

Evidence-based Clinical Practice Guidelines on Some Important Aspects of the Care of Critically-ill Surgical Patients Part I : Fluids for Resuscitation, Blood Transfusion, Assessment of Volume Resuscitation, Nutritional Support, Pharmacologic Cardiovascular Support

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EXECUTIVE SUMMARY

The clinical area identified by the Philippine College of Surgeons (PCS) for the second evidence-based clinical practice guidelines (EBCPGs) was on the care of the critically ill surgical patient. A research grant was provided by GlaxoWellcome Philippines, Inc. and a Technical Working Group (TWG) was formed, composed of 6 general surgeons, one thoracic/cardiovascular surgeon, one cardiologist and two pulmonologists. The TWG was tasked to identify the clinical questions, and to adhere to the PCS-approved method of developing EBCPGs.

The TWG began work on May 1, 2000. The literature search, limited to English publications, used both electronic and manual methods. Three electronic databases were used: 1) The Cochrane Library, Issue 2, 2000; 2) National Library of Medicine - Medline (PubMed, no time limit); and HERDIN (Health Research and Development Information Network) Version 1, 1997 of DOST-PCHRD.

was composed of one thoracic/cardiovascular surgeon and one cardiologist. Group III was assigned to appraise the evidence on ventilatory support, and Group IV looked at pharmacological cardiovascular support. Groups I and II appraised the evidence on fluid resuscitation, blood transfusion, monitoring and nutritional support.

The printed abstracts were given to the members of each group, who then decided which articles were to be included for full text retrieval. The full texts were obtained from the University of the Philippines Manila Library, and were appraised using standard forms. The TWG then compiled, summarized and classified the evidence according to 3 levels and proposed a first draft of recommendations according to 3 categories:

LEVELS OF EVIDENCE

I. Evidence from at least one properly designed randomized controlled trial, meta-analysis.

Titles of all articles were printed and all members of the TWG went over the list and checked the titles of articles whose abstract they felt should be read. The abstracts of all checked articles were printed.

The TWG was divided into 4 groups: Group I was composed of 3 general surgeons; Group II was composed of 2 general surgeons; Group III was composed of one thoracic/cardiovascular surgeon and 2 pulmonologists; and Group IV

II. Evidence from at least one well-designed clinical trial without proper randomization, from prospective or retrospective cohort or case-control analytic studies (preferably from one center), from multiple time-series studies, or from dramatic results in uncontrolled experiments.

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III. Evidence from opinions of respected authorities on the basis of clinical experience, descriptive studies, or reports of expert committees.

CATEGORIES OF RECOMMENDATIONS

Category A : Recommendations that were approved by consensus (75% of the multisectoral expert panel).

Category B : Recommendations that were somewhat controversial and did not meet consensus.

Category C : Recommendations that caused real disagreements among members of the panel.

The following were the clinical questions:

- 1. What is the appropriate type of intravenous fluid to be used in the resuscitation of hypovolemic critically ill surgical patients?**
- 2. What are the adverse effects of blood transfusion?**
- 3. What are the indications for blood transfusion in critically ill surgical patients?**
- 4. What are the clinical and/or diagnostic indicators that have been shown to be useful in assessing the adequacy of resuscitation of**

Shangri-la Hotel. The guidelines were approved by the PCS Board of Regents 13 December 2000.

RECOMMENDATIONS OF FLUIDS FOR RESUSCITATION

1. Crystalloids are the appropriate intravenous fluids to be used in the resuscitation of hypovolemic surgical patients. The use of colloids does not decrease mortality, and may result in higher mortality in trauma patients. Albumin may increase the risk of death in patients with hypovolemia, burns and hypoalbuminemia. (Level I, Category A)

RED BLOOD CELL TRANSFUSION

1. Aggressive and early control of hemorrhage should be considered an integral part of resuscitation. (Level II, Category A)
2. In a patient who is hypovolemic secondary to acute hemorrhage, volume resuscitation should be initiated. (Level I, Category A)
3. In a normovolemic patient whose level of anemia is associated with evidence of an increased risk of major adverse outcomes, the major indication of RBC transfusion is to increase oxygen delivery. This should be corrected to achieve a level of anemia wherein there is evidence that the increased risk is no longer present.

The traditional "10/30 rule", or a transfusion

hypovolemic critically ill surgical patients?

5. Are there patients who will benefit from postoperative nutritional support?

6. What is the most effective way of delivering postoperative nutritional support?

7. What is the most effective composition of postoperative nutritional support?

8. When is pharmacological cardiovascular support beneficial among critically ill surgical patients?

9. What is the appropriate method of pharmacological cardiovascular support of the critically ill surgical patient?

A total 3,846 titles were printed, out of which 546 abstracts were reviewed, 114 full text articles appraised, and 71 full text articles used.

The TWG prepared a first draft of the manuscript which consisted of a summary of the strongest evidence associated with the clinical questions and suggested recommendations. The first draft was discussed and modified by a Panel of Experts convened by the PCS on November 4 and 11, 2000 at the PCS building. A second draft was prepared by the TWG and this was discussed in a Public Forum on December 13, 2000 during the 56th Clinical Congress of the PCS held at Edsa

trigger of an Hb concentration of less than 10 g / dL or a hematocrit concentration of less than 30 per cent should no longer be utilized. (Level 1, Category A)

4. There is evidence that there is no benefit of RBC transfusion for patients whose Hb concentration is equal or more than 10 g / dL. (Level I, Category A)

5. In general, there may be an increased risk of adverse outcomes in normovolemic patients with acute anemia whose Hb concentration is less than 7 g / dL. (Level I, Category A)

6. Normovolemic patients with acute anemia who have cardiac disease or are at risk of cardiac disease may benefit from RBC transfusion when their Hb concentration is less than 7 g / dL. Factors that increase the risk of postoperative cardiac events, and the corresponding evidence are contained in PCS EBCPG on Seeking Referral for Preoperative Cardiac Evaluation for Elective Noncardiac Surgery (PJSS 1999; 54 (4): 171 - 233). (Level I, Category A)

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Patients with acute myocardial infarction or unstable angina may benefit from a transfusion trigger higher than 7 g / dL. (Level II, Category A)

7. Packed red blood cells is preferred when blood transfusion is necessary. (Level II, Category A)

ASSESSMENT OF RESUSCITATION OF HYPOVOLEMIA

PHARMACOLOGIC CARDIOVASCULAR SUPPORT

1. When volume resuscitation is considered adequate based on clinical judgment and the clinical response is suboptimal, vasoactive drugs may improve hemodynamics, oxygen transport and clinical condition. (Level I, Category A)

2. Hemodynamic monitoring using a pulmonary artery catheter (PAC) may improve

1. The clinical judgment of a well-trained and experienced surgeon, utilizing clinical parameters, such as blood pressure, heart rate and urine output should still be the best "monitor" of the adequacy of resuscitation. (Level II, Category A)

2. At present there is no evidence that the routine use of tests such as serum lactate levels, base deficits and pulmonary artery catheters (PAC) improve major clinical outcomes and therefore are not recommended. (Level I, Category A)

3. Indications for the use of tests should be based on specific circumstances in which there is strong evidence that their use is associated with an improvement in major clinical outcomes, such as a decrease in mortality and serious complications. (Level I, Category A)

POSTOPERATIVE NUTRITIONAL SUPPORT

1. Early nutritional support (within 24 hours) of critically ill surgical patients should be instituted because it decreases the risk of postoperative morbidity, particularly septic complications, and more so in malnourished patients (greater than 10% preoperative weight loss). (Level I, Category A)

2. Among critically ill surgical patients, there is evidence that enteral nutrition (EN) delivered into the jejunum and started within 24 hours after operation results in lower septic complications compared to total parenteral nutrition (TPN). TPN is used only when the enteral route is not feasible. (Level I, Category A)

The clinical trials that had demonstrated benefits of early TEN had used commercial TEN formulations.

3. TEN using commercial immune-enhancing formulae may be associated with a greater decrease in the risk of septic complications compared to standard TEN formulae in selected critically ill patients. (Level I, Category A)

4. The routine use of postoperative enteral nutrition (EN) in noncritical, nonmalnourished patients is not recommended. (Level I, Category A)

clinical decision making in selected critically ill patients. (Level II, Category A)

3. When vasoactive drugs are used, the goals of therapy remain normalization of hemodynamics, oxygen transport, and improvement in the clinical manifestations of shock, but not supranormal resuscitation endpoints. (Level I, Category A)

4. After restoring volume, clinical judgment should be exercised in the particular choice of a vasoactive drug, with consideration of hemodynamic parameters including heart rate, blood pressure, cardiac index, volume status and cardiac filling pressures, vascular resistance, and preexisting cardiac and medical status of an individual patient.

4a. Dobutamine is the drug of choice to increase cardiac index and oxygen delivery if blood pressure is acceptable but there are still signs of inadequate tissue perfusion. (Level II, Category A)

4b. Dopamine should be used initially for persistent mild hypotension > 70 and < 90 mmHg and shock to support blood pressure; and dobutamine may then be added to optimize cardiac index and oxygen delivery. (Level II, Category A)

4c. Dopamine and/or norepinephrine should generally be used for severe hypotension with systolic blood pressure < 70 mmHg. (Level II, Category A)

4d. Inappropriate bradycardia or tachycardia, and abnormal cardiac rhythm should be addressed by appropriate pharmacologic therapy and/or adjunctive devices (such as temporary pacemaker, external cardioverter-defibrillator). (Level II, Category A)

Technical Working Group

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Group II Narciso S. Navarro Jr. (general surgeon)

Ma. Luisa D. Aquino (general surgeon)

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Abundio A. Balgos (pulmonologist)

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Group IV Eduardo R. Bautista (thoracic and cardiovascular surgeon)

Donato R. Marañon (cardiologist)

Research Assistant Jaimelly P. Buenbrazo

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2. Nestor E. dela Cruz (general surgeon, PCS)
3. Adriano V. Laudico (general surgeon, PCS)
4. Narciso S. Navarro Jr. (general surgeon, PCS)
5. M. Francisco T. Roxas (general surgeon, PCS)
6. Ma. Luisa D. Aquino (general surgeon, PCS)
7. Edgardo R. Cortez (general surgeon, PCS)
8. Camilo C. Roa (pulmonologist, Philippine College of Chest Physicians)
9. Eduardo Bautista (thoracic and cardiovascular surgeon, PCS)
10. Abundio A. Balgos (pulmonologist, Philippine College of Chest Physicians)
11. Donato R. Marañon (cardiologist, Philippine College of Physicians)
12. Ramon S. Inso (general surgeon, Surgical Oncology Society of the Philippines)
13. Teresita S. de Guia (pulmonologist, Philippine College of Chest Physicians)
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16. Edgardo F. Fernandez (general surgeon,

Background

The Philippine College of Surgeons (PCS) had identified the development, dissemination and implementation of evidence-based clinical practice guidelines (EBCPG), as an important strategy in improving surgical care, training and research. The Philippine Council for Health Research and Development (PCHRD) of the Department of Science and Technology (DOST) had also identified the development of EBCPGs as one of the top priorities in the national research agenda, and in 1999 the DOST-PCHRD, PCS and the Department of Surgery of the University of the Philippines Manila College of Medicine signed a trilateral Memorandum of Agreement on the development of EBCPGs on certain areas of surgical care in the Philippines. These areas of surgical care should be those wherein current practice may not be truly evidence-based, and have a large potential of improving major outcomes and even decreasing costs, and the recommended EBCPGs can be implemented nationwide in both government and private health facilities. The first PCS-EBCPG was on seeking referral for perioperative cardiac evaluation for noncardiac surgery and on when the intraoperative presence of a cardiologist/internist would be beneficial.¹

The fourth Surgical Forum, also known as the "Subic Bay Forum" was held on 25-27 July 1997 and dealt with the "Immune Consequences of Trauma, Shock and Sepsis," co-sponsored by the Philippine College of Surgeons' Surgical Infection Committee and MSD Philippines. This new concept, also called SIRS/MODS/MOF (systemic inflammatory response syndrome / multiple organ dysfunction syndrome/ multiple organ failure) which is extremely crucial to the better understanding of the prevention and successful management of critical surgical illnesses, has since been, and will continue to be, widely disseminated through continuing medical education activities nationwide.²⁻⁴

On 29-30 July 1999, a symposium on surgical critical care was held in Phuket, Thailand, co-sponsored by the PCS and GlaxoWellcome Philippines Inc., and the symposium revealed that there was still no general agreement on certain key aspects in the management of critically ill surgical patients, and that there

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were current practice variations, some of which may not be cost-

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effective and may also lead to higher mortality and morbidity. The symposium participants unanimously recommended that the PCS come up with an EBCPG, and that GlaxoWellcome Philippines support the project.⁵

Methods

The PCS appointed a Technical Working Group (TWG) composed of 6 general surgeons, one thoracic/cardiovascular surgeon, 2 pulmonologists and 1 cardiologist. The group was instructed to adhere to the methods used in the development of the guidelines on preoperative cardiac evaluation (Roxas 1999) and were given a free hand to formulate the specific clinical questions on areas considered important in the perioperative care of the critically ill surgical patient such as intravenous fluids for resuscitation, blood transfusion, monitoring of resuscitation, nutritional support, pharmacological cardiovascular support and ventilatory support.

The TWG began work on 1 May 2000 and initial clinical questions were listed, then revised several times as the search of the literature progressed.

The literature search, limited to English publications, used both electronic and manual

drugs, hemoglobin, congestive heart failure, intravenous fluids, monitoring, platelet concentrate, surgical intensivist, trauma, resuscitation, packed red blood cells, laboratory tests, nutrition, respirator, surveillance, ventilatory support, surgery, pharmacologic support, medications, nutritional support, respiratory failure, transfusion, work-up, plasma, surgical intensive care, 3) HERDIN : colloids, crystalloids, nutrition, critical injuries, blood transfusion, central venous pressure, resuscitation, surgery, blood volume, intensive care, fluid resuscitation. In the case of subjects where there were relatively few or absent RCTs, cohort studies, case-control studies, case series reports and review articles were included, and their references manually searched. The primary outcome of interest was mortality.

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methods. Three electronic databases were used: 1) The Cochrane Library, Issue 2, 2000; 2) National Library of Medicine - Medline (PubMed, no time limit); and HERDIN (Health Research and Development Information Network) Version 1, 1997 of DOST-PCHRD. Manual searching of the reference lists of review articles and some important meta-analyses and randomized controlled trials (RCTs) were also done. The search terms used were: 1) Cochrane Library : critical injuries, benefits, blood volume, crystalloids, drugs, hypotension, hypovolemia, surgical intensive care, central venous pressure, nutrition, survival, colloids, complications, dopamine, blood transfusion, hypovolemic shock, fluid resuscitation, 2) Medline : anemia, cardiac failure, colloids, critically injured, diagnosis, fresh whole blood, hemorrhagic shock, blood components, cardiogenic shock, critical care, crystalloids, diagnostic tests, hematocrit, hypovolemia, blood transfusion, cardiovascular failure, critically ill, inotropic drugs,

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3. What are the indications for blood transfusion in critically ill surgical patients?
4. What are the clinical and/or diagnostic indicators that have been shown to be useful in assessing the adequacy of resuscitation of hypovolemic critically ill surgical patients?
5. Are there patients who will benefit from postoperative nutritional support?
6. What is the most effective way of delivering postoperative nutritional support?
7. What is the most effective composition of postoperative nutritional support?

Results

A total of 3,846 titles were printed, out of which 546 abstracts were reviewed. A total of 114 full text articles were critically appraised, of which 71 were included in the manuscript.

FLUIDS FOR RESUSCITATION

1. What is the appropriate type of intravenous fluid to be used in the resuscitation of hypovolemic critically ill surgical patients?

There were 5 systematic reviews (meta-analyses) that assessed the effects on mortality of colloids compared to crystalloids for fluid resuscitation in critically ill patients.

Alderson, et al⁶ (2000) using the Cochrane Injuries Group methods for search, study selection, assessment of methodological quality, data collection and analysis⁷, looked at all randomized and quasi-random trials of any type of colloids (either alone or in combination with crystalloids) compared to crystalloids (any type) in patients requiring volume replacement (excluding

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neonates, pregnant women and cross-over trials). Forty eight studies, involving 2,884 patients, were included. The authors concluded that: "There is no evidence from randomized clinical trials that resuscitation with colloids reduces the risk of death compared to crystalloids in patients with trauma, burns and following surgery." A sample of the meta-analysis, looking at hydroxymethyl starch, modified gelatin and dextran is shown in Figure 1.⁸⁻⁵⁵

Choi, et al.⁵⁶ (1999), looked at 105 clinical trials of adult patients requiring fluid resuscitation comparing isotonic crystalloids (lactated Ringer's solution, normal saline, Ringer's acetate and balanced electrolyte solution) versus colloids. They included 17

confidence intervals are wide and do not exclude significant differences between colloids." ^{8-9,17,35,36c,42,62-93,94a-94b,95-102}

The Albumin Reviewers of the Cochrane Injuries Group focused on the benefits or harm in using human albumin solutions for resuscitation and volume expansion in critically ill patients (1998¹⁰³, 2000¹⁰⁴). They included 24 RCTs (N=1,204). They placed the patients into 3 categories (hypovolemia, burns, hypoalbuminemia), and for each category the risk of death was higher in the albumin group compared to the comparison group (Figure 5). The authors concluded that: "There is no evidence that albumin administration reduces the risk of death in critically ill patients with hypovolemia, burns or hypoalbuminemia, and

studies involving 814 patients, and concluded: "Overall, there is no apparent difference in pulmonary edema, mortality or length of stay between isotonic crystalloids and colloid resuscitation. Crystalloid resuscitation is associated with a lower mortality in trauma patients" (Figures 2,3).
10,13,18,23,24,25a,25c,26d,30,31b,34,36,39,41,48,57,58

Schierhout and Roberts⁵⁹ (1998) reported their systematic review of 19 unconfounded RCTs that compared mortality and the use of pure colloids with crystalloids (N= 1,315) for volume replacement of critically ill patients, and stratified according to patient type and quality of allocation concealment. Colloids were associated with an increased absolute risk of mortality of 4% (95% confidence interval 0%, 8%) or 4 extra deaths for every 100 patients resuscitated, when only trials with adequate allocation concealment were included. There was no evidence for differences among patients with different types of injuries (trauma, surgery, burns, others) (Figure 4). The authors concluded that the meta-analysis "does not support the continued use of colloids for volume replacement in critically ill patients."
10,13,18-20,22-23,25,30-32,36,42,45,47-49,52,60

Bunn, et al⁶¹ (1999) reported a meta-analysis that compared the effects of different colloid solutions on mortality in patients that were thought to need volume replacement: hydroxyethyl starch (HES), albumin, plasma protein fractions (PPF), gelatin and dextran. They included 46 studies (N=2,884), and concluded that: "From this review, there is no evidence that one colloid solution is more effective or safe than any other, although the

a strong suggestion that it may increase the risk of death."
10,18,19b,22d,25a,26d,36c,38,42,48,54-55,105-116

Recommendations

1. Crystalloids are the appropriate intravenous fluids to be used in the resuscitation of hypovolemic surgical patients. The use of colloids does not decrease mortality, and may result in higher mortality in trauma patients. Albumin may increase the risk of death in patients with hypovolemia, burns and hypoalbuminemia. (Level 1, Category A)

RED BLOOD CELL TRANSFUSION

The HIV/AIDS scare generated a global interest in blood transfusion, and in developed countries, the last two decades had seen heightened activities on the safety and proper utilization of blood transfusion. In the Philippines, two additional factors have to be strongly considered in the decision process. First, there still is a relative scarcity of blood products, and the deficits can vary widely not only between different areas in the country, but even between hospitals in the same area. Second, the technical and procedural standards used in developed countries so that transfusion risks may be minimized are still not evenly enforced owing to a variety of reasons.



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Figure 5. Fixed effects model of relative risks (95% confidence interval) of death associated with intervention (fluid resuscitation with albumin or plasma protein fraction) compared with control (no albumin or plasma protein fraction or resuscitation with a crystalloid solution) in critically ill patients. (Cochrane Injuries Group Albumin Reviewers, BMJ 1998; 317)



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2. What are the adverse effects of blood transfusion?

There were several reviews on the many reported perils associated with allogeneic blood transfusion (ABT). The term ABT was used to mean the infusion of either whole blood or any red blood cell (RBC) product from an unrelated donor. (Autologous transfusion refers to the transfusion of the patient's own blood, obtained through various methods such as intraoperative/postoperative salvage, preoperative donation, and isovolemic hemodilution). Three articles are cited.

which were invariably related to blood group incompatibility resulted mainly from clerical errors, such as transfusing the wrong unit to a misidentified patient.



In the United States, the National Institutes of Health (NIH) together with other agencies convened a Consensus Development Conference on Perioperative Red Blood Cell

Transfusion on June 1988, which cautioned that "the need for possibly improved oxygenation must be weighed against the risks of adverse consequences, both short-term and long-term." Transmission of infectious agents are the most feared which consists of not only a host of viruses (known and unknown) such as HIV, HBV, HCV, cytomegalovirus, HTLV, EBV and parvoviruses, but other microorganisms such as malaria, *Trypanozoma cruzi* and bacteria. Noninfectious morbidities are mainly attributed to immune mechanisms and include hemolytic and nonhemolytic reactions, immunosuppression and graft-versus-host disease.¹

Goodnough and Schuk followed with a more extensive review in 1990.² They reported that of a total of 121,171 AIDS cases in the United States by 1990, 3,120 cases (2.6%) were transfusion-associated. Even with state-of-the-art screening, it was estimated that 67 to 227 persons might acquire transfusion-associated AIDS yearly.³ This was similar to the risk of dying from a fatal hemolytic transfusion reaction, which was 30 to 60 deaths yearly out of 4 million blood transfusion recipients.⁴ The Joint Committee on Accreditation of Health Care Organizations required the audit of each transfusion event to ensure that transfusion practice guidelines are implemented. The American Association of Blood Banks had recommended that informed consent be obtained and documented so that the recipient is made fully aware of the potential hazards of blood transfusion.

Klein published a review on ABT in 1995 which included the estimated risks in the United States of some adverse events (Table 1).⁵ Fatal hemolytic reactions

Of special interest to surgeons is the strong possibility that ABT, particularly those containing components other than RBC, may have immunomodulatory consequences and may increase the risk of immediate and long-term postoperative morbidity and even mortality.⁶⁻¹¹

There is some amount of fear that ABT may be associated with an increased risk of postoperative infections, as well as increased recurrence and mortality among cancer patients. It is not easy to compare the postoperative sequelae of patients who were transfused and those who did not receive blood transfusion because of many real and potential confounding variables present among the two groups, the wide variations in transfusion practices, and the difficulty of undertaking a large RCT. Some of the difficulties may be reduced by focusing on the patients who were in fact transfused, and comparing those who received autologous blood, or leucocyte-depleted RBC (since the immunomodulatory effect of ABT seems to be white cell mediated).

Duffy and Neal¹² (1996) published a meta-analysis of reports on postoperative infection rates comparing patients who received autologous blood compared with allogeneic blood. Out of 9 studies published after 1989, 7 met their inclusion criteria, with a total of 1,060 patients.¹³⁻¹⁹ The 5 retrospective studies and 2 RCTs did

not have any significant statistical heterogeneity between them and removing any one study from the meta-analysis changed neither statistical significance nor the direction

been established by the observational studies, nor did they exclude the possibility of a small adverse effect.

of the effect. The risk of postoperative infection was greater in the allogeneic group, odds ratio 2.37 (95%CI, 1.6, 3.6, $p < 0.0001$).

McAlister, et al.²⁰ (1998) published a meta-analysis of reports on outcomes of patients with localized malignancy who underwent elective potentially curative surgery. Patients who received perioperative ABT (24 hours before to 30 days after operations) were compared with those who were given perioperative autologous blood or leucocyte-depleted packed RBC. The major outcomes were all-cause mortality, cancer recurrence, and postoperative infection. Initial search identified 2,172 citations, of which 26 were retrieved, and 8 included in the meta-analysis (6 RCTs and 2 prospective cohort studies).²¹⁻
²⁹ There was no difference in all-cause mortality (5 RCTs and one cohort study, $N=2,196$), the summary risk ratio being 0.95 (95% CI 0.79, 1.15). There was also no difference in cancer recurrence rates (3 RCTs and 2 cohort studies, $N=1,536$), as the summary risk ratio was 1.06 (95% CI 0.88, 1.28). There was significant heterogeneity in the 6 RCTs that reported postoperative infections, and when 2 studies which differed sufficiently from the rest with regards patient mix and study design were excluded from the meta-analysis, the 4 RCTs ($N=1,316$) showed a risk ratio of 1.00 (95% < 1 0.76, 1.32). The authors cautioned that because of the sample sizes of the 8 studies, the meta-analysis lacked the power to detect a relative difference of less than 20 per cent in the frequency of death, cancer recurrence or postoperative infection between the 2 groups.

Vamvakas³⁰ (1995) looked at 60 observational studies published in English from 1982 - 1994 which compared transfused and untransfused cancer patients. He commented that for colorectal cancer, he could find only one factor that may explain the disagreements between studies, and it was that retrospective studies showed a significant negative outcome (tumor recurrence, death due to recurrence, or death due to any cause), whereas prospective studies did not. He likewise stressed that because of the effect of uncontrolled confounding it may be prudent to conclude that a deleterious effect had not

In 1964, Lacson reported 83 cases of transfusion reactions among 1,400 transfusions at the University of the East Ramon Magsaysay Memorial Medical Center. Two thirds were febrile reactions. There was also one case of malaria transmission, and 8 positive bacteriologic cultures out of 90 bottles cultured at random.³¹

In 1995, Ratula and De Leon reported that in the province of La Union, out of a total of 8,231 units of blood used from January to December 1993, 86 per cent came from commercial blood banks, 5.4 per cent were from paid donation, and only 4.8 per cent were from voluntary donation.³² In 1995, Castillo and Tayag reported a survey of residents in 2 barangays in Lipa City, Batangas that revealed an increased resistance to the idea of donating blood, which may be attributed to a low level of knowledge, coupled with prevalent beliefs.³³

3. What are the indications for red blood cell transfusion in the critically ill surgical patient?

There are two aspects about RBC transfusion that most physicians will agree on, although they have to be constantly reminded about them. First, transfusion causes a real risk of serious short-term and long-term harmful effects. Second, the main justification for transfusions is that the patient's level of anemia results in a global oxygen delivery which is below a critical level which is associated with a high risk of mortality and serious morbidity, and transfusion is known to lower that risk. The major controversy in the Philippines, as well as many other countries, is on what this critical level is, also known as the "transfusion trigger".

The rather persistent habit of using the "10/30 rule" (Hb less than 10 gms/dL, hematocrit less than 30 per cent) started about a century ago, particularly after Da Costa and Kaltryer associated anemia and anesthesia with operative risks.³⁴ This rigid rule had been hammered down from generation to generation, and even now many anesthesiologists, internists and even surgeons blindly adhere to it, regardless of how healthy the patient is, or the absence of comorbid conditions, or the magnitude of the planned operation.

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Fortunately, since the 1950s, investigators began to clarify the physiologic responses to anemia through animal and human studies, as well as improving our understanding of oxygen delivery (DO_2) and oxygen consumption (VO_2). In fact, our species could not have survived without developing physiologic responses to anemia, particularly to blood loss. Cardiac output increases through an increase in heart rate, stroke volume and contractility. Peripheral vascular resistance is reduced mainly by a decrease in blood viscosity. There is increased release of oxygen by red blood cells by a shift to the right of the oxyhemoglobin curve. Even the lungs come in to help. Meanwhile, decreased blood volume is compensated for by the many physiologic responses familiar to surgeons.³⁵⁻⁴⁹

Meanwhile, the notion of a "universal trigger" was increasingly questioned. The experience of the United States military during the Korean War revealed that maintaining a patient's Hb concentration at around 7g/dL was not associated with serious outcomes as long as the blood volume was adequately restored.⁵⁰ Anecdotal experiences and case reports involving Jehovah's Witnesses added impetus to the re-evaluation of the "10/30 rule".⁵¹⁻⁵⁴

At long last, the HIV/AIDS scare in the United States spurred the National Institutes of Health to convene a Consensus Development Conference on Perioperative Red Cell Transfusion on June 27, 1988, since around two thirds of all RBC transfusions were then given in the perioperative period.

Among the statements were:¹

1. Available evidence does not support the use of a single criterion such as a hemoglobin concentration of less than 100 g/dL. No single measure can replace good clinical judgment as the basis for decision-making regarding perioperative transfusion.

2. There is no evidence that mild-to-moderate anemia contributes to perioperative morbidity.

3. Otherwise healthy patients with Hb values of 100 g/dL or greater rarely require perioperative transfusion, whereas those with acute anemia with resulting Hb values of less

4. It is important to separate the effects of hypovolemia and decreased perfusion from the effects of anemia. If there is normal intravascular volume and normal tissue perfusion there is no adverse effect on cardiovascular function until anemia is profound.

5. Wound healing is not compromised by normovolemic anemia unless it is extreme. Likewise there is no evidence that anemia increases the frequency or severity of postoperative infections.

6. Transfusion should not be considered a substitute for good surgical and anesthetic techniques.

7. Perioperative transfusion of homologous red blood cells carries documented risks of infection and immune changes. Therefore, the number of homologous transfusions should be kept to a minimum.

8. There are being developed a variety of promising alternatives to homologous transfusion.

On January 12-14, 1995, a Blood Management Practice Guidelines Conference was convened, involving 15 physicians that included surgeons, anesthesiologists, intensivists and a lawyer, as well as 2 spokespersons for the Jehovah's Witness. The recommended Blood Management Surgical Practice Guidelines included transfusion practice policies, sections on risks of allogeneic blood transfusion, morbidity risk assessment, alternatives to ABT (erythropoietin, autotransfusion, perioperative donation, acute normovolemic hemodilution), and specific surgical situations (cardiovascular, orthopedic and urologic surgery).⁵⁵ The NIH guidelines were reiterated, including indications: "transfusion should not be used as a primary means of restoring blood volume or simply to "raise hematocrit" in the absence of a clinically defined need for improved DO_2 ". They recommended a transfusion trigger of 7 g/dL in a healthy low risk patient with no evidence of cardiopulmonary disease, and 10 g/dL for patients with cardiopulmonary disease.⁵⁶ They reiterated the risks for ABT⁵⁷, and recommended that a "higher threshold should be used in patients who have or are at risk of

than 70 gm/dL frequently will require red blood cell transfusion.

cardiac or pulmonary disease".⁵⁸ Unlike the NIH guidelines, the authors included a fair amount of references, although

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it was neither mentioned if an electronic search was used nor how the evidence was appraised.

The Canadian Medical Association sponsored the most extensive review of the literature on ABT. Electronic search of Medline from January 1966 to July 1996 revealed 189 articles (111 observational studies and 78 interventional studies). The authors identified 6 RCTs (N=813) comparing two transfusion strategies.⁶⁰⁻⁶⁵ From their systematic evaluation, they were able to draw 19 inferences, which were graded according to the strength of supporting evidence (Table 2).⁵⁹ Some of the inferences were:

1. A transfusion threshold of [Hb] 100 g/L is optimal in high risk patients (RCTs, heterogeneity, CIs all on one side of threshold NNT)

2. A transfusion threshold between [Hb] 70 g/L and 80 g/L is optimal in all patients, independent of risk (RCTs, heterogeneity, CIs overlap threshold NNT).

The Canadian Medical Society sponsored a second systematic review, on published recommendations and guidelines on ABT. A total of 8,426 titles were identified, of which 1,424 were initially deemed relevant, and 42 review articles and 17 guidelines were included in the review. Only 2 articles were considered as systematic reviews.^{66,67} There were 8 guidelines that fulfilled all aspects of the CPG definition. The most rigorously developed guidelines were those of the American Society of Anesthesiologists⁶⁸, as it was the only one that specified an electronic search, a literature selection criteria, and graded the evidence.⁶⁹

The American Society of Anesthesiology Task

1. Transfusion is rarely indicated when the hemoglobin concentration is greater than 10 g/dL and is almost always indicated when it is less than 6 g/dL, especially when the anemia is acute.

2. The determination of whether intermediate hemoglobin concentrations (6-10 g/dL) justify or require RBC transfusion should be based on the patient's risk for complications of inadequate oxygenation.

3. The use of a single hemoglobin "trigger" for all patients and other approaches that fail to consider all important physiologic and surgical factors affecting oxygenation are not recommended.

4. When appropriate, preoperative autologous blood donation, intraoperative and postoperative blood recovery, acute normovolemic hemodilution, and measures to decrease blood loss (deliberate hypotension and pharmacologic agents) may be beneficial.

5. The indications for transfusion of autologous RBCs may be more liberal than for allogeneic RBCs because of the lower (but still significant) risks associated with the former.

The most current RCT was reported by Hebert, et al. in 1999, of the Transfusion Requirements in Critical Care Investigators for the Canadian Critical Care Trials Group. They enrolled 838 critically ill normovolemic patients who had hemoglobin concentration of less than 9 g/dL within 72 hours after admission to the ICU, and randomly assigned 418 patients to a restrictive transfusion group (R) in which red cells were transfused if the Hb dropped below 7 g/dL and were maintained at Hb concentrations of 7-9 g/dL, and 420 patients to a liberal strategy group (L) in which transfusions were given when Hb fell

Force on Blood Component Therapy began work in 1994 to develop evidence-based indications for transfusion in perioperative and peripartum settings. Recommendations were for typical surgical and obstetric patients, and were based on scientific evidence and expert opinion on effectiveness of the intervention, which considered clinical benefits, adverse effects, and costs. Regarding RBC transfusion, 5 recommendations were given.

The task force bases its recommendations on available category II-2 and II-3 evidence and expert opinion. The task force concluded that:

below 10 g/dL and were maintained at Hb concentrations of 10-12 g/dL. The primary diagnosis were respiratory disease (242, 28.9%), cardiovascular disease (170, 20.3%), and trauma (165, 19.7%), comprising 577 cases (68.9%). Overall, the 30-day mortality was similar (R=18.7%, L=23.3%, p=0.11). Mortality rates were significantly lower in the R group among those who were less ill (APACHE II score of less/equal 20), and among those who were less than 55

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years old. There was no mortality difference among patients who had significant cardiac disease (R=20.5%, L=22.9%, p=0.69) (Table 3). The authors concluded that "A restrictive strategy of red-cell transfusion is at least as effective and possibly superior to a liberal transfusion strategy in critically ill patients, with the possible exception of patients with acute myocardial infarction and unstable angina."⁷⁰



Recommendations:

- 1. Aggressive and early control of hemorrhage should be considered an integral part of resuscitation. (Level II, Category A)*
- 2. In a patient who is hypovolemic secondary to acute hemorrhage, volume resuscitation should be initiated. (Level I, Category A)*
- 3. In a normovolemic patient whose level of anemia is associated with evidence of an increased risk of major adverse outcomes, the major indication of RBC transfusion is to increase oxygen delivery. This should be corrected to achieve a level of anemia wherein there is evidence that the increased risk is no longer present.*

The traditional "10/30 rule", or a transfusion trigger of an Hb concentration of less than 10 g

/ dL or a hematocrit concentration of less than 20 per cent should no longer be utilized. (Level I, Category A)

4. There is evidence that there is no benefit of RBC transfusion for patients whose Hb concentration is equal or more than 10 g / dL. (Level I, Category A)

5. In general, there may be an increased risk of adverse outcomes in normovolemic patients with acute anemia whose Hb concentration is less than 7 g / dL. (Level I, Category A)

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6. Normovolemic patients with acute anemia who have cardiac disease or are at risk of cardiac disease may benefit from RBC transfusion when their Hb concentration is less than 7 g / dL. Factors that increase the risk of postoperative cardiac events, and the corresponding evidence are contained in PCS EBCPG on Seeking Referral for Preoperative Cardiac Evaluation for Elective Noncardiac Surgery (PJSS 1999; 54 (4): 171 - 233). (Level

clinical picture of shock (uncompensated shock) emerges, and it used to be believed that when the clinical picture improved and even became "normal" and "stable" that adequate perfusion had been restored and that resuscitation was adequate.⁴ However, a profusion of reports in the past 2 decades by investigators using different tests had demonstrated that some of those hydrated patients with an apparently normal clinical

I, Category A)

Patients with acute myocardial infarction or unstable angina may benefit from a transfusion trigger higher than 7 g / dL. (Level II, Category A)

7. Packed red blood cells is preferred when blood transfusion is necessary. (Level II, Category A)

ASSESSMENT OF RESUSCITATION OF HYPOVOLEMIA

4. What are the clinical and/or diagnostic indicators that have been shown to be useful in assessing the adequacy of resuscitation of hypovolemic critically ill surgical patients?

Shock may be viewed as "a series of sequelae of tissue perfusion that is inadequate to maintain normal metabolic and nutritional functions."¹ This recent review by Dabrowski, et al., and those by Henry and Scalea², and McGee, et al.³, looked at the published evidence on the accuracy and usefulness of clinical and physiological parameters in determining the existence of shock, and the ability of resuscitation measures to improve tissue perfusion.

Early on, patients are able to compensate for a decreasing blood volume through a number of evolutionary responses, and many may appear normal even though decreased tissue perfusion may already be present (compensated shock). This compensatory ability varies between athletes, healthy but sedentary individuals, and those with co-morbid conditions particularly cardiac and pulmonary diseases. When increasing volume loss exceeds this initial compensatory ability, the classical

picture were in fact still hypoperfused (in compensatory shock again), and if unrecognized and not corrected may not exhibit all the classical clinical picture of uncompensated shock even when nearing death (irreversible shock). This had led some to advocate the almost routine use of certain tests, which are indicators of tissue perfusion, in the assessment of volume resuscitation. The difficulties are in the additional costs, the invasive nature of some of the methods, and in the result's lag time of some tests. But most importantly, many of the evidence used to promote the utility of these tests identified physiological parameters as surrogate of clinical outcomes, and there is a relative paucity of Level I evidence on major clinically relevant outcomes. " Given the clear record of successful treatment of most patients in shock using nothing more than clinically evident outcomes, however, whether one need progress beyond the use of bedside tests to resuscitate patients in shock, whatever the cause, remains controversial" (Dabrowski, et al.).

Serum lactate⁵⁻⁷ is not as rapidly available as its surrogate, the arterial blood base deficit (BD) which is readily computed from blood gas analysis results.⁸⁻¹³

Pulmonary artery catheterization (PAC) using the Swan-Ganz catheter was introduced in 1970¹⁴, rapidly became widely used in intensive care areas in developed countries, and by 1996 more than 2 million catheters were being sold worldwide every year.¹⁵ Even now, the PAC stands as a symbol of the state-of-the-art in the monitoring of critically ill patients, highly desirable but unaffordable in most developing countries. However, because " A possibility exists that the accuracy of data obtained from the PAC is often variable, potentially inaccurate, and the information obtained may not be applied appropriately", and the fact that "unambiguous proof that information derived from the PAC improves patient outcome measures is scarce", led the Society of

Critical Care Medicine (SCCM) to host, in 1996, a Pulmonary Artery Catheter Consensus Conference, with participation and endorsement of: American Association of Critical Care Nurses; American College of Chest Physicians; American Thoracic Society; and European Society of Intensive Care Medicine. The process followed that recommended for EBCPGs, including an electronic search and assigning levels of evidence. Specific questions were identified, and the multidisciplinary expert panel convened on December 6-8, 1996.¹⁶ Some of the pertinent recommendations were:

1. The PAC may be useful in the management of patients with shock unresponsive to fluid resuscitation and use of vasopressors. Clinical trials are needed to determine whether management of various types of shock with the PAC leads to better outcomes than management using less invasive means of monitoring.

2. Until further data are forthcoming, routine use of the PAC does not appear to be necessary in low-risk patients undergoing cardiac surgery. The PAC may be useful in high-risk patients undergoing cardiac surgery, especially in those patients with clinically important left ventricular dysfunction. Research is needed to determine whether high-risk patients managed with the PAC have better outcomes from coronary artery bypass grafting than those patients managed by less invasive means.

3. Use of the PAC may lead to fewer complications in patients undergoing peripheral vascular surgery. Further study of PAC use is needed in this population to confirm the reduced rate of complications and to determine the effect of the PAC on other outcomes especially mortality.

4. The PAC may be useful in the management of some patients undergoing aortic surgery, although recent studies have identified populations of patients that can be safely monitored by less invasive means. Further study is needed to determine whether PAC use improves patient outcomes in patients undergoing aortic surgery.

5. Routine perioperative use of the PAC does not appear to be appropriate because of age alone.

Further research is needed to define the proper role of the PAC in geriatric patients.

6. Until data are forthcoming it is not possible to accurately assess the overall impact of PAC use on complications and mortality in patients undergoing neurosurgical procedures. However, use of the PAC to monitor and treat air embolism in this group of patients does not appear to be appropriate.

7. Based on expert opinion, the PAC may be helpful in selected traumatically injured patients. Randomized, controlled trials of PAC-guided therapy are needed to validate the indications and effectiveness of PAC use in the traumatically injured patient.

8. The PAC may be useful in patients with septic shock who have not responded to initial aggressive fluid resuscitation and low dose inotropic/vasoconstrictor therapy. Various management strategies for sepsis and septic shock (intravenous fluids, vasoactive medications, inotropic medications, etc.) should be evaluated in prospective, randomized, controlled trials. Patient groups should be carefully defined, by source of sepsis, severity of illness and organ dysfunction.

9. PAC-guided hemodynamic intervention to augment DO_2 to supranormal values in patients with systemic inflammatory response syndrome-related organ dysfunction from sepsis, trauma, or postoperative complications is not recommended. Carefully designed, multicenter, randomized, controlled trials are needed to establish whether augmenting DO_2 improves organ-specific outcomes and survival in patients with systemic inflammatory response syndrome-related organ dysfunction after sepsis, trauma, acute inflammation and postoperative complications.

10. Further research must be performed before a recommendation can be made about goal-oriented hemodynamic intervention utilizing the PAC to augment DO_2 to supranormal levels before high-risk surgery. There is a need for well-designed, multicenter, randomized, controlled trials focusing on whether prospective

preoperative augmentation of DO₂ to supranormal levels compared with normative values in stable ICU patients decreases subsequent organ dysfunction and death after surgical operation in high risk patients and, if so, by what mechanism(s).

There are other technologies being investigated as alternatives or adjuncts to serum lactate, base deficit and PAC (which are global indicators of perfusion). Since there is a preferential shunting of blood flow in the hypovolemic state, away from the viscera and soft tissues and towards the vital organs, determination of perfusion in these "sacrificial areas" has attracted attention as they may give more accurate information and may be simpler to use. Gastric tonometry allows the estimation of mucosal PO₂ and PCO₂ and calculation of intramucosal pH, wherein a pH lower than normal (cutoff pH 7.3) is interpreted as inadequate tissue perfusion.¹⁷⁻²² Tissue oximetry had also been investigated as a method of determining whether measurements of regional perfusion (subcutaneous tissue, muscle) have advantages over, or may complement, global perfusion parameters in determining the adequacy of resuscitation.²³⁻²⁶ More research on the instrumentation and techniques, and more importantly on whether the use of regional perfusion measurements will actually improve clinical outcomes of patients compared to those in whom the tests were not used are still needed. Dabrowski et al.¹ summarized their review: "Because no one test or device can be relied on to identify the presence of shock in all situations, the best "tool" is a well-trained clinician."

Recommendations:

1. *The clinical judgment of a well-trained and experienced surgeon, utilizing clinical parameters, such as blood pressure, heart rate and urine output should still be the best "monitor" of the adequacy of resuscitation. (Level II, Category A)*

2. *At present, there is no evidence that the routine use of tests such as serum lactate levels, base deficits and pulmonary artery catheters (PAC)*

improve major clinical outcomes and therefore are not recommended. (Level I, Category A)

3. *Indications for the use of tests should be based on specific circumstances in which there is strong evidence that their use is associated with an improvement in major clinical outcomes, such as a decrease in mortality and serious complications. (Level I, Category A)*

POSTOPERATIVE NUTRITIONAL SUPPORT

5. *Are there patients who will benefit from postoperative nutritional support?*

6. *What is the most effective way of delivering postoperative nutritional support?*

7. *What is the most effective composition of postoperative nutritional support?*

Dabrowski and Rombeau¹ published a review with some very practical clinical aids on the nutritional management of critically ill trauma patients, and gave a relevant definition of malnutrition as "a nutritional deficit associated with an increased risk of adverse clinical events and with a decreased risk of such events when corrected." The catabolic, hypermetabolic response initiated by injury (including surgical procedures), shock and sepsis is a beneficial, evolutionary adaptive response that had enabled our ancestors to survive, at least those who had access to fluids until help arrived, and they could begin healing themselves under the care of family and friends. Severe malnutrition has long been recognized to increase the risk of adverse postoperative sequelae.²⁻⁴ More recently, the role of the "gut barrier" and the importance of early enteral feeding and maintaining the integrity of the gastrointestinal mucosa in preventing or modulating SIRS, MODS, MOF has been repeatedly emphasized.⁵⁻¹²

Nevertheless, many surgeons continue to follow the traditional practice of starting oral alimentation only in the presence of flatus. Since the practice causes delay in starting enteral feeding, particularly among critically ill surgical patients in whom flatus is commonly

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delayed, total parenteral nutrition (TPN) became the most popular method for delivering nutritional needs for almost 3 decades.

Heyland, et al.¹³ (1998) published a meta-analysis on the effects of TPN versus standard care (usual oral diet plus intravenous glucose) on major clinical outcomes of critically ill adult patients and adult surgical patients. They conducted a computerized search (MEDLINE 1980-1998, English) as well as a manual search from review articles. The authors used explicit criteria for study selection and a methodologic quality assessment scoring system. They included 26 RCTs (N=2211), and aggregated data showed that TPN had no effect on mortality (RR 1.03, 95% CI, 0.8,1.31) (Figure 6) and some tendency to have a lower major complications rate (RR=0.84, 95% CI 0.64, 1.09) (Figure 7). They also performed five-subgroup analyses, each based on an a priori hypothesis (Figure 8)¹⁴⁻³⁹



1. Regarding pre-morbid nutritional status, there were no differences in mortality among either malnourished patients (RR=1.13, 95% CI 0.75-1.71), or adequately nourished patients (RR=1.00, 95% CI 0.71, 1.39). Major complications were significantly lower among malnourished patients who received TPN (RR=0.52, 95% CI 0.30,0.91), while there was no difference among adequately nourished patients (RR=1.02, 95% 0.75, 1.40).

2. They also compared studies with higher methodological quality scores ((7) to those with lower scores. Regarding mortality, RCTs with higher scores showed no effect of TPN (RR=1.17, 95% CI 0.88, 1.56), and a trend to lower mortality in RCTs with lower scores (RR=0.76, 95% CI 0.49, 1.19). For complication rates, RCTs with higher scores showed no treatment effects (RR=1.13, 95% CI 0.86-1.50), while RCTs with lower scores showed a significant reduction (RR=0.54, 95% CI 0.33, 0.87).

3. They also compared studies published in 1988 or earlier with those published later. Regarding mortality, earlier RCTs showed a trend toward a lower rate with TPN (RR=0.70, 95% CI, 0.44-1.13), while later RCTs showed no treatment effects (RR=1.18, 95% CI 0.89,1.57). For major complications, earlier RCTs showed lower rates with TPN (RR=0.49, 95% CI 0.29-0.81), while later RCTs showed no effect (RR=1.19, 95% CI 0.93-1.53).

4. They compared trials in which the TPN contained lipids with those that did not. There was no difference in mortality in either RCTs that used lipids (RR=1.03, 95% CI 0.78,1.36), or those that did not (RR=0.98, 95% CI 0.49, 1.95). For complications, rates in RCTs that used lipids showed no effect (RR=0.96, 95% CI 0.69, 1.34), but in RCTs that did not use lipids the rate was significantly lower (RR=0.59, 95% CI 0.38, 0.90).

5. They compared studies of critically ill patients with those on surgical patients. For mortality, the rate of critically ill patients on TPN were higher (RR=1.78, 95% CI 1.11, 2.85), while there was no treatment effect on surgical patients (RR=0.91, 95% CI 0.69, 1.21). For complications, RCTs on critically ill patients showed a trend

toward an increase in the rate (RR=2.4, 95% CI 0.88, 6.58), while RCTs on surgical patients showed lower rates (RR=0.76, 95% CI 0.48, 1.0).

The authors concluded: "Total parenteral nutrition does not influence the overall mortality rate of surgical or critically ill patients. It may reduce the complication rate, especially in malnourished patients, but study results are influenced by study population, use of lipids, methodological quality and year of publication."

Moore, et al.⁴⁰ (1989) published a RCT (N=59) comparing TPN with enteral feeding (TEN) following major abdominal trauma, initiated within 12 hours after operation. TEN (Vivonex TEN) via a needle catheter jejunostomy was well tolerated. Though not statistically significant (p=0.5644), there was a tendency for lower major septic complications (1/29 or 3%) in the TEN group compared to 20% (6/30) in the TPN group (RR=0.17, 95% CI 0.02, 1.35).

Moore, et al.⁴¹ then published a meta-analysis of 8 RCTs that compared TPN and TEN (Vivonex TEN by tube/needle catheter jejunostomy) in high-risk surgical patients (N=230). There was negligible heterogeneity across and within studies. The time to start postoperative nutritional support was similar (TEN, 32.5 ± 1.8 hours; TPN, 32.8 ± 1.7 hours), and 85 per cent of patients tolerated TEN well. Intention-to-treat analysis revealed higher septic complications in the TPN group (35%) compared to the TEN group (16%) (p = 0.01) (Table 4) among trauma patients. There was no difference among nontrauma patients. There were also no significant differences in 10-day and 30-day mortality rates.⁴²⁻⁴⁹

Meanwhile, more evidence from animal as well as human studies strengthened the fact that enterocytes derived most of their nutritional needs from nutrients absorbed from the intestinal lumen. Some investigators then expanded the concept of TEN to formulas that included specific nutrients that had been shown to improve immune function and would help modulate the etiopathogenesis of SIRS/MODS/MOF now commonly called "immunonutrition". Beale, et al.⁵⁰ (1999) published a meta-analysis of 12 RCTs (N=1,482) that compared outcomes of

critically ill patients (medical, surgical, trauma) requiring TEN (nasogastric jejunostomy), wherein one group receiving standard TEN and another group had TEN with arginine with or without glutamine,

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nucleotides and omega-3 fatty acids (IMPACT, Immune-aid) and analyzed on an intention-to-treat basis. There was no effect of immunonutrition on mortality (RR=1.05, 95% CI 0.78, 1.41; p=0.76).

There were significant reductions in infection rate (RR=0.67, 95% CI 0.1, 1.51; p=0.04), and hospital length of stay (2.9 days, 95% CI 1.4, 4.4; p=0.0002) in the immunonutrition group (Figure 9).⁵¹⁻⁶²



The authors concluded, "The benefits of immunonutrition were most pronounced in surgical patients, although they were present in all groups. The reduction in hospital length of stay and infections has resource implications."

With the increasing evidence that postoperative TEN did indeed improve major outcomes of critically ill surgical patients, the next issue to be investigated was if the improved outcomes could also be achieved in noncritical patients. Carr, et al.⁶³ (1996) published a small RCT (N=30) on patients who underwent elective gastrointestinal resection for chronic gastrointestinal disease. The treatment group, upon returning from the operating room, were given an isovolemic feed (Fresubin) via a nasojejunal tube. The control group received intravenous fluids and nothing by mouth until flatus returned. TEN was well tolerated in all patients who received it, resulting in a mean daily intake of 1622 kcal and positive nitrogen balance before oral feeding was started. There was also no increase in gut mucosal permeability in the TEN group. There were no significant differences in clinical outcomes.

A larger RCT (N=195) was published by Heslin, et al.⁶⁴ involving patients who underwent resection for upper gastrointestinal cancer at the Memorial Sloan-Kettering

Recommendations:

1. Early nutritional support (within 24 hours) of critically ill surgical patients should be instituted because it decreases the risk of postoperative morbidity, particularly septic complications and more so in malnourished patients (greater than 10% preoperative weight loss). (Level I, Category A)

2. Among critically ill surgical patients, there is evidence that enteral nutrition (EN) delivered into the jejunum and started within 24 hours after operation results in lower septic complications compared to total parenteral nutrition (TPN). TPN is used only when the enteral route is not feasible. (Level I, Category A)

The clinical trials that had demonstrated benefits of early TEN had used commercial TEN formulations.

3. TEN using commercial immune-enhancing formulas may be associated with a greater decrease in the risk of septic complications compared to standard TEN formulae in selected critically ill patients. (Level I, Category A)

4. The routine use of postoperative enteral nutrition in noncritical, nonmalnourished patients is not recommended. (Level I,

Cancer Center. The treatment group received TEN via a jejunostomy tube using an immune-enhancing formula (IEF) (IMPACT) which was started within 24 hours after operation. The control group received crystalloids until oral feeding resumed. As expected, all of the physiological nutritional parameters were significantly better in the TEN group. There were no differences in clinical outcomes (mortality, morbidity, length of hospital stay), and the authors concluded "Early enteral feeding with an IEF was not beneficial and should not be used in a routine fashion after surgery for upper GI malignancies." The paper was presented at the 117th Annual Meeting of the American Surgical Association in Quebec and was thoroughly discussed by a panel of notables. Important points included: 1) the patients were generally not malnourished. The subset who were malnourished (greater than 10% perioperative weight loss) also did not benefit from IEF; 2) outcomes were also reflective of the staff's surgical skills; and 3) it was a good RCT.

Category A)

PHARMACOLOGIC CARDIOVASCULAR SUPPORT

8. When is pharmacological cardiovascular support beneficial among critically ill surgical patients?

Cardiovascular failure is the inability of the heart to provide sufficient blood to meet the metabolic demands of the body, resulting in low flow, hypoxia and metabolic acidosis. This failure as a single cause of mortality in the post-injury period is unusual because most trauma patients are young. Cardiovascular collapse is a component of the multiorgan failure syndrome and is most commonly due to inadequate resuscitation.

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Reducing the risk of cardiovascular failure must start with the basic principles of trauma care, including adequate treatment of hypovolemic shock. Treatment principles should emphasize an overall concern for physiologic responses rather than just treating the heart as an isolated organ.

Understanding the Frank-Starling Law is crucial in managing cardiovascular failure in critically ill surgical patients. This law demonstrates that cardiac output is directly proportional to filling pressures. As pressure increases, myocardial fiber length increases, producing increased tension and greater contractile force.¹

The most important concept of support for cardiovascular function is that fluids should be given in the appropriate volume. Vasopressors have no role in the initial treatment of hypovolemic shock. Studies have shown benefit from vasopressors only after volume has been restored. Furthermore, the

The clinical challenge of pulmonary artery catheter use is to properly interpret the information provided. It should be used with an understanding of its assumptions and limitations.⁷

Pulmonary artery pressure monitoring may be useful in selected critically ill trauma patients where tissue perfusion is less than optimal and the balance between intravascular volume and cardiac competence is not known.⁸ The appropriate titration of volume (preload), inotropic support and afterload agents can be effectively controlled with these hemodynamic measurements. Frequent changes in amount and type of treatment is possible if pulmonary pressure readings are available.

Quinn and Quebbman used PAC for unknown fluid status in 43 patients, for hypotension in 28 patients and for sepsis in 13 patients. Therapy was altered by pulmonary artery pressure and cardiac output measurements in 30 per cent of these patients. Eight patients

administration of vasopressors during hypovolemia reduces the already depleted plasma volume.^{2,3}

Central venous pressure (CVP) monitoring may be used as a measure of right sided filling pressure or right sided preload. CVP monitoring provides data for appropriate fluid management especially in young patients with normal cardiac function.^{4,5}

Central venous pressure reading however is affected by blood volume, distensibility and contractility of the right heart, venomotor tone and intrathoracic pressure. The measured CVP is the result of all these factors and does not always reflect the adequacy of the circulating blood volume or the competence of the right and left ventricle.⁶

Trends and pressure response to fluid administration are much more important than the absolute value. In general, a low CVP suggests that hypovolemia may exist and that fluid challenge is not likely to be harmful. The rate of infusion should be gauged by CVP response. A rapid rise in pressure suggests an adequate blood volume or poor right ventricular reserve. A minimal response suggests hypovolemia. CVP monitoring can be useful in many patients if its limitations are recognized. However, in severely ill surgical patients where the CVP does not reflect changes in blood volume, Swan Ganz pulmonary artery catheter placement may be performed.

A lot of controversy has been generated by the appropriate use of pulmonary artery catheters (PAC).

were thought to have cardiac failure but actually required volume replacement, whereas 7 patients thought to have volume depletion had volume overload.⁹

Under optimal conditions, a ventricular response curve can be generated by measuring the cardiac output sequentially as the volume is increased. When the cardiac output no longer increases or begins to decrease, optimal volume loading has been attained.

When the PCWP (pulmonary capillary wedge pressure) is at 12-18 and the cardiac output is still low, the next step is to improve cardiac output by giving inotropic agents. Unless the peripheral vascular resistance is greater than 1800 dynes/sec/cm², no afterload unloading agents are given.¹⁰ On the other hand when systemic vascular resistance is low, vasopressors are indicated.

The choice of inotropic agents should be individualized to each patient and his hemodynamic status at a given time. The patient should be frequently examined and pharmacologic drugs titrated based on the hemodynamics and the overall clinical picture of the patient.

There has been a controversy whether "supranormal" delivery of oxygen by supranormal cardiac index resuscitation goals improves outcome in patients with trauma, septic shock as well as in heterogeneous groups of critically ill patients. This topic will be discussed in the next section.

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9. What is the appropriate method of pharmacological cardiovascular support of the critically ill surgical patient?

In the Philippines, the adrenergic agonists dopamine, dobutamine and epinephrine are widely utilized for pharmacologic

on the one hand, or noncompensatory tachycardia on the other hand, needs to have the heart rate problem appropriately treated as well. A full vagolytic dose of atropine, and dopamine and/or epinephrine drips are appropriate agents in the setting of bradycardia-related hypotension.

cardiovascular support in critically ill patients, while norepinephrine is only available in some hospitals. More recently, milrinone, a phosphodiesterase III inhibitor with inotropic and vasodilatory properties has been released in the country.



When there is clear evidence of cardiogenic shock based on preexisting or complicating acute, chronic or mixed acute and chronic cardiac disease in a critically ill surgical patient (e.g. postoperative acute myocardial infarction with pulmonary congestion and hypotension after aortic surgery), these inotropic agents generally in combination with diuretics with or without vasodilators are appropriate initial therapy. Further discussion of the recognition and management of this clinical situation is beyond the scope of this guideline.

In the setting of shock with relative or absolute hypovolemia in the critically ill surgical patient, as occurs in hemorrhagic conditions, third-spacing, trauma, sepsis or SIRS, vasoactive agents may favorably affect hemodynamic and oxygen transport and tissue utilization when volume resuscitation is adequate or at least ongoing. Vasopressors in a volume-depleted patient may cause cardiac decompensation and hemodynamic deterioration, particularly in patients with ischemic heart disease and therefore should not be administered prior to fluid replacement.¹³

The choice of vasoactive agent (Table 5) depends on the blood pressure, cardiac index, heart rate and systemic vascular resistance, and it may be appropriate to change from one drug to another or combine drugs as the hemodynamic parameters and clinical situation changes. Close patient monitoring cannot be overemphasized. Consideration of intraarterial invasive monitoring of blood pressure in a patient with extreme peripheral vasoconstriction and cool extremities, and insertion of a central venous or pulmonary arterial catheter in this situation have been discussed above.

With simultaneous volume replacement, a hypotensive patient with absolute or relative bradycardia

In a volume-replete patient, persistent mild hypotension (systolic blood pressure less than 90 but not less than 70 mmHg) and shock independent of heart rate problems should generally be treated with dobutamine (with or without dopamine) in an attempt to increase the cardiac index and oxygen delivery. In the lower range of systolic blood pressure (70-80 mmHg) and especially if there are more profound signs and symptoms of shock, dopamine should be started first, and dobutamine then added when the blood pressure improves. Dopamine and/or norepinephrine should generally be used for severe hypotension with systolic blood pressure less than 70 mmHg.¹³ Milrinone has been shown to increase cardiac index and oxygen delivery in critically-ill patients,¹⁴ and may be regarded as a therapeutic alternative to dobutamine, or when dobutamine fails. Special situations involving unique pathophysiologic mechanisms of cardiovascular collapse may require particular vasoactive agents in addition to volume replacement, such as dopamine for spinal shock; epinephrine for anaphylactic shock, or to counteract the excessive effects of beta-blocker or alpha-blocker drugs; and norepinephrine to offset the untoward effects of alpha-blocker drugs.¹³ Phenylephrine, isoproterenol, glucagons, and recently vasopressin²⁴ have been reportedly useful for special

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cardiovascular collapse situations, but are currently unavailable in our setting. The end-effect of all these drugs on survival remains unclear however at this time.

While the pharmacologic approach outlined above is generally accepted by most cardiologists and intensivists, it is remarkable that there are only a limited number of reported randomized trials involving the use of these vasoactive agents, primarily dobutamine, to augment hemodynamic and oxygen transport parameters in critically ill patients. There are also few case-control trials in this regard. The randomized trials that have looked at the most important outcomes of in-hospital morbidity and mortality focus on alternative resuscitation strategies, i.e. achieving supranormal target levels of cardiac index and oxygen transport vs. conventional hemodynamic targets, especially normal cardiac index and blood pressure. Because of its hemodynamic effects on cardiac index and oxygen delivery,¹⁵ most studies largely utilized dobutamine as primary vasoactive drug, on top of adequate fluid resuscitation and other add-on vasopressor agents. Shoemaker et al. earlier observed that survivors of high-risk surgical operations had significantly higher mean values of cardiac index (CI), oxygen delivery (DO_2) and oxygen consumption (VO_2) than nonsurvivors.¹⁶ Since these supranormal hemodynamic and metabolic patterns might represent circulatory compensations for increased postoperative metabolism necessary for survival, it was hypothesized that supranormal CI, DO_2 and VO_2 values as resuscitation goals might improve the outcome in critically ill patients. The randomized trials testing this hypothesis among various surgical patient populations, tabulated in Table 6, have had conflicting results. Smaller studies have shown a favorable effect of supranormal goals on mortality^{16,17} but many other trials and the largest randomized study reported a negative effect.^{18-20,23} One trial reported excess mortality with supranormal resuscitation goals.¹² Except for the study by Gattinoni et al²⁰, a more consistent finding in secondary analyses among the various studies was that survival was significantly improved among patients who reached supranormal values of DO_2 whether treated or self-generated as compared with patients who reached only

15,18,19,23

$r= 0.94$ ($p=0.016$).²³ Beyond fluid replacement, the contribution of vasopressor therapy to achievement of goals and its impact on mortality is less clear. It is possible that the ability to achieve desired levels of cardiac output, oxygen delivery and consumption (regardless of therapy employed) identifies a population with a larger physiologic reserve, less severe illness, and consequently a better prognosis.¹⁵ It remains unproved that supranormal hemodynamic values should serve as endpoints of resuscitation.

The tabulated studies also reported a variable effect of supranormal goals of resuscitation on secondary clinical outcomes. Compared to controls, the treatment group had reduced complications,^{16,17,11} length of ICU stay,^{16,23} and length of hospitalization and hospital costs.¹⁶ Other studies, however, reported no difference in these secondary outcomes of interest.^{18,19} One other randomized study involving critically ill surgical patients found that the frequency of myocardial infarction was not higher among patients in whom supranormal values were achieved with inotropic therapy, although analysis was not performed according to the "intent to treat" principle.²⁰ Another randomized trial on postoperative cardiac surgical patients found that aiming for supranormal oxygen delivery to achieve normal SvO_2 values and lactate concentration during the immediate postoperative period after cardiac surgery can shorten the length of hospital stay.²²

There are no randomized trials directly comparing the effects of various vasoactive agents on mortality in critically ill surgical patients. Furthermore, while the hemodynamic effects of various vasoactive agents have been well characterized in short-term controlled clinical studies, not one randomized trial comparing the effect of vasoactive drugs vs. placebo comprising volume resuscitation alone on mortality and morbid outcomes was retrieved from an exhaustive literature search. There may actually be some difficulties or limitations compromising optimal design of clinical trials in this area, including a heterogeneous patient population comprising critically ill surgical patients - nature of primary illness (e.g. trauma, sepsis, elective surgery), type of surgery, timing of presentation; coexisting medical illnesses and complications; variable appropriate timing of

normal DO₂ values. The correlation between postresuscitation oxygen delivery and mortality was a strongly inverse one with a correlation coefficient of aggressive intervention - before, during or after surgery; and ethical issues regarding withholding of conventional treatment.

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Recommendations:

- 1. When volume resuscitation is considered adequate based on clinical judgment and the clinical response is suboptimal, vasoactive drugs may improve hemodynamics, oxygen transport and clinical condition. (Level I, Category A)*
- 2. Hemodynamic monitoring using a pulmonary artery catheter (PAC) may improve clinical decision making in selected critically ill patients. (Level II, Category A)*
- 3. When vasoactive drugs are used, the goals of therapy remain normalization of hemodynamics, oxygen transport, and improvement in the clinical manifestations of shock, but not supranormal resuscitation endpoints. (Level I, Category A)*
- 4. After restoring volume, clinical judgment should be exercised in the particular choice of a vasoactive drug, with consideration of hemodynamic parameters including heart rate, blood pressure, cardiac index, volume status and cardiac filling pressures, vascular*

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and preexisting cardiac and medical status of an individual patient.

4a. Dobutamine is the drug of choice to increase cardiac index and oxygen delivery if blood pressure is acceptable but there are still signs of inadequate tissue perfusion. (Level II, Category A)

4b. Dopamine should be used initially for persistent mild hypotension > 70 and < 90 mmHg and shock to support blood pressure; and dobutamine may then be added to optimize cardiac index and oxygen delivery. (Level II, Category A)

4c. Dopamine and/or norepinephrine should generally be used for severe hypotension with systolic blood pressure < 70 mmHg. (Level II, Category A)

4d. Inappropriate bradycardia or tachycardia, and abnormal cardiac rhythm should be addressed by appropriate pharmacologic therapy and/or adjunctive devices (such as temporary pacemaker, external cardioverter-defibrillator). (Level II, Category A)

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RECOMMENDATIONS

Fluids for Resuscitation

1. Crystalloids are the appropriate

2. Nestor E.dela Cruz (general surgeon, PCS)

intravenous fluids to be used in the resuscitation of hypovolemic surgical patients. The use of colloids does not decrease mortality, and may result in higher mortality in trauma patients. Albumin may increase the risk of death in patients with hypovolemia, burns and hypoalbuminemia. (Level I, Category A)

Red Blood Cell Transfusion

1. Aggressive and early control of hemorrhage should be considered an integral part of resuscitation. (Level II, Category A)

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2. In a patient who is hypovolemic secondary to acute hemorrhage, volume resuscitation should be initiated. (Level I, Category A)

should still be the best "monitor" of the adequacy of resuscitation. (Level II, Category A)

3. In a normovolemic patient whose level of anemia is associated with evidence of an increased risk of major adverse outcomes, the major indication of RBC transfusion is to increase oxygen delivery. This should be corrected to achieve a level of anemia wherein there is evidence that the increased risk is no longer present.

2. At present, there is no evidence that the routine use of tests such as serum lactate levels, base deficits, and pulmonary artery catheters (PAC) improve major clinical outcomes and therefore are not recommended. (Level I, Category A)

The traditional "10/30 rule", or a transfusion trigger of an Hb concentration of less than 10 g / dL or a hematocrit concentration of less than 30 per cent should no longer be utilized. (Level I, Category A)

3. Indications for the use of tests should be based on specific circumstances in which there is strong evidence that their use is associated with an improvement in major clinical outcomes, such as a decrease in mortality and serious complications. (Level I, Category A)

4. There is evidence that there is no benefit of RBC transfusion for patients whose Hb concentration is equal or more than 10 g / dL. (Level I, Category A)

Postoperative Nutritional Support

1. Early nutritional support (within 24 hours) of critically ill surgical patients should be instituted because it decreases the risk of postoperative morbidity, particularly septic complications, and more so in malnourished patients (greater than 10% preoperative weight loss). (Level I, Category A)

5. In general, there may be an increased risk of adverse outcomes in normovolemic patients with acute anemia whose Hb concentration is less than 7 g / dL. (Level I, Category A)

6. Normovolemic patients with acute anemia who have cardiac disease or are at risk of cardiac disease may benefit from RBC transfusion when their Hb concentration is less than 7 g / dL. Factors that increase the risk of postoperative cardiac events, and the

2. Among critically ill surgical patients, there is evidence that enteral nutrition (EN) delivered into the jejunum and started within 24 hours after operation results in lower septic complications compared to total parenteral nutrition (TPN). TPN is used only when the enteral route is not feasible. (Level I,

corresponding evidence are contained in PCS EBCPG on Seeking Referral for Preoperative Cardiac Evaluation for Elective Noncardiac Surgery (PJSS 1999; 54 (4): 171 - 233). (Level I, Category A)

Patients with acute myocardial infarction or unstable angina may benefit from a transfusion trigger higher than 7 g / dL. (Level II, Category A)

7. Packed red blood cells is preferred when blood transfusion is necessary. (Level II, Category A)

Assessment of Resuscitation of Hypovolemia

1. The clinical judgment of a well-trained and experienced surgeon, utilizing clinical parameters, such as blood pressure, heart rate and urine output

Category A)

The clinical trials that had demonstrated benefits of early TEN had used commercial TEN formulations.

3. TEN using commercial immune-enhancing formulae may be associated with a greater decrease in the risk of septic complications compared to standard TEN formulae in selected critically ill patients. (Level I, Category A)

4. The routine use of postoperative enteral nutrition (EN) in noncritical, nonmalnourished patients is not recommended. (Level I, Category A)

Pharmacologic Cardiovascular Support

1. When volume resuscitation is considered adequate based on clinical judgment and the clinical response

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is suboptimal, vasoactive drugs may improve hemodynamics, oxygen transport and clinical condition. (Level I, Category A)

2. Hemodynamic monitoring using a pulmonary artery catheter (PAC) may improve clinical decision making in selected critically ill patients. (Level II, Category A)

3. When vasoactive drugs are used, the goals of therapy remain normalization of hemodynamics, oxygen transport, and improvement in the clinical manifestations of shock, but not supranormal resuscitation endpoints. (Level I, Category A)

4. After restoring volume, clinical judgment should be exercised in the particular choice of a vasoactive drug, with consideration of hemodynamic parameters including heart rate, blood pressure, cardiac index, volume status and cardiac filling pressures, vascular resistance, and preexisting cardiac and medical status of an individual patient.

4a. Dobutamine is the drug of choice to

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increase cardiac index and oxygen delivery if blood pressure is acceptable but there are still signs of inadequate tissue perfusion. (Level II, Category A)

4b. Dopamine should be used initially for persistent mild hypotension > 70 and < 90 mmHg and shock to support blood pressure; and dobutamine may then be added to optimize cardiac index and oxygen delivery. (Level II, Category A)

4c. Dopamine and/or norepinephrine should generally be used for severe hypotension with systolic blood pressure <70 mmHg. (Level II, Category A)

4d. Inappropriate bradycardia or tachycardia, and abnormal cardiac rhythm should be addressed by appropriate pharmacologic therapy and/or adjunctive devices (such as temporary pacemaker, external cardioverter-defibrillator). (Level II, Category A)

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