concentration of oxygen (TcO_2) required for wound healing can be maintained at lower serum hematocrits.

Evidence:

1. Tadros T, Wobbes T, Hendriks T. Blood transfusion impairs the healing of experimental intestinal anastomoses. *Ann Surg* 1992; 215: 276–81. (EXP)
2. Rappolee DA, Mark D, Banda MJ, Werb Z. Wound macrophages express TGF-beta and other growth-factors in vivo: analysis by mRNA phenotyping. *Science* 1988; 241: 708–12. (EXP)
3. Thornton FJ, Schaffer MR, Barbul A. Wound healing in sepsis and trauma. *Shock* 1997; 8: 391–401. (LIT REV)
4. Schaffer MR, Barbul A. Lymphocyte function in wound healing and following injury. *Br J Surg* 1998; 85: 444–60. (LIT REV)
5. Tartter P. Immunologic effects of blood transfusion. *Immunol Invest* 1995; 24: 2777–88. (LIT REV)
6. Ohwada S, Sato Y, Sato N, Toyama Y, Okano T, Nakasone Y, Ogawa T, Morishita Y. Effect of transfusion in gastrointestinal anastomotic wound healing and leukocyte function in rats. *Eur Surg Res* 2000; 32: 353–8. (EXP)
7. Apostolidis SA, Michalopoulos AA, Hytiroglou PM, Papadopoulos BN, Fachantidis EP, Basdanis GA, Catsohis CD. Prevention of blood-transfusion-induced impairment of anastomotic healing by leukocyte depletion in rats. *Eur J Surg* 2000; 166: 562–7. (EXP)

8. Artioukh DY, Smith RA, Gokul K. Risk factors for impaired healing of the perineal wound after abdominoperineal resection of rectum for carcinoma. *Colorectal Dis* 2007; 9: 362–7. (CLIN S)
9. Brown CV, Velmahos GC, Neville AL, Rhee P, Salim A, Sangthong B, Demetriades D. Hemodynamically "stable" patients with peritonitis after penetrating abdominal trauma: identifying those who are bleeding. *Arch Surg* 2005; 140: 767–72. (CLIN S)
10. Weber EW, Slappendel R, Prins MH, van der Schaaf DB, Durieux ME, Strümper D. Perioperative blood transfusions and delayed wound healing after hip replacement surgery: effects on duration of hospitalization. *Anesth Analg* 2005; 100: 1416–21. (CLIN S)
11. Okano T, Ohwada S, Sato Y, Sato N, Toyama Y, Nakasone Y, Ogawa T, Morishita Y. Blood transfusions impair anastomotic wound healing, reduce luminol-dependent chemiluminescence, and increase interleukin-8. *Hepato-Gastroenterology* 2001; 48: 1669–74. (EXP)
12. Mandai R, Eguchi Y, Tanaka M, Sai Y, Nosaka S. Effects of profound hemodilution on small-intestinal wound healing in rabbits. *J Surg Res* 2001; 99: 107–13. (EXP)
13. Ohwada S, Sato Y, Sato N, Toyama Y, Okano T, Nakasone Y, Ogawa T, Morishita Y. Effects of transfusion on gastrointestinal anastomotic wound healing and leukocyte function in rats. *Eur Surg Res* 2000; 32: 353–8. (EXP)
14. Chmell MJ, Schwartz HS. Analysis of variables affecting wound healing after musculoskeletal sarcoma resections. *J Surg Oncol* 1996; 61: 185–9. (RETRO S)

#7: GUIDELINES TO DECREASE THE IMPEDIMENT TO ACUTE WOUND HEALING CAUSED BY CANCER AND ITS TREATMENT

Preamble: Malignant diseases will soon overtake cardiovascular disease as the leading cause of mortality in the United States. Malignant neoplasia is fundamentally dysregulated cellular proliferation, while wound healing represents regulated or controlled cellular proliferation. The mechanism of cancer therapy, therefore, usually involves the inhibition of cellular proliferation and function, which also will impair or prevent wound healing.

Guideline #7.1: Chemotherapeutic drugs impair wound healing. Attempts should be made to maximize the time between neo-adjuvant and adjuvant therapies and surgical wounding.

Level of evidence: I

Principle: The most common chemotherapeutic agents are cytotoxic (nitrogen mustards and methylating agents), antiproliferative (microtubule stabilizers and DNA synthesis inhibitors), or antimetabolic (folic acid synthesis inhibitors). All of these pathways are normally activated during normal wound healing (benign neoplasia). Chemotherapeutic drugs therefore impair wound healing by the same mechanisms that they inhibit malignant cell growth.

Evidence:

1. Shirafuji T, Oka T, Sawada T, Tamura K, Nagayasu T, Takeya M, Yoshimura T, Ayabe H. Effects of induction therapy on wound healing at bronchial anastomosis sites in rats. *Jpn J Thorac Cardiovasc Surg* 2003; 51: 217–24. (EXP)
2. Shamberger RC, Devereux DF, Brennan MF. The effect of chemotherapeutic agents on wound healing. *Int Adv Surg Oncol* 1981; 4: 15–58. (LIT REV)
3. Best PJ, Daoud MS, Pittelkow MR, Petitt RM. Hydroxyurea-induced leg ulceration in 14 patients. *Ann Intern Med* 1998; 128: 29–32. (RETRO S)
4. Coleman JJ III, Walker AP, Didolkar MS. Treatment of adriamycin-induced skin ulcers: a prospective controlled study. *J Surg Oncol* 1983; 22: 129–35. (CLIN S)
5. Cohen MH, Gootenberg J, Keegan P, Pazdur R. FDA drug approval summary: bevacizumab plus FOLFOX4 as second-line treatment of colorectal cancer. *Oncologist* 2007; 12: 356–61. (RCT)
6. Arbeit JM, Hilaris BS, Brennan MF. Wound complications in the multimodality treatment of extremity and superficial truncal sarcomas. *J Clin Oncol* 1987; 5: 480–8. (RCT)
7. Graf W, Ivarsson M, Gerdin B, Hellsing K, Påhlman L, Glimelius B. The influence of early postoperative intraperitoneal chemotherapy on human wound healing. *J Surg Res* 1994; 57: 394–400. (CLIN S)
8. Ariyan S, Craft RL, Goldberg NH. An experimental model to determine the effects of adjuvant therapy on the incidence of postoperative wound infection: II. Evaluating preoperative chemotherapy. *Plast Reconstr Surg* 1980; 65: 338–45. (EXP)
9. Ferguson MK. The effect of antineoplastic agents on wound healing. *Surg Gynecol Obstet* 1982; 154: 421–9. (LIT REV)
10. Cohen SC, Gabelnick HL, Johnson RK, Goldin A. Effects of antineoplastic agents on wound healing in mice. *Surgery* 1975; 78: 238–44. (EXP)
11. Desprez JD, Kiehn CL. The effects of cytoxan (cyclophosphamide) on wound healing. *Plast Reconstr Surg Transplant Bull* 1960; 26: 301–8. (LIT REV)
12. Cohen SC, Gabelnick HL, Johnson RK, Goldin A. Effects of cyclophosphamide and adriamycin on the healing of surgical wounds in mice. *Cancer* 1975; 36: 1277–81. (EXP)
13. Rath H, Enquist IF. The effect of thio-TEPA on wound healing. *Arch Surg* 1959; 79: 812–4. (CLIN S)
14. Farhat SM, Miller DM, Musselman MM. Effect of triethylenethiophosphoramide (thio-TEPA) upon healing abdominal wounds. *Arch Surg* 1959; 78: 729–31. (EXP)
15. Hardesty WH. The effect of cytotoxic drugs on wound healing in rats. *Cancer Res* 1958; 18: 581–4. (EXP)
16. Fisher B, Ravdin RG, Ausman RK, Slack NH, Moore GE, Noer RJ. Surgical adjuvant chemotherapy in cancer of the breast: results of a decade of cooperative investigation. *Ann Surg* 1968; 168: 337–56. (STAT)
17. Mrazek R, Economou S, McDonald GO, Slaughter DP, Cole WH. Prophylactic and adjuvant use of nitrogen mustard in the surgical treatment of cancer. *Ann Surg* 1959; 150: 745–55. (CLIN S)

18. Falcone RE, Nappi JF. Chemotherapy and wound healing. *Surg Clin North Am* 1984; 64: 779–94. (LIT REV)
19. Hendricks T, Martens MF, Huyben CM, Wobbes T. Inhibition of basal and TGF beta-induced fibroblast collagen synthesis by antineoplastic agents. Implications for wound healing. *Br J Cancer* 1993; 67: 545–50. (EXP)
20. Devereux DF, Thibault L, Boretos J, Brennan MF. The quantitative and qualitative impairment of wound healing by adriamycin. *Cancer* 1979; 43: 932–8. (EXP)
21. Devereux DF, Kent H, Brennan MF. Time dependent effects of adriamycin and x-ray therapy on wound healing in the rat. *Cancer* 1980; 45: 2805–10. (EXP)
22. Ehrlich HP, Hunt TK. Effects of cortisone and vitamin A on wound healing. *Ann Surg* 1968; 167: 324–8. (LIT REV)

Guideline #7.2: Radiated tissue does not heal normally. Efforts should be made to operate through nonradiated tissue, or to optimize the healing of radiated tissue once it is injured.

Level of evidence: I

Principle: The healing of radiated tissue is impaired due mainly to fibrotic microangiopathy. The result is subthreshold tissue oxygen levels for normal acute wound healing. Technically, tissue planes are distorted due to fibrosis. Healing may be improved by increasing tissue oxygen levels, as with hyperbaric oxygen therapy.

Evidence:

1. Michalowski AS. On radiation damage to normal tissues and its treatment. II. Anti-inflammatory drugs. *Acta Oncol* 1994; 33: 139–57. (LIT REV)
2. Halperin EC, Gaspar L, George S, Darr D, Pinnell S. A double-blind, randomized, prospective trial to evaluate topical vitamin C solution for the prevention of radiation dermatitis. CNS Cancer Consortium. *Int J Radiat Oncol Biol Phys* 1993; 26: 413–6. (RCT)
3. Kouvaris JR, Kouloulias VE, Plataniotis GA, Balafouta EJ, Vlahos LJ. Dermatitis during radiation for vulvar carcinoma: prevention and treatment with granulocyte-macrophage colony-stimulating factor impregnated gauze. *Wound Rep Regen* 2001; 9: 187–93. (CLIN S)
4. Wong RKS, Tandan V, De Silva S, Figueredo A. Preoperative radiotherapy and curative surgery for the management of localized rectal carcinoma. Cochrane Colorectal Cancer Group. *Cochrane Database Syst Rev* 2007; 4. (STAT)
5. van Doorn HC, Ansink A, Verhaar-Langereis M, Stalpers L. Neoadjuvant chemoradiation for advanced primary vulvar cancer. Cochrane Gynaecological Cancer Group. *Cochrane Database Syst Rev* 2007; 4. (STAT)
6. Bennett MH, Feldmeier J, Hampson N, Smee R, Milross C. Hyperbaric oxygen therapy for late radiation tissue injury. Cochrane Gynaecological Cancer Group. *Cochrane Database Syst Rev* 2007; 4. (STAT)
7. Hillmann A, Ozaki T, Rübe C, Hoffmann C, Schuck A, Blasius S, Haas A, Jürgens H, Winkelmann W. Surgical complications after preoperative irradiation of Ewing's sarcoma. *J Cancer Res Clin Oncol* 1997; 123: 57–62. (CLIN S)
8. Bernstein EF, Sullivan FJ, Mitchell JB, Salomon GD, Glatstein E. Biology of chronic radiation effects on tissues and wound healing. *Clin Plast Surg* 1993; 20: 435–53. (LIT REV)
9. Mendelsohn FA, Divino CM, Reis ED, Kerstein MD. Wound care after radiation therapy. *Adv Skin Wound Care* 2002; 15: 216–24. (LIT REV)
10. Dobbs WGH. A statistical study of the effects of roentgen rays on wound healing. *Am J Roentgenol* 1939; 41: 625–32. (EXP)
11. Kindwall EP. Hyperbaric oxygen's effect on radiation necrosis. *Clin Plast Surg* 1993; 20: 473–83. (LIT REV)
12. Luce EA. The irradiated wound. *Surg Clin North Am* 1984; 64: 821–9. (LIT REV)
13. Marcial VA, Gelber R, Kramer S, Snow JB, Davis LW, Vallecillo LA. Does preoperative irradiation increase the rate of surgical complications in carcinoma of the head and neck? *Cancer* 1982; 49: 1297–301. (LIT REV)
14. Joseph DL, Shumrick DL. Risks of head and neck surgery in previously irradiated patients. *Arch Otolaryngol* 1973; 97: 381–4. (LIT REV)
15. Vikram B. Importance of the time interval between surgery and postoperative radiation therapy in the combined management of head and neck cancer. *Int J Radiat Oncol Biol Phys* 1979; 5: 1837–40. (RETRO S)
16. Isaacs JH Jr., Thompson WB, Cassisi NJ, Million RR. Postoperative radiation of open head and neck wounds. *Laryngoscope* 1987; 97 (Part 1): 267–70. (RETRO S)
17. Porock D. Factors influencing the severity of radiation skin and oral mucosal reactions: development of a conceptual framework. *Eur J Cancer Care (Engl)* 2002; 116: 33–43. (LIT REV)
18. Martin M, Vozenin MC, Gault N, Crechet F, Pfarr CM, Lefaix JL. Coactivation of AP-1 activity and TGF-beta 1 gene expression in the stress response of normal skin cells to ionizing radiation. *Oncogene* 1997; 15: 981–9. (EXP)

Guideline #7.3: Cancer patients may develop unique malnutrition syndromes (cancer cachexia). This is, in part, due to elevated tumor associated cytokine levels (tumor necrosis factor [TNF]). Enteral nutrient supplementation, but not parenteral nutrient supplementation, improves wound healing in cancer patients.

Level of evidence: I

Principle: Hypoalbuminemia is a well-established marker for surgical complications, including impaired wound healing. Cancer patients often express protein malnutrition. In addition, cancer patients may express a unique malnutrition syndrome, cancer cachexia or cancer anorexia. It is believed that part of the mechanism for this paraneoplastic syndrome is elevated stress or inflammatory cytokines, especially TNF-α (cachexin). Cancer cachexia is also associated with surgical complications and poor wound healing.

Evidence:

1. de Luis DA, Izaola O, Cuellar L, Terroba MC, Aller R. Randomized clinical trial with an enteral arginine-

enhanced formula in early postsurgical head and neck cancer patients. *Eur J Clin Nutr* 2004; 58: 1505–8. (RCT)
2. Farreras N, Artigas V, Cardona D, Rius X, Trias M, González JA. Effect of early postoperative enteral immunonutrition on wound healing in patients undergoing surgery for gastric cancer. *Clin Nutr* 2005; 24: 55–65. (RCT)
3. Milne AC, Potter J, Avenell A. Protein and energy supplementation in elderly people at risk from malnutrition. Cochrane Metabolic and Endocrine Disorders Group. *Cochrane Database Syst Rev* 2007; 4. (STAT)
4. Sako K, Lore JM, Kaufman S, Razack MS, Bakamjian V, Reese P. Parenteral hyperalimentation in surgical patients with head and neck cancer: a randomized study. *J Surg Oncol* 1981; 16: 391–402. (RCT)
5. Aoki K, Ikeda K, Sato N. Clinical appraisal of the additional total parenteral nutrition combined with postoperative enteral feeding on the patient of thoracic esophageal cancer surgery. *Jpn J Gastroenterol Surg* 2000; 33: 693–702. (RCT)
6. Ollenschläger G, Veill B, Thomas W, Konkol K, Bürger B. Tumor anorexia: causes, assessment, treatment. *Recent Results Cancer Res* 1991; 121: 249–59. (LIT REV)
7. The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. Perioperative total parenteral nutrition in surgical patients. *N Engl J Med* 1991; 325: 525–32. (STAT)
8. Marino PL, Finnegan MJ. Nutrition support is not beneficial and can be harmful in critically ill patients. *Crit Care Clin* 1996; 12: 667–76. (CLIN S)
9. Fischer JE. Nutritional support in the seriously ill patient. *Curr Prob Surg* 1980; 8: 469–532. (LIT REV)
10. Moore FA, Feliciano DV, Andrassy RJ, McArdle AH, Booth FV, Morgenstein-Wagner TB, Kellum JM Jr., Welling RE, Moore EE. Early enteral feeding, compared with parenteral, reduces postoperative septic complications: the results of a meta-analysis. *Ann Surg* 1992; 216: 172–83. (STAT)
11. Rivadeneira DE, Evoy D, Fahey TJ III, Lieberman MD, Daly JM. Nutritional support of the cancer patient. *CA Cancer J Clin* 1998; 48: 69–80. (LIT REV)
12. Lawrence WT, Norton JA, Harvey AK, Gorschboth CM, Talbot TL, Grotendorst GR. Wound healing in sarcoma-bearing rats: tumor effects on cutaneous and deep wounds. *J Surg Oncol* 1987; 35: 7–12. (EXP)
13. Heys SD, Gough DB, Eremin O. Is nutritional support in patients with cancer undergoing surgery beneficial? *Eur J Surg Oncol* 1999; 22: 292–7. (LIT REV)
14. Nixon DW, Heymsfield SB, Cohen AE, Kutner MH, Ansley J, Lawson DH, Rudman D. Protein-calorie undernutrition in hospitalized cancer patients. *Am J Med* 1980; 66: 683–90. (CLIN S)

#8: GUIDELINES TO DECREASE THE IMPEDIMENT TO ACUTE WOUND HEALING CAUSED BY SYSTEMIC CONDITIONS SUCH AS DIABETES MELLITUS, AGE, OBESITY, MALNUTRITRION, ETC.

Preamble: There are systemic conditions or diseases that affect the ability of wounds to heal in an orderly and timely manner. Optimizing aspects of these conditions or diseases can aid in maximizing the wound healing trajectory, even when the condition or disease cannot be completely eliminated.

Guideline #8.1: Optimizing glucose control improves wound healing.

Level of evidence: II

Principle: In patients with diabetes, wound healing is more likely to be optimal in the setting of good glucose control. Abnormal glucose levels also affect the character of infection.

Evidence:

1. Marston WA, Dermagraft Diabetic Foot Ulcer Study Group. Risk factors associated with healing chronic diabetic foot ulcers: the importance of hyperglycemia. *Ostomy Wound Manage* 2006; 52: 26–8. (RCT)
2. Rubinstein A, Pierce CE. Rapid healing of diabetic foot ulcers with a meticulous blood glucose control. *Acta Diabetol Lat* 1988; 25: 25–32. (CLIN S)
3. Lazar HL, Chipkin SR, Fitzgerald CA, Bao Y, Cabral H, Apstein CS. Tight glycemic control in diabetic coronary artery bypass graft patients improves perioperative outcomes and decreases recurrent ischemic events. *Circulation* 2004; 109: 1497–52. (RCT)
4. Rai NK, Suryabhan, Ansari M, Kumar M, Shukla VK, Tripathi K. Effect of glycaemic control on apoptosis in diabetic wounds. *J Wound Care* 2005; 14: 277–81. (CLIN S)
5. Robson MC, Heggers JP. Variables in host resistance pertaining to septicemia. I. Blood glucose level. *J Am Geriatr Soc* 1969; 17: 991–6. (CLIN S)
6. Blondet JJ, Beilman GJ. Glycemic control and prevention of perioperative infection. *Curr Opin Crit Care* 2007; 13: 421–7. (LIT REV)
7. Robson MC. A new look at diabetes mellitus and infection. *Am J Surg* 1970; 120: 681–2. (EXP)
8. Follak N, Kloting I, Merk H. Influence of diabetic metabolic state on fracture healing in spontaneously diabetic rats. *Diabetes Metab Res Rev* 2005; 21: 288–96. (EXP)
9. Duckworth WC, Fawcett J, Reddy S, Page JC. Insulin-degrading activity in wound fluid. *J Clin Endocrinal Metab* 2004; 89: 847–51. (EXP)
10. Beam HA, Parsons JR, Lin SS. The effects of blood glucose control upon fracture healing in the BB Wistar rat with diabetes mellitus. *J Orthop Res* 2002; 20: 1210–6. (EXP)
11. Verhofstad MH, Hendriks T. Complete prevention of impaired anastomatic healing in diabetic rats requires preoperative blood glucose control. *Br J Surg* 1996; 83: 1717–21. (EXP)
12. Spravchikov N, Sizyakov G, Gartsbein M, Accili D, Tennenbaum T, Wertheimer E. Glucose effects on skin keratinocytes: implications for diabetes skin complications. *Diabetes* 2001; 50: 1627–35. (EXP)
13. Greenhalgh DG. Wound healing and diabetes mellitus. *Clin Plast Surg* 2003; 30: 37–45. (LIT REV)
14. Golden SH, Peart-Vigilance C, Kao WH, Brancati FL. Perioperative glycemic control and the risk of infectious complications in a cohort of adults with diabetes. *Diabetes Care* 1999; 22: 1408–14. (CLIN S)

15. Deveci M, Gilmont RR, Dunham WR, Mudge BP, Smith DJ, Marcelo CL. Glutathione enhances fibroblast collagen contraction and protects keratinocytes from apoptosis in hyperglycemic culture. *Br J Dermatol* 2005; 152: 217–24. (EXP)

Guideline #8.2: Although older patients may have physiologic impairments in wound healing, the incidence of healing is similar to younger patients but at a slower rate.

Level of evidence: II

Principle: In elderly patients without other significant medical conditions, the rate of wound healing is normal or mildly impaired. Systemic and regional medical conditions are more common in the aged and account for many of the delays in healing.

Evidence:

1. Aschcroft GS, Horan MA, Ferguson MW. Aging is associated with reduced deposition of specific extracellular matrix components, an upregulation of angiogenesis, and an altered inflammatory response in a murine incisional wound healing model. *J Invest Dermatol* 1997; 108: 430–7. (EXP)
2. Fatah MF. The morbidity of split-skin graft donor sites in the elderly: the case for mesh-grafting the donor site. *Br J Plast Surg* 1984; 37: 184–90. (RCT)
3. Brem H, Tomic-Canic M, Tarnovskaya A, Ehrlich HP, Baskin-Bey E, Gill K, Carasa M, Weinberger S, Entero H, Vladeck B. Healing of elderly patients with diabetic foot ulcers, venous stasis ulcers, and pressure ulcers. *Surg Technol Int* 2003; 11: 161–7. (LIT REV)
4. Quirinia A, Viidik A. The influence of age on the healing of normal and ischemic skin wounds. *Mech Ageing Dev* 1991; 58: 221–32. (EXP)
5. Gosain A, DiPietro LA. Aging and wound healing. *World J Surg* 2004; 28: 321–6. (LIT REV)
6. Gerstein AD, Phillips TJ, Rogers GS, Gilchrest BA. Wound healing and aging. *Dermatol Clin* 1993; 11: 749–57. (LIT REV)
7. Van de Kerkhof PC, Van Bergen B, Spruijt K, Kuiper JP. Age-related changes in wound healing. *Clin Exp Dematol* 1994; 19: 369–74. (LIT REV)
8. Holt D, Kirk SJ, Regan MC, Hurson M, Lindblad WJ, Barbul A. Effect of age on wound healing in healthy humans. *Surgery* 1992; 112: 293–8. (EXP)

Guideline #8.3: Obesity is associated with a higher incidence of wound complications. This should be considered when deciding whether to perform elective operations.

Level of evidence: II

Principle: There is an epidemic of obesity in the Western culture. Obesity is associated with an increased risk of surgical site infections, wound dehiscence, and hernia. Complications at sites distant from the wound also are increased.

Evidence:

1. Gendall KA, Raniga S, Kennedy R, Frizelle FA. The impact of obesity on outcome after major colorectal surgery. *Dis Colon Rectum* 2007; 50: 2223–37. (LIT REV)
2. Anaya DA, Dellinger EP. The obese surgical patient: a susceptible host for infection. *Surg Infect (Larchmt)* 2006; 7: 473–80. (LIT REV)
3. Bamgbade OA, Rutter TW, Nafiu OO, Dorje P. Postoperative complications in obese and non-obese patients. *World J Surg* 2007; 31: 556–60. (RETRO S)
4. Yap CH, Zimmet A, Mohajeri M, Yii M. Effect of obesity on early morbidity and mortality following cardiac surgery. *Heart Lung Circ* 2007; 16: 31–6. (CLIN S)
5. Kaye KS, Sloane R, Sexton DJ, Schmader KA. Risk factors for surgical site infections in older people. *J Am Geriatr Soc* 2006; 54: 391–6. (RETRO S)
6. Gamboa-Bobadilla GM, Killingsworth C. Large-volume reduction mammoplasty: the effect of body mass index on postoperative complications. *Ann Plast Surg* 2007; 58: 246–9. (CLIN S)
7. Villavicencio MA, Sundt TM III, Daly RC, Dearani JA, McGregor CG, Mullany CJ, Orszulak TA, Puga FJ, Schaff HV. Cardiac surgery in patients with body mass index of 50 or greater. *Ann Thorac Surg* 2007; 83: 1403–11. (CLIN S)
8. Friedman ND, Sexton DJ, Connelly SM, Kaye KS. Risk factors for surgical site infection complicating laminectomy. *Infect Control Hosp Epidemiol* 2007; 28: 1060–5. (CLIN S)
9. Patel VI, Hamdan AD, Schermerhorn ML, Hile C, Dahlberg S, Campbell DR, LoGerfo FW, Pomposelli FB. Lower extremity arterial revascularization in obese patients. *J Vasc Surg* 2007; 46: 738–42. (CLIN S)
10. Derzie A, Silvestri F, Liriano E, Benott I. Wound closure technique and acute wound complications in gastric surgery for morbid obesity: a prospective randomized trial. *J Am Coll Surg* 2000; 191: 238–48. (RCT)

Guideline #8.4: Nutrition must be adequate to provide metabolic support for healing. Weight and prealbumin and albumin levels are helpful in identifying patients who are malnourished and may need nutritional support.

Level of evidence: I

Principle: The nutritional status of most people will allow normal healing to occur. Elderly patients, those with gastrointestinal problems or other debilitating illnesses, and patients institutionalized in long-term care facilities are at greater risk for malnutrition. Obesity, low albumin, and low protein levels are associated with an increased risk of wound dehiscence and infection. Nutritional supplements, including proteins, carbohydrates, fats, vitamins, minerals, and trace elements, improve healing and reduce the likelihood of surgical site infection, wound dehiscence, and hernia.

Evidence:

1. Bourdel-Marchasson I, Barateau M, Rondeau V, Dequae-Merchadou L, Salles-Montaudon N, Emeriau JP, Manciet G, Dartigues JF. A multi-center trial of the effects of oral nutritional supplementation in critically ill older patients. GAGE Group. Group Aquitain

Geriaritrique d'Evaluation. *Nutrition* 2000; 16: 1–5. (RCT)
2. Collins CE, Kershaw J, Brockington S. Effect of nutritional supplements on wound healing in home-nursed elderly: a randomized trial. *Nutrition* 2005; 21: 147–55. (RCT)
3. Braga M, Gianotti L, Nespoli L, Radaelli G, Di Carlo V. Nutritional approach in malnourished surgical patients: a prospective randomized study. *Arch Surg* 2002; 137: 174–80. (RCT)
4. Lee SK, Posthauer ME, Dorner B, Redovian V, Maloney MJ. Pressure ulcer healing with a concentrated, fortified, collagen protein hydrolysate supplement: a randomized controlled trial. *Adv Skin Wound Care* 2006; 19: 92–6. (RCT)
5. Waitzberg DL, Saito H, Plank LD, Jamieson GG, Jagannath P, Hwang TL, Mijares JM, Bihari D. Post-surgical infections are reduced with specialized nutrition support. *World J Surg* 2006; 30: 1592–604. (STAT)
6. Kirk SJ, Hurson M, Regan MC, Holt DR, Wasserkrug HL, Barbul A. Arginine stimulates wound healing and immune function in elderly human beings. *Surgery* 1993; 114: 155–9. (RCT)
7. Lansdown AB. Nutrition 2: a vital consideration in the management of skin wounds. *Br J Nurs* 2004; 13: 1199–210. (LIT REV)
8. Okada A, Takagi Y, Nezu R, Lee S. Zinc in clinical surgery—a research review. *Jpn J Surg* 1990; 20: 635–44. (LIT REV)
9. Doweiko JP, Nompleggi DJ. The role of albumin in human physiology and pathophysiology. Part III: albumin and disease states. *J Parenter Enteral Nutr* 1991; 15: 476–83. (LIT REV)
10. Pedersen NW, Pedersen D. Nutrition as a prognostic indicator in amputations. A prospective study of 47 cases. *Acta Orthop Scand* 1992; 63: 675–8. (CLIN S)
11. Pollack SV. Wound healing: a review. III. Nutritional factors affecting wound healing. *Dermatol Surg Oncol* 1979; 5: 615–9. (LIT REV)
12. Del Savio GC, Zelicof SB, Wexler LM, Byrne DW, Reddy PD, Fish D, Ende KA. Preoperative nutritional status and outcome of elective total hip replacement. *Clin Orthop Relat Res* 1996; 32: 153–61. (CLIN S)
13. Riou JP, Cohen JR, Johnson H Jr. Factors influencing wound dehiscence. *Am J Surg* 1992; 163: 324–30. (RETRO S)
14. Greene KA, Wilde AH, Stulberg BN. Preoperative nutritional status of total joint patients. Relationship to postoperative wound complications. *Arthroplasty* 1991; 6: 321–5. (RETRO S)
15. Makela JT, Kiviniemi H, Juvonen T, Laitinen S. Factors influencing wound dehiscence after midline laparotomy. *Am J Surg* 1995; 170: 387–90. (RETRO S)
16. Shi HP, Wang SM, Zhang GX, Zhang YJ, Barbul A. Supplemental L-arginine enhances wound healing following trauma/hemorrhagic shock. *Wound Rep Regen* 2007; 15: 66–70. (EXP)
17. Williams JG, Barbul A. Nutrition and wound healing. *Surg Clin North Am* 2003; 83: 571–6. (LIT REV)

#9: GUIDELINES TO DECREASE THE IMPEDIMENT TO ACUTE WOUND HEALING CAUSED BY BURN INJURIES

Preamble: Burn injury results in alterations in the normal function of all physiologic systems. These alterations can affect wound healing. The burn victim can have up to four types of wounds that require specialized treatment, and several of these wound types can coexist. The wounds include shallow partial-thickness wounds, which will epithelialize within 21 days; deep wounds that require removal of necrotic tissue and wound closure; donor-site wounds resulting from harvesting of skin grafts; and interstitial wounds resulting from meshed skin graft application. When the combination of these wounds covers a significant total body surface area (TBSA), the manner in which the wounds heal can be the final determinant of morbidity and mortality.

Guideline #9.1: For deep burn wounds, early eschar excision and wound closure is indicated.
Level of evidence: I

Principle: Early removal of necrotic tissue decreases abnormalities to the immune system, decreases the risk of infection, improves survival, and initiates a normal healing trajectory.

Evidence:

1. Ong YS, Samuel M, Song C. Meta-analysis of early excision of burns. *Burns* 2006; 32: 145–50. (STAT)
2. Engrav LH, Heimbach DM, Reus JL, Harnar TJ, Marvin JA. Early excision and grafting vs. nonoperative treatment of burns of indeterminant depth: a randomized prospective study. *J Trauma* 1983; 23: 1001–4. (RCT)
3. Gray DT, Pine RW, Harnar TJ, Marvin JA, Engrav LH, Heimbach DM. Early surgical excision versus conventional therapy in patients with 20 to 40 percent burns. A comparative study. *Am J Surg* 1982; 144: 76–80. (RCT)
4. Herndon DN, Barrow RE, Rutan RL, Rutan TC, Desai MH, Abston S. A comparison of conservative versus early excision therapies in severely burned patients. *Ann Surg* 1989; 209: 547–52. (RCT)
5. Herndon DN, Parks DH. Comparison of serial debridement and autografting and early massive excision with cadaver skin overlay in the treatment of large burns in children. *J Trauma* 1986; 26: 149–52. (RCT)
6. Sorensen B, Fisker NP, Steensen JP, Kalaja E. Acute excision or exposure treatment? Final results of a three-year randomized controlled clinical trial. *Scand J Plast Reconstr Surg* 1984; 18: 87–93. (RCT)
7. Tompkins RG, Burke JF, Schoenfeld DA, Bondoc CC, Quinby WC Jr, Behringer GC, Ackroyd FW. Prompt eschar excision: a treatment system contributing to reduced burn mortality. A statistical evaluation of burn care at the Massachusetts General Hospital (1974–1984). *Ann Surg* 1986; 204: 272–81. (CLIN S)
8. Janzekovic Z. The burn wound from a surgical point of view. *J Trauma* 1975; 15: 42–62. (CLIN S)
9. Muangman P, Sullivan SR, Honari S, Engrav LH, Heimbach DM, Gibran NS. The optimal time for early

excision in major burn injury. *J Med Assoc Thai* 2006; 89: 29–36. (RETRO S)

Guideline #9.2: Scald burns in children, burns in the elderly, burns in patients with severe inhalation injury, and burns of special areas (hands and face) may be considered exceptions to early excision and grafting of deep burns.

Level of evidence: II
Principle: Early excision and grafting can impose a significant insult to patients at the extremes of age or with significant comordid conditions such as smoke inhalation. It has been difficult to prove superior results for early excision and grafting of hand or facial burns.

Evidence:

1. Desai MH, Rutan RL, Herndon DN. Conservative treatment of scald burns is superior to early excision. *J Burn Care Rehabil* 1991; 12: 482–4. (RCT)
2. Irei M, Abston S, Bonds E, Rutan T, Desai M, Herndon DN. The optimal time for excision of scald burns in toddlers. *J Burn Care Rehabil* 1986; 7: 508–10. (RETRO S)
3. Kirn DS, Luce EA. Early excision and grafting versus conservative management of burns in the elderly. *Plast Reconstr Surg* 1998; 102: 1013–7. (RETRO S)
4. Housinger T, Saffle J, Ward S, Warden G. Conservative approach to the elderly patient with burns. *Am J Surg* 1984; 148: 817–20. (RETRO S)
5. Ong YS, Samuel M, Song C. Meta-analysis of early excision of burns. *Burns* 2006; 32: 145–50. (STAT)
6. Edstrom L, Robson MC, Macchiaverna JR, Scala AD. Management of deep partial thickness dorsal hand burns. *Orthoped Rev* 1979; 8: 27–33. (RCT)
7. Salisbury RE, Wright P. Evaluation of early excision of dorsal burns of the hand. *Plast Reconstr Surg* 1982; 69: 670–5. (RCT)
8. Cole JK, Engrav LH, Heimbach DM, Gibran NS, Costa BA, Nakamura DY, Moore ML, Blayney CB, Hoover CL. Early excision and grafting of the face and neck burns in patients over 20 years. *Plast Reconstr Surg* 2002; 109: 1266–73. (CLIN S)
9. Fraulin FO, Illmayer SJ, Tredget EE. Assessment of cosmetic and functional result of conservative versus surgical management of facial burns. *J Burn Care Rehabil* 1996; 17: 19–29. (CLIN S)

Guideline #9.3: When an excised burn TBSA is so large that donor sites for split-thickness skin grafts are insufficient, permanent skin substitutes can serve as skin replacement without fear of rejection.

Level of evidence: I
Principle: Skin substitutes that are not immunogenic can serve as permanent skin replacement without fear of rejection.

Evidence:

1. Pham C, Greenwood J, Cleland H, Woodruff P, Maddern G. Bioengineered skin substitutes for management of burns: a systematic review. *Burns* 2007; 33: 946–57. (STAT)
2. Odessey R. Addendum: multicenter experience with cultured epidermal autograft for treatment of burns. *J Burn Care Rehabil* 1992; 13: 174–80. (STAT)
3. Boyce ST, Goretsky MJ, Greenhalgh DG, Kagan RJ, Rieman MT, Warden GD. Comparative assessment of cultured skin substitute and native skin autograft for treatment of full-thickness burns. *Ann Surg* 1995; 222: 743–52. (RCT)
4. Rue LW, Cioffi WG, McManus WF, Pruitt BA. Wound closure and outcome in extensively burned patients treated with cultured autologous keratinocytes. *J Trauma* 1993; 34: 662–7. (CLIN S)
5. Barret JP, Wolf SE, Desai MH, Herndon DN. Cost-efficacy of cultured epidermal autografts in massive pediatric burns. *Ann Surg* 2000; 231: 869–76. (CLIN S)
6. Herndon DN, Rutan RL. Comparison of cultured epidermal autograft and massive excision with serial autografting plus homograft overlay. *J Burn Care Rehabil* 1992; 13: 154–7. (CLIN S)
7. Arons JA, Wainwright DJ, Jordon RE. The surgical applications and implications of cultured human epidermis: a comprehensive review. *Surgery* 1992; 111: 4–11. (LIT REV)
8. Heimbach D, Luterman A, Burke J, Cram A, Herndon D, Hunt J, Jordan M, McManus W, Solem L, Warden G. Artificial dermis for major burns: a multicenter randomized clinical trial. *Ann Surg* 1988; 208: 313–20. (RCT)
9. Branski LK, Herndon DN, Pereira C, Mlcak RP, Celis MM, Lee JO, Sanford AP, Norbury WB, Zhang XJ, Jeschke MG. Longitudinal assessment of Integra in primary burn management: a randomized pediatric clinical trial. *Crit Care Med* 2007; 11: 2615–23. (RCT)
10. Heimbach DM, Warden GD, Luterman A, Jordan MH, Ozobia N, Ryan CM, Voigt DW, Hickerson WL, Saffle JR, DeClement FA, Sheridan RL, Dimick AR. Multicenter postapproval clinical trial of Integra dermal regeneration template for burn treatment. *J Burn Care Rehabil* 2003; 24: 42–8. (CLIN S)
11. Wainwright DJ. Use of acellular allograft dermal matrix (AlloDerm) in the management of full-thickness burns. *Burns* 1995; 21: 243–8. (CLIN S)

Guideline #9.4: Temporary skin substitutes are effective on partial-thickness burns while awaiting epithelialization and on excised full-thickness burns while awaiting skin graft application.

Level of evidence: I
Principle: Temporary biologic, synthetic, biosynthetic, or bioengineered dressings cannot provide permanent burn wound closure, but can maintain a wound free of infection until permanent wound closure occurs.

Evidence:

1. Pham C, Greenwood J, Cleland H, Woodruff P, Maddern G. Bioengineered skin substitutes for the management of burns: a systematic review. *Burns* 2007; 33: 946–57. (STAT)
2. Noordenbos J, Dore C, Hansbrough JF. Safety and efficacy of transcyte for the treatment of partial-thickness burns. *J Burn Care Rehabil* 1999; 20: 275–81. (RCT)

3. Kumar RJ, Kimble RM, Boots R, Pegg SP. Treatment of partial-thickness burns: a prospective, randomized trial using Transcyte. *Aust NZ J Surg* 2004; 74: 622–6. (RCT)
4. Hansbrough JF, Mozingo DW, Kealey GP, Davis M, Gidner A, Gentzkow GD. Clinical trials of a biosynthetic temporary skin replacement, dermagraft-transitional covering, compared with cryo-preserved human cadaver skin for temporary coverage of excised burn wounds. *J Burn Care Rehabil* 1997; 18: 43–59. (RCT)
5. Purdue GF, Hunt JL, Still JM Jr, Law EJ, Herndon DN, Goldfarb IW, Schiller WR, Hansbrough JF, Hickerson WL, Himel HN, Kealey GP, Twomey J, Missavage AE, Solem LD, Davis M, Totoritis M, Gentzkow GD. A multicenter clinical trial of a biosynthetic skin replacement, Dermagraft-TC, compared with cryopreserved human cadaver skin for temporary coverage of excised burn wounds. *J Burn Care Rehabil* 1997; 18: 52–7. (RCT)
6. Purdue GF, Hunt JL, Gillespie RW, Hansbrough JF, Dominic WJ, Robson MC, Smith DJ, MacMillan BG, Waymac JP, Herndon DN. Biosynthetic skin substitute versus frozen human cadaver allograft for temporary coverage of excised burn wounds. *J Trauma* 1987; 27: 155–7. (RCT)
7. Barret JP, Dziewulski P, Ramzy PI, Wolf SE, Desai MH, Herndon DN. Biobrane versus 1% silver sulfadiazine in second-degree pediatric burns. *Plast Reconstr Surg* 2000; 105: 62–5. (RCT)
8. Gerding RL, Emerman CL, Effron D, Lukens T, Imbembo AL, Fratianne RB. Outpatient management of partial-thickness burns: biobrane versus 1% silver sulfadiazine. *Ann Emerg Med* 1990; 19: 121–4. (RCT)
9. Lal S, Barrow RE, Wolf SE, Chinkes DL, Hart DW, Heggers JP, Herndon DN. Biobrane improves wound healing in burned children without increased risk of infection. *Shock* 2000; 14: 314–8. (CLIN S)

Guideline #9.5: Peptide growth factors accelerate healing of the various types of wounds seen in the burn patient.

Level of evidence: I
Principle: Cytokines and growth factors that can accelerate epithelialization should benefit wound closure in wounds healing by epithelialization.

Evidence:

1. Smith PD, Polo M, Soler PM, McClintock JS, Maggi SP, Kim YJ, Ko F, Robson CM. Efficacy of growth factors in the accelerated closure of interstices in explanted meshed human skin grafts. *J Burn Care Rehabil* 2000; 21: 5–9. (EXP)
2. Fu X, Shen Z, Chen Y, Xie J, Guo Z, Zhang M, Sheng Z. Randomized placebo-controlled trial of use of topical bovine basic fibroblast growth factor for second-degree burns. *Lancet* 1998; 352: 1661–4. (RCT)
3. Fu X, Shen Z, Chen Y, Xie J, Guo Z, Zhang M, Sheng Z. Recombinant bovine basic fibroblast growth factor accelerates wound healing in patients with burns, donor sites, and chronic dermal ulcers. *Chin Med J* 2000; 113: 367–71. (RCT)
4. Greenhalgh DG, Rieman M. Effects of basic fibroblast growth factor on the healing of partial-thickness donor sites. A prospective, randomized, double-blind trial. *Wound Rep Regen* 1994; 2: 113–21. (RCT)
5. Ma B, Cheng DS, Xia ZF, Ben DF, Lu W, Cao ZF, Wang Q, He J, Chai JK, Shen CA, Sun YH, Zhang GA, Hu XH. Randomized, multicenter, double-blind, and placebo-controlled trial using topical recombinant human acidic fibroblast growth factor for deep partial-thickness burns and skin graft donor sites. *Wound Rep Regen* 2007; 15: 795–9. (RCT)
6. Brown GL, Nanney LB, Griffen J, Cramer AB, Yancey JM, Curtsinger LJ III, Holtzin L, Schultz GS, Jurkiewicz MJ, Lynch JB. Enhancement of wound healing by topical treatment with epidermal growth factor. *N Engl J Med* 1989; 321: 76–9. (RCT)
7. Gilpin DA, Barrow RE, Rutan RL, Broemeling L, Herndon DN. Recombinant human growth hormone accelerates wound healing in children with large cutaneous burns. *Ann Surg* 1999; 220: 19–24. (RCT)
8. Pelzer M, Hartmann B, Blome-Eberwein S, Raff T, Germann G. Effect of recombinant growth hormone on wound healing in severely burned patients. A placebo controlled, randomized double-blind phase II study. *Chirurg* 2000; 71: 1352–8. (RCT)
9. Herndon DN, Barrow RE, Kunkel KR, Broemeling L, Rutan RL. Effects of recombinant human growth hormone on donor-site healing in severely burned children. *Ann Surg* 1990; 212: 424–9. (RCT)
10. Losada F, Garcia-Luna PP, Gómez-Cía T, Garrido M, Pereira JL, Marín F, Astorga R. Effects of human recombinant growth hormone on donor-site healing in burned patients. *World J Surg* 2002; 26: 2–8. (RCT)

Guideline #9.6: For deep burns that cannot undergo early excision and wound closure, topical antibacterial agents are indicated. For shallow wounds, donor sites, and meshed skin grafts, topical antibacterial agents have not proved necessary.

Level of evidence: II
Principle: Systemically administered antibiotics do not affect the bacteria–host defense equilibrium in wounds with necrotic tissue, decreased blood supply, or granulation tissue. Topical antimicrobials are more effective in these circumstances.

Evidence:

1. Robson MC, Edstrom LE, Krizek TJ, Groskin MG. The efficacy of systemic antibiotics in the treatment of granulating wounds. *J Surg Res* 1974; 16: 299–306. (EXP)
2. Hermans MHE. Results of an internet survey on the treatment of partial-thickness burns, full-thickness burns, and donor sites. *J Burn Care Res* 2007; 28: 835–47. (STAT)
3. Monafo WW, West MA. Current treatment recommendation for topical burn therapy. *Drugs* 1990; 40: 364–73. (LIT REV)
4. Heggers JP, Linares H, Edgar P, Villarreal C, Herndon D. Treatment of infection in burns. In: Herndon DN, editor. *Total burn care*. Philadelphia: W.B. Saunders Co., 1996: 98–135. (LIT REV)

5. Tredget EE, Shankowsky HA, Groeneveld A, Burrell R. A matched-pair randomized study evaluating the efficacy of Acticoat silver-coated dressing for the treatment of burn wounds. *J Burn Care Rehabil* 1998; 19: 531–7. (RCT)
6. Innes ME, Umraw N, Fish JS, Gomez M, Cartotto RC. The use of silver coated dressings on donor site wounds: a prospective, controlled matched pair study. *Burns* 2001; 27: 621–7. (RCT)
7. Silver GM, Robertson SW, Halerz MM, Conrad P, Supple KG, Gamelli RL. A silver-coated antimicrobial barrier dressing used postoperatively on meshed autografts: a dressing comparison study. *J Burn Care Res* 2007; 28: 715–9. (RCT)
8. Heinrich JJ, Brand DA, Cuono CB. The role of topical treatment as a determinant of infection in outpatient burns. *J Burn Care Rehabil* 1988; 9: 253–57. (CLIN S)
9. Rodgers GL, Fisher MC, Lo A, Cresswell A, Long SS. Study of antibiotic prophylaxis during burn wound debridement in children. *J Burn Care Rehabil* 1997; 18: 342–6. (RCT)
10. Durtschi MB, Orgain C, Counts GW, Heimbach DM. A prospective study of prophylactic penicillin in acutely burned hospitalized patients. *J Trauma* 1982; 22: 4–14. (RCT)

Guideline #9.7: Advanced wound care dressings are more effective than simple impregnated gauze dressings at accelerating healing and decreasing pain in skin graft donor sites. The small differences in improvement must be balanced with the differences in cost and patient comfort.

Level of evidence: I
Principle: Donor sites heal by epithelialization and epithelialization is facilitated in a moist environment. Simple impregnated gauze dressings do not provide adequate moisture retention.

Evidence:

1. Pham C, Greenwood J, Cleland H, Woodruff P, Maddern G. Bioengineered skin substitutes for the management of burns: a systematic review. *Burns* 2007; 33: 946–51. (STAT)
2. Beldon P. Comparison of four different dressings on donor site wounds. *Br J Nurs* 2004; 13: S38–45. (RCT)
3. Barnea Y, Amir A, Leshem D, Zaretski A, Weiss J, Shafir R, Gur E. Clinical comparative study of aquacel and paraffin gauze dressing for split-skin donor site treatment. *Ann Plast Surg* 2004; 53: 132–6. (RCT)
4. Martini L, Reali UM, Borgognoni L, Brandani P, Andriessen A. Comparison of two dressings in the management of partial-thickness donor sites. *J Wound Care* 1999; 8: 457–60. (RCT)
5. Rennekampff HO, Rabbels J, Reinhard V, Becker ST, Schaller HE. Comparing the Vancouver Scar Scale with the cutometer in the assessment of donor site wounds treated with various dressings in a randomized trial. *J Burn Care Res* 2006; 27: 345–51. (RCT)
6. Griswold JA, Cepica T, Rossi L, Wimmer JS, Merrifield HH, Hester C, Sauter T, Baker CR. A comparison of Xeroform and Skin Temp dressings in the healing of skin graft donor sites. *J Burn Care Rehabil* 1995; 16: 136–40. (RCT)
7. Hickerson WL, Kealey GP, Smith DJ, Thomson PD. A prospective comparison of a new, synthetic donor site dressing versus an impregnated gauze dressing. *J Burn Care Rehabil* 1994; 15: 359–63. (RCT)
8. Zapata-Sirvent R, Hansbrough JF, Carroll W, Johnson R, Wakimoto A. Comparison of Biobrane and Scarlet Red dressings for treatment of donor site wounds. *Arch Surg* 1985; 120: 743–5. (RCT)
9. Prasad JK, Feller I, Thomson PD. A prospective controlled trial of Biobrane versus scarlet red on skin graft donor areas. *J Burn Care Rehabil* 1987; 8: 384–6. (RCT)
10. Innes ME. Umraw N, Fish JS, Gomez M, Cartotto RC. The use of silver coated dressings on donor site wounds: a prospective, controlled matched pair study. *Burns* 2001; 27: 621–7. (RCT)
11. Verstraelen P. Comparison of calcium sodium alginate (KALTOSTAT) and porcine xenograft (E-Z DERM) in the healing of split-thickness skin graft donor sites. *Burns* 1992; 18: 145–8. (RCT)
12. Muhart M, McFalls S, Kirsner RS, Elgart GW, Kerdel F, Sabolinski ML, Hardin-Young J, Eaglstein WH. Behavior of tissue-engineered skin: a comparison of living skin equivalent, autograft, and occlusive dressing in human donor sites. *Arch Dermatol* 1999; 135: 913–8. (RCT)

#10: GUIDELINES TO DECREASE THE IMPEDIMENT TO ACUTE WOUND HEALING CAUSED BY EXTERNAL AGENTS SUCH AS TOBACCO, DRUGS, ETC.

Preamble: External agents that a patient is using, such as tobacco or drugs, can be detrimental to wound healing. When possible, these agents should be avoided or discontinued. If they cannot be discontinued, measures to counter or minimize their effects are required.

Guideline #10.1: Cigarette smoking is associated with decreased healing and a higher incidence of wound complications. Patients should stop smoking at least 3–4 weeks before elective surgery and should not resume smoking in the postoperative period.

Level of evidence: I
Principle: Cigarette smoking has been shown to cause decreased synthesis of collagen types I and III, carbon monoxide formation, vasoconstriction with reduced blood flow, and decreased oxygen transport. This leads to an increased rate of infection, higher incidence of skin flap necrosis, increase in epidermolysis, a higher amputation rate, and a worse cosmetic result.

Evidence:

1. Freiman A, Bird G, Metelitsa AI, Barankin B, Lauzon GJ. Cutaneous effects of smoking. *J Cutan Med Surg* 2004; 8: 415–23. (LIT REV)
2. Theadom A, Cropley M. Effects of preoperative smoking cessation on the incidence and risk of intraoperative and postoperative complications in adult smokers: a systematic review. *Tobacco Control* 2006; 15: 352–8. (STAT)
3. Sorensen LT, Karismark T, Gottrup F. Abstinence from smoking reduces incisional wound infection: a

randomized controlled trial. *Ann Surg* 2003; 238: 1–5. (RCT)
4. Padubidri AN, Yetman R, Browne E, Lucas A, Papay F, Larive B, Zins J, Vasconez LO. Complications of postmastectomy breast reconstructions in smokers, ex-smokers, and nonsmokers. *Plast Reconst Surg* 2001; 107: 342–9. (RETRO S)
5. Booi DI, Debats IB, Boeckx WD, van der Hulst RR. Risk factors and blood flow in the free transverse rectus abdominis (TRAM) flap: smoking and high flap weight impair the free TRAM flap microcirculation. *Ann Plast Surg* 2007; 59: 364–71. (CLIN S)
6. Sorensen LT, Horby J, Friis E, Pilsgaard B, Jørgensen T. Smoking as a risk factor for wound healing and infection in breast cancer surgery. *Eur J Surg Oncol* 2002; 28: 815–20. (CLIN S)
7. Kuri M, Nakagawa M, Tanaka H, Hasuo S, Kishi Y. Determination of the duration of preoperative smoking cessation to improve wound healing after head and neck surgery. *Anesthesiology* 2005; 102: 892–6. (RETRO S)
8. Manassa EH, Herti CH, Olbrisch RR. Wound healing problems in smokers and nonsmokers after 132 abdominoplasties. *Plast Reconstr Surg* 2003; 111: 2082–7. (RETRO S)
9. Nguyen TH, Gordon IL, Whalen D, Wilson SE. Transmetatarsal amputation: predictors of healing. *Am Surg* 2006; 72: 973–7. (CLIN S)
10. Jorgensen LN, Kallehave F, Christensen E, Siana JE, Gottrup F. Less collagen production in smokers. *Surgery* 1998; 123: 450–5. (CLIN S)
11. Knuutinen A, Kokkonen N, Risteli J, Vähäkangas K, Kallioinen M, Salo T, Sorsa T, Oikarinen A. Smoking affects collagen synthesis and extracellular matrix turnover in human skin. *Br J Dermatol* 2002; 146: 588–94. (EXP)
12. Raitio A, Tuomas H, Kokkonen N, Salo T, Sorsa T, Hanemaaijer R, Oikarinen A. Levels of matrix metalloproteinase-2, -9 and -8 in the skin, serum and saliva of smokers and non-smokers. *Arch Dermatol Res* 2005; 197: 242–8. (EXP)
13. Reus WF 3rd, Colen LB, Straker DJ. Tobacco smoking and complications in elective microsurgery. *Plast Reconstr Surg* 1992; 89: 490–4. (RETRO S)
14. Siana JE, Rex S, Gottrup F. The effect of cigarette smoking on wound healing. *Scand J Plast Reconstr Surg Hand Surg* 1989; 23: 207–9. (CLIN S)
15. Lind J, Kramhoft M, Bedtker S. The influence of smoking on complications after primary amputations of the lower extremity. *Clin Orthop Relat Res* 1991; 267: 211–7. (RETRO S)
16. Rogliani M, Labardi L, Silvi E, Maggiulli F, Grimaldi M, Cervelli V. Smokers: risks and complications in abdominal dermolipectomy. *Aesthet Plast Surg* 2006; 30: 422–4. (RETRO S)
17. Lindström D, Wladis A, Linder S, Nåsell H, Adami J. Preoperative cessation of smoking seems to reduce the frequency of complications. *Lakartidningen* 2004; 101: 1920–2. (LIT REV)

Guideline #10.2: Chronic corticosteroid usage should be minimized whenever possible before surgical procedures and until the acute wound is healed. When this is not possible, various agents may be useful in decreasing the detrimental effects of corticosteroids on healing.

Level of evidence: II

Principle: The humoral and cellular inflammatory response is a fundamental part of the mechanism of acute wound healing. Corticosteroids can adversely affect several wound healing processes. Agents that can abrogate or ameliorate some of the effects of corticosteroids should benefit healing.

Evidence:

1. Hunt TK. Disorders of wound healing. *World J Surg* 1980; 4: 271–7. (LIT REV)
2. Stephens FO, Dunphy JE, Hunt TK. Effect of delayed administration of corticosteroids on wound contraction. *Ann Surg* 1971; 173: 214–8. (EXP)
3. Gupta A, Jain GK, Raghubir R. A time course study for the development for an immunocompromised wound model using hydrocortisone. *J Pharmacol Toxicol Meth* 1999; 4: 183–7. (EXP)
4. Hunt TK, Ehrlich HP, Garcia JA, Dunphy JE. Effect of vitamin A on reversing the inhibitory effect of cortisone on healing of open wounds in animals and man. *Ann Surg* 1969; 170: 633–41. (EXP)
5. Ehrlich HP, Tarver H, Hunt TK. Effects of vitamin A and glucocorticoids upon inflammation and collagen synthesis. *Ann Surg* 1973; 177: 222–7. (EXP)
6. Smith KP, Zardiakas LD, Didlake RH. Cortisone, vitamin A, and wound healing: the importance of measuring wound surface area. *J Surg Res* 1986; 40: 120–5. (EXP)
7. Ehrlich HP, Hunt TK. Effects of cortisone and vitamin A on wound healing. *Ann Surg* 1968; 167: 324–8. (LIT REV)
8. Ehrlich HP, Hunt TK. The effects of corticosteroid and anabolic steroids on the tensile strength of healing wounds. *Ann Surg* 1969; 170: 203–6. (EXP)
9. Demling RH. Oxandrolone, an anabolic steroid, enhances the healing of a cutaneous wound in a rat. *Wound Rep Regen* 2000; 8: 97–102. (EXP)
10. Kim CS, Buchmiller TL, Fonkalsrud EW, Phillips JD. The effect of anabolic steroids on ameliorating the adverse effects of chronic corticosteroids on intestinal anastomotic healing in rabbits. *Surg Gynecol Obstet* 1993; 176: 73–9. (EXP)
11. Kelley SF, Felix AM, Ehrlich HP. The antagonism of glucocorticoid inhibition of wound healing in rats by growth hormone-releasing factor. *Proc Soc Exp Biol Med* 1990; 194: 320–6. (EXP)
12. Garrel DR, Gaudreau P, Zhang LM, Reeves I, Brazeau P. Chronic administration of growth hormone-releasing factor increases wound strength and collagen maturation in granulation tissue. *J Surg Res* 1991; 51: 297–302. (EXP)
13. Dinc S, Durmus E, Gulcelik MA, Kuru B, Ustun H, Renda N, Alagol H. Effects of beta-D-glucan on steroid-induced impairment of colonic anastomotic healing. *Acta Chir Beig* 2006; 106: 63–7. (EXP)

Guideline #10.3: Zinc therapy improves healing in zinc-deficient patients. Its benefit in patients without zinc deficiency has not been substantiated.

Level of evidence: III
Principle: Zinc is an essential trace element and serves as a cofactor in numerous transcription factors and enzyme systems necessary for wound healing. However, exogenous zinc does not augment healing except in the presence of zinc deficiency.

Evidence:

1. Lansdown AB, Mirastschijski U, Stubbs N, Scanlon E, Agren MS. Zinc in wound healing: theoretical, experimental, and clinical aspects. *Wound Rep Regen* 2007; 15: 2–16. (LIT REV)
2. Agren MS. Studies on zinc in wound healing. *Acta Derm Venereol* 1990; 154 (Suppl.): 1–36. (EXP)
3. Faure H, Peyrin JC, Richard MJ, Favier A. Parental supplementation with zinc in surgical patients corrects postoperative serum-zinc drop. *Biol Trace Elem Res* 1991; 30: 27–45. (RCT)
4. Agren MS, Ostenfeld U, Kallehave F, Gong Y, Raffn K, Crawford ME, Kiss K, Friis-Møller A, Gluud C, Jorgensen LN. A randomized, double-blind, placebo-controlled multicenter trial evaluating topical zinc oxide for acute open wounds following pilonidal disease excision. *Wound Rep Regen* 2006; 14: 526–35. (RCT)
5. Greenway SE, Filler LE, Greenway FL. Topical insulin in wound healing: a randomized, double-blind, placebo-controlled trial. *J Wound Care* 1999; 8: 526–8. (RCT)

Guideline #10.4: There is insufficient evidence to recommend specific exogenous nutrients such as vitamins to improve acute wound healing in patients who are not deficient in those nutrients.

Level of evidence: II
Principle: Although specific actions of many individual nutrients could benefit acute wound healing, data are not available for definitive recommendations.

Evidence:

1. Silverstein RJ, Landsman AS. The effects of a moderate and high dose of vitamin C on wound healing in a controlled guinea pig model. *J Foot Ankle Surg* 1999; 38: 333–8. (EXP)
2. Vaxman F, Olender S, Lambert A, Nisand G, Grenier JF. Can the wound healing process be improved by vitamin supplementation? Experimental study on humans. *Eur Surg Res* 1996; 28: 306–14. (RCT)
3. Baumann LS, Spencer J. The effects of topical vitamin E on the cosmetic appearance of scars. *Dermatol Surg* 1999; 25: 311–5. (RCT)
4. Barbul A, Fishel RS, Shimazu S, Wasserkrug HL, Yoshimura NN, Tao RC, Efron G. Intravenous hyperalimentation with high arginine levels improves wound healing and immune function. *J Surg Res* 1985; 38: 328–34. (EXP)
5. Barbul A, Lazarou SA, Efron DT, Wasserkrug HL, Efron G. Arginine enhances wound healing and lymphocyte immune responses in humans. *Surgery* 1990; 108: 336–7. (RCT)
6. Kirk SJ, Hurson M, Regan MC, Holt DR, Wasserkrug HL, Barbul A. Arginine stimulates wound healing and immune function in elderly human beings. *Surgery* 1993; 114: 155–9. (RCT)
7. Shi HP, Most D, Efron DT, Witte MB, Barbul A. Supplemental L-arginine enhances wound healing in diabetic rats. *Wound Rep Regen* 2003; 11: 198–203. (EXP)
8. Shi HP, Wang SM, Zhang GX, Zhang YJ, Barbul A. Supplemental L-arginine enhances wound healing following trauma/hemorrhagic shock. *Wound Rep Regen* 2007; 15: 66–70. (EXP)

(The effects of hyperbaric oxygen on acute wound healing are discussed in Guideline #1.3. The effects of anticoagulants on acute wound healing are discussed in Guideline #3.1. The effects of chemotherapeutic drugs on acute wound healing are discussed in Guideline #7.1.)

#11: GUIDELINES TO DECREASE THE IMPEDIMENT TO ACUTE WOUND HEALING CAUSED BY EXCESSIVE SCAR FORMATION

Preamble: In excessive healing or proliferative scarring, it is as if the equilibrium point between collagen deposition and collagen lysis is never reached. It is unclear why some wounds seem to continue in the repair processes without an apparent turnoff switch. Because of these unknowns, there is no universally accepted treatment regimen. In a recent meta-analysis of excessive scarring treatments, the mean amount of improvement to be expected was only 60%.

Guideline #11.1: Pressure garments or compression dressings are effective in decreasing scarring in burn injuries that require > 21 days to heal.

Level of evidence: I
Principle: Excessive or hypertrophic scarring is rare in burn injuries that heal within 21 days. The exact mechanism by which pressure is effective is unknown.

Evidence:

1. Van den Kerckhove E, Stappaerts K, Fieuws S, Laperre J, Massage P, Flour M, Boeckx W. The assessment of erythema and thickness on burn related scars during pressure garment therapy as a preventive measure for hypertrophic scarring. *Burns* 2005; 31: 696–702. (RCT)
2. Klopp R, Niemer W, Frankel M, von der Weth A. Effect of four treatment variants on the functional and cosmetic state of mature scars. *J Wound Care* 2000; 9: 319–24. (RCT)
3. Chang P, Laubenthal KN, Lewis RW II, Rosenquist MD, Lindley-Smith P, Kealey GP. Prospective, randomized study of the efficacy of pressure garment therapy in patients with burns. *J Burn Care Rehabil* 1995; 16: 473–5. (RCT)
4. Huang TT, Blackwell SJ, Lewis SR. Ten years of experience in managing patients with burn contractures of axilla, elbow, wrist, and knee joints. *Plast Reconstr Surg* 1978; 61: 70–6. (RETRO S)
5. Van den Kerckhove E, Fieuws S, Massagé P, Hierner R, Boeckx W, Deleuze JP, Laperre J, Anthonissen M. Reproducibility of repeated measurements with the Kikuhime pressure sensor under pressure garments in burn scar treatment. *Burns* 2007; 33: 572–8. (CLIN S)
6. Cheng JC, Evans JH, Leung KS, Clark JA, Choy TT, Leung PC. Pressure therapy in the treatment of post-burn hypertrophic scar—a critical look into its

usefulness and fallacies by pressure monitoring. *Burns Incl Therm Inj* 1984; 10: 154–63. (CLIN S)
7. Deitch EA, Wheelahan TM, Rose MP, Clothier J, Cotter J. Hypertrophic burn scars: analysis of variables. *J Trauma* 1983; 23: 895–8. (CLIN S)
8. Cubison TC, Pape SA, Parkhouse N. Evidence for the link between healing time and the development of hypertrophic scars (HTS) in paediatric burns due to scald injury. *Burns* 2006; 32: 992–9. (CLIN S)

Guideline #11.2: Silicone sheeting is useful in prevention and treatment of proliferative scars.

Level of evidence: I

Principle: Although the exact mechanism by which silicone sheeting is effective is not agreed upon, it does decrease fibroblast activity and downregulates the fibrogenic isoforms of transforming growth factor-β (TGF-β).

Evidence:

1. O'Brien L, Pandit A. Silicon gel sheeting for preventing and treating hypertrophic and keloid scars. *Cochrane Database Syst Rev* 2006; 1: CD003826. (STAT)
2. Ziegler UE. International clinical recommendations on scar management. *Zentralbl Chir* 2004; 129: 296–306. (STAT)
3. Leventhal D, Furr M, Reiter D. Treatment of keloids and hypertrophic scars: a meta-analysis and review of the literature. *Arch Facial Plast Surg* 2006; 8: 362–8. (STAT)
4. Li-Tsang CW, Lau JC, Choi J, Chan CC, Jianan L. A prospective randomized clinical trial to investigate the effect of silicone gel sheeting (Cica-Care) on post-traumatic hypertrophic scar among the Chinese population. *Burns* 2006; 32: 678–83. (RCT)
5. Gold MH, Foster TD, Adair MA, Burlison K, Lewis T. Prevention of hypertrophic scars and keloids by the prophylactic use of topical silicone gel sheets following a surgical procedure in an office setting. *Dermatol Surg* 2001; 27: 641–4. (RCT)
6. Ahn ST, Monafo WW, Mustoe TA. Topical silicone gel: a new treatment for hypertrophic scars. *Surgery* 1989; 106: 781–6. (RCT)
7. Ahn ST, Monafo WW, Mustoe TA. Topical silicone gel for the prevention and treatment of hypertrophic scar. *Arch Surg* 1991; 126: 499–504. (CLIN S)
8. Kuhn MA, Moffit MR, Smith PD, Lyle WG, Ko F, Meltzer DD, Robson MC. Silicone sheeting decreases fibroblast activity and downregulates TGF-B2 in hypertrophic scar model. *Int J Surg Investig* 2001; 2: 467–74. (EXP)
9. Berman B, Perez OA, Konda S, Kohut BE, Viera MH, Delgado S, Zell D, Li Q. A review of the biologic effects, clinical efficacy, and safety of silicone elastomer sheeting for hypertrophic and keloid scar treatment and management. *Dermatol Surg* 2007; 33: 1291–302. (LIT REV)

Guideline #11.3: Intralesional corticosteroids, especially triamcinolone acetonide (Kenalog), can be a useful treatment of proliferative scars.

Level of evidence: I

Principle: Intralesional corticosteroid injections have been successful in treating hypertrophic scars and keloids, but the mechanism of action has not been defined despite a great deal of investigation.

Evidence:

1. Ziegler UE. International clinical recommendations on scar management. *Zentralbl Chir* 2004; 129: 296–306. (STAT)
2. Manuskiatti W, Fitzpatrick RE. Treatment response of keloidal and hypertrophic sternotomy scars: comparison among intralesional corticosteroid, 5-fluorouracil, and 585-nm flashlamp-pumped pulsed-dye laser treatments. *Arch Dermatol* 2002; 138: 1149–55. (RCT)
3. Kiil J. Keloids treated with topical injections of triamcinolone acetonide (Kenalog). Immediate and long-term results. *Plast Reconstr Surg* 1977; 11: 169–72. (RCT)
4. Asilian A, Darougheh A, Shariati F. New combination of triamcinolone, 5-fluorouracil, and pulsed-dye laser for treatment of keloid and hypertrophic scars. *Dermatol Surg* 2006; 32: 907–15. (RCT)
5. Layton AM, Yip J, Cunliffe WJ. A comparison of intralesional triamcinolone and cryosurgery in the treatment of acne keloids. *Br J Dermatol* 1994; 130: 498–501. (RCT)
6. Sclafani AP, Gordon L, Chadha M, Romo T III. Prevention of earlobe keloid recurrence with postoperative corticosteroid injections versus radiation therapy: a randomized, prospective study and review of the literature. *Dermatol Surg* 1996; 22: 569–74. (RCT)
7. Ketchum LD, Smith J, Robinson DW, Masters FW. Treatment of hypertrophic scars, keloid, and scar contracture by triamcinolone acetonide. *Plast Reconstr Surg* 1966; 38: 209–18. (CLIN S)

Guideline #11.4: Agents that neutralize or abrogate the action of the fibrogenic isoforms of TGF-β (TGF-β1, TGF-β2) may be useful in preventing or treating proliferative scars.

Level of evidence: II

Principle: It has been demonstrated that persistent overexpression or dysregulated activation of TGF-β1 and TGF-β2 can lead to fibrosis and scar formation, while TGF-β3 tends to decrease fibrosis and scarring.

Evidence:

1. Shah M, Foreman DM, Ferguson MW. Neutralization of TGF-beta1 and TGF-beta2 or exogenous administration of TGF-beta3 to cutaneous rat wounds reduces scarring. *J Cell Sci* 1995; 108: 985–1002. (EXP)
2. Tredget EE, Wang R, Shen Q, Scott PG, Ghahary A. Transforming growth factor-beta mRNA and protein in hypertrophic scar tissues and fibroblasts: antagonism by IFN-alpha and IFN-gamma in vitro and in vivo. *J Interferon Cytokine Res* 2000; 20: 143–51. (EXP)
3. Granstein RD, Rook A, Flotte TJ, Haas A, Gallo RL, Jaffe HS, Amento EP. A controlled trial of intralesional recombinant interferon-gamma in the treatment of keloidal scarring. Clinical and biologic findings. *Arch Dermatol* 1990; 126: 1295–302. (RCT)
4. Davison SP, Mess S, Kauffman LC, Al-Attar A. Ineffective treatment of keloids with interferon alpha-2b. *Plast Reconstr Surg* 2006; 117: 247–52. (RCT)
5. Tredget EE, Shankowsky HA, Pannu R, Nedelec B, Iwashina T, Ghahary A, Taerum TV, Scott PG. Transforming growth factor-beta in thermally injured patients with hypertrophic scars: effects of interferon alpha-2b. *Plast Reconstr Surg* 1998; 102: 1317–28. (CLIN S)

6. Ferguson MW, O'Kane S. Scar-free healing: from embryonic mechanisms to adult therapeutic intervention. *Philo Trans R Soc Lond B Biol Sci* 2004; 359: 839–50. (LIT REV)
7. Robson MC. Proliferative scarring. *Surg Clin North Am* 2003; 83: 557–69. (LIT REV)
8. Payne WG, Ko F, Anspaugh S, Wheeler CK, Wright TE, Robson MC. Down-regulating causes of fibrosis with tamoxifen: a possible cellular/molecular approach to treat rhinophyma. *Ann Plast Surg* 2006; 56: 301–5. (EXP)

Guideline #11.5: Postoperative radiotherapy following excision of keloids may be useful in preventing recurrence. However, dosage regimens are not agreed upon, and there remains a theoretical argument against use of radiotherapy for benign conditions.

Level of evidence: II
Principle: Ionizing radiation can prevent recurrence of scar proliferation. Techniques vary widely, making results difficult to interpret.

Evidence:

1. Ziegler UE. International clinical recommendations on scar management. *Zentralbl Chir* 2004; 129: 296–306. (STAT)
2. van de Kar AL, Kreulen M, van Zuijien PP, Oldenburger F. The results of surgical excision and adjuvant irradiation for therapy-resistant keloids: a prospective clinical outcome study. *Plast Reconstr Surg* 2007; 119: 2248–54. (RCT)
3. Sclafani AP, Gordon L, Chadha M, Romo T III. Prevention of earlobe keloid recurrence with postoperative corticosteroid injections versus radiation therapy: a randomized, prospective study and review of the literature. *Dermatol Surg* 1996; 22: 569–74. (RCT)
4. Ogawa R, Miyashita T, Hyakusoku H, Akaishi S, Kuribayashi S, Tateno A. Postoperative radiation protocol for keloids and hypertrophic scars: statistical analysis of 370 sites followed for over 18 months. *Ann Plast Surg* 2007; 59: 688–91. (CLIN S)
5. Akita S, Akino K, Yakabe A, Imaizumi T, Tanaka K, Anraku K, Yano H, Hirano A. Combined surgical excision and radiation therapy for keloid treatment. *J Craniofac Surg* 2007; 18: 1164–9. (CLIN S)
6. Guix B, Henriquez I, Andrés A, Finestres F, Tello JI, Martínez A. Treatment of keloids by high-dose brachytherapy: a seven year study. *Int J Radiat Oncol Biol Phys* 2001; 50: 167–72. (CLIN S)

Guideline #11.6: Laser therapy may be useful for the treatment of proliferative scars.

Level of evidence: II
Principle: Lasers used at nondestructive power levels have been demonstrated to cause inhibition of collagen production by keloid-derived fibroblasts. The almost endless variety of lasers and dosages prevent compilation of similar studies.

Evidence:

1. Abergel RP, Dwyer RM, Meeker CA, Lask G, Kelly AP, Uitto J. Laser treatment of keloids: a clinical trial and an in vitro study with Nd:Yag laser. *Lasers Surg Med* 1984; 4: 291–5. (CLIN S)
2. Manuskiatti W, Fitzpatrick RE. Treatment response of keloidal and hypertrophic sternotomy scars: comparison among intralesional corticosteroids, 5-fluorouracil, and 585-nm flashlamp-pumped pulsed-dye laser treatments. *Arch Dermatol* 2002; 138: 1149–55. (RCT)
3. Alster T. Laser scar revision: comparison study of 585-nm pulsed-dye laser with and without intralesional corticosteroids. *Dermatol Surg* 2003; 29: 25–9. (RCT)
4. Jih MH, Friedman PM, Goldberg LH, Robles M, Glaich AS, Kimyai-Asadi A. The 1450-nm diode laser for facial inflammatory acne vulgaris: dose–response and 12-month follow-up study. *J Am Acad Dermatol* 2006; 55: 80–7. (RCT)
5. Weiss RA, Gold M, Bene N, Biron JA, Munavalli G, Weiss M, Beasley K. Prospective clinical evaluation of 1440-nm laser delivered by microarray for treatment of photoaging and scars. *J Drugs Dermatol* 2006; 8: 740–4. (CLIN S)
6. Hasegawa T, Matsukura T, Mizuno Y, Suga Y, Ogawa H, Ikeda S. Clinical trial of a laser device called fractional photothermolysis system for acne scars. *J Dermatol* 2006; 55: 80–7. (RCT)

Guideline #11.7: Several treatments to minimize scarring or prevent recurrence of scars are based on biologic principles but, as yet, lack sufficient data for a recommendation. These include surgical techniques, lathrogens, Imiquimod, and vitamin E.

Level of evidence: III
Principle: Attacking the collagen deposition–collagen lysis equilibrium by mechanical, molecular, or pharmacologic means should lead to advances in treatment of excessive scarring.

Evidence:

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2. Engrav LH, Gottlieb JR, Millard SP, Walkinshaw MD, Heimbach DM, Marvin JA. A comparison of intramarginal and extramarginal excision of hypertrophic burn scars. *Plast Reconstr Surg* 1988; 81: 40–5. (RETRO S)
3. Peacock EE. Pharmacologic control of surface scarring in human beings. *Ann Surg* 1981; 193: 592–7. (CLIN S)
4. Chuangsuwanich A, Gunjitisomram S. The efficacy of 5% Imiquimod cream in the prevention of recurrence of excised keloids. *J Med Assoc Thai* 2007; 90: 1363–7. (CLIN S)
5. Stashower ME. Successful treatment of earlobe keloids with Imiquimod after tangential shave excision. *Dermatol Surg* 2006; 32: 380–6. (CLIN S)
6. Bauman LS, Spencer J. The effects of topical vitamin E on the cosmetic appearance of scars. *Dermatol Surg* 1999; 25: 311–5. (RCT)
7. Ehrlich HP, Tarver H, Hunt TK. The inhibitory effects of vitamin E on collagen synthesis and wound repair. *Ann Surg* 1972; 175: 235–40. (EXP)
8. Lawrence WT. In search of the optimal treatment for keloids: report of a series and review of the literature. *Ann Plast Surg* 1991; 27: 164–78. (LIT REV)