DEVELOPMENT AND TESTING OF A NURSING ASSESSMENT OF HYPOCALCEMIA IN SEPTIC SYNDROME

By

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Abstract

TITLE: DEVELOPMENT AND TESTING OF A NURSING ASSESSMENT OF HYPOCALCEMIA IN SEPTIC SYNDROME

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The purpose of this methodological descriptive study was to develop an instrument for nursing assessment of hypocalcemia in septic syndrome patients and to examine its practicability as a pilot study. The convenience sample was 15 adult septic syndrome patients entering a CCU and three ICUs at a university hospital. Subject entry criteria for septic syndrome included: (a) diagnosis of infection, (b) fever, (c) tachycardia, (d) tachypnea, and (e) impaired organ system function or perfusion.

There was no significant difference in signs and symptoms occurrence between normo- (n = 22) and hypo-calcemic (n = 24) data points (N = 46). Twitching and a prolonged QT interval (n = 2 each) were observed only for hypocalcemic data points. Grimacing (n = 12) was observed more frequently for hypocalcemic data points. Agitation and arrhythmia were not good indicators for hypocalcemia. Patients over 70 ($X2$ = 18.6, p=.0003) and females ($X2$ = 7.3, p=.0068) tended toward hypocalcemia. The risk factors of pancreatitis (n = 3), minimal sunlight exposure (n = 3) and high risk for hypomagnesemia (n = 5) were identified only from hypocalcemic patients. The mean albumin levels between normo- and hypo-calcemic groups were significantly different (t = 4.060, p=.0002); the mean phosphate levels were close to a significant difference (t = 1.919, p=.0623). The only two data points of hypomagnesemia were from hypocalcemic patients. The assessment sheet appeared organized in theoretical aspects, but needed further consideration for practical use.

The study has significant limitations. However, it has given initial information about signs and symptoms, risk factors and profiles of septic syndrome patients with hypocalcemia.

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Chapter 1

Introduction

Most patients in a critical care setting have lines, tubes, catheters and monitoring systems in order to sustain their lives. As a result of these invasive procedures, the body's first defense, the skin, is broken, and patients become vulnerable to infection. If early detection and treatment for infection have been unsuccessful, the patient's condition may progress to septic syndrome and multiple organ failure (MOF). Septic syndrome makes the patient's recovery difficult, and MOF threatens the patient's life. Breaking the progression of infection-septic syndrome-MOF is a challenge for all health care providers.

A large number of clinical researchers have investigated the progression of infection-septic syndrome-MOF. The early identification and explication of the mechanism of mediators in septic syndrome appears to be the best approach. Some researchers have focused on calcium (Ca++) homeostasis at the cellular level. They believe that hypocalcemia is a mediator or a marker of organ dysfunction and mortality rate during septic syndrome (Aderka, Schwartz, Dan, & Levo, 1987; Desai, Carlson, & Geheb, 1988; Zaloga, Malcolm,

Chernow, & Holaday, 1988).

Two definitions of hypocalcemia make research interpretation complex: One is based on total Ca++ level; another is based on ionized Ca++ level. Measurement of ionized Ca++ level has become possible for critically ill patients just recently. Only 350-400 facilities in the U.S. measure ionized Ca++ levels routinely (T.Green, personal communication, September 28, 1993).

The exact cause of hypocalcemia and its role in septic syndrome remain unclear at present; however, it is clear that Ca++ plays an important role in the contraction of all forms of muscle tissue. Septic syndrome affects both the peripheral vascular tissue and the myocardium such that hypocalcemia appears directly to be related to physiological mechanisms in septic syndrome.

Ca++ administration for the treatment of hypocalcemia is, at present, common practice in many cases to improve cardiac function. Unfortunately, the results are not always successful in septic syndrome patients (Woo, Carpenter, & Trunkey, 1979; Zaloga & Chernow, 1987). In fact Ca++ antagonists have improved depressed cardiac function in some septic cases in both

animal and human research (Bosson, Kuenzig, & Schwarts, 1986; Malcolm, Zaloga, & Holaday, 1989; Steinhorn, Sweeney, & Layman, 1990). Moreover, when the patients recover, their Ca++ levels seem to return to normal with or without Ca++ administration (Zaloga & Chernow, 1987). Thus, there is controversy regarding Ca++ administration for treatment of hypocalcemia in septic syndrome. More research needs to be done to establish a standard treatment protocol.

Statement of Problem

Most research articles about hypocalcemia in septic syndrome focus on laboratory data, not on clinical manifestations. Focusing on "numbers" or technology frequently is the trend of modern health care analysis. However, the present state of the U.S. health care system requires urgent changes. Two components of Rogers' analysis of innovation (1983) shed a light on this trend. The two components consist of: a hardware aspect, a material or a physical object; and a software aspect, an information base.

Nursing can take a part in this challenging trend. By combining laboratory data with a reliable and valid nursing assessment, a nursing assessment tool would be

an important direction to aim at quality patient care. If the nursing assessment of clinical signs and symptoms became more reliable and valid, the assessment would contribute to earlier therapeutic intervention and improved patient care. As a result, nursing practice could contribute to improve cost effectiveness, convenience and usefulness of the nursing role anywhere, especially in small community or rural settings. Therefore, further research involving hypocalcemia should be pursued not only in the laboratory area, but also in nursing assessment.

Before this study, no clinical nursing assessment tool for hypocalcemia in septic syndrome existed. The purpose of this project was to develop an instrument for nursing assessment of hypocalcemia in septic syndrome patients and to examine its practicability at a large multi-disciplinary ICU and CCU as a pilot study.

CHAPTER 2

Review of the Related Literature

Four topics composing the review of literature are septic syndrome, blood calcium, hypocalcemia, and nursing assessment. First, definition, risk factors, physiologic and pathophysiologic mechanisms involved in septic syndrome are described. Then, function of Ca++ and regulation of Ca++ metabolism are reviewed. The topic of hypocalcemia is presented as definition, the incidence and risk factors in septic syndrome patients, and clinical manifestations. Lastly, guideline for nursing assessment is identified.

Definition of Septic Syndrome

Current research trends reflect a change in the definition of septic syndrome. The concept of "septic syndrome" is currently replacing the concept of "sepsis".

The definition of "sepsis" includes: (a) the presence of positive blood culture (bacteremia or septicemia: microorganisms identified in the blood); (b) leukocytosis or leukopenia; (c) alterations in blood pressure; or (d) changes in body temperature (Balk & Bone, 1989). The "septic syndrome" is defined

by five criteria: (a) Clinical evidence of infection; (b) fever or hypothermia; (c) tachycardia; (d) tachypnea; and (e) impaired organ system function or perfusion, including altered mentation, hypoxemia, elevated plasma lactate, or oliguria (Bone et al., 1987). When more than two organ systems are impaired, multiple organ failure (MOF) is declared (Balk & Bone, 1989).

Thus, the primary difference between "sepsis" and "septic syndrome" is that the definition of sepsis includes documentation of septicemia. The time required for the evidence of septicemia might be crucial since early detection of septic syndrome allows earlier therapeutic intervention, including the discovery of the underlying pathophysiologic mechanisms. For this reason, expansion of the definition is logical although 45-60% of patients in septic syndrome have septicemia (Balk & Bone, 1989; Deitch, 1990; Huddleston, 1992). However, a consensus of current researchers has not yet been established. The choice of the definition and eligibility criteria depend on the target population for each investigator.

Risk Factors for Septic Syndrome

The incidence of sepsis has not been documented because of its difficulty, except by Balk and Bone (1989) who estimated sepsis incidence in the U.S. was 1% of hospitalized patients based on Parker and Parrillo's report in 1983. The increasing aggressive use of invasive medical devices, procedures and immunosuppressive agents is increasing the incidence of septic syndrome (Parker & Parrillo, 1983).

Elebute and Stoner have reported four risk factors related to the severity of sepsis for a general hospital: local effects of infection; pyrexia; secondary effects of sepsis; and laboratory data (1983). This grading system was evaluated, supported and modified by Dominioni et al. for surgical patients (1987). Stevens has developed a septic severity score (SSS) for surgical sepsis (1983). The accuracy of SSS with dysfunction of seven key organ systems has been supported in patients with intra-abdominal infection (Skau, Nystrom, & Carlsson 1985).

Integrating these reports, the elderly, and patients with shock, organ transplantation, inflammatory or immunosuppressed disease, blood transfusion, malnutrition, malignancy, alcoholism

and/or bowel infarction are considered at high risk for septic syndrome (Parker & Parrillo, 1983; Pine et al., 1985).

Physiologic and Pathophysiologic Mechanisms Involved in Septic Syndrome

Septic syndrome is initiated through an infection by triggering the inflammatory response. When an insult to the body occurs, the neuroendocrine system is activated within seconds, and inflammatory mediators start their reactions to change in four major areas: (a) vasodilation; (b) microvascular permeability; (c) cellular activation; and (d) coagulation (Huddleston, 1992).

When the body's defensive inflammatory response does not succeed, infection results. Fever is the most frequent clinical finding in septic patients (Balk & Bone, 1989). The inflammatory response also causes peripheral vascular and direct myocardial effects.

Vasodilation by histamine from mast cells and by serotonin from activated platelets decreases systemic vascular resistance (SVR). Decreased cardiac afterload increases circulatory blood flow due to lowered blood pressure during the early stage. This increased blood

flow leads to tachycardia and to increased cardiac output and thus worsens the peripheral pooling phenomenon since SVR does not improve by the time septic shock occurs (Abraham, Shoemaker, Bland, & Cobo, 1983). Insufficient peripheral circulation ultimately results. Increased blood flow also causes a reduced ejection fraction and left ventricular dilation, resulting in myocardial depression (Parker & Parrillo, 1983).

Moreover, a defect in oxygen uptake by the cell and ventilation/perfusion mismatch (shunt) due to decreased tidal volume, tachypnea and increased blood flow, result in reduction of oxygen consumption (Abraham et al., 1983; Harkema & Chaudry, 1990; Nespoli et al., 1983). Three out of five septic syndrome criteria, specifically tachycardia, tachypnea and impaired organ system function, including altered mentation, hypoxemia, elevated plasma lactate and/or oliguria may be the result of insufficient oxygenation.

Hypoxia causes numerous physiological changes in septic syndrome. First, hypoxia and increased microvascular permeability lead to decreased adenosine triphosphate (ATP) production, intracellular water and sodium retention, and potassium extrusion. As a

result, cellular swelling, hypovolemia and increased urine osmolality occur (Walker, Cumming, Lindsay, Solez, & Linton, 1986). Hypovolemia activates the renin-angiotensin-aldosterone system, which helps to keep the hypovolemia from getting worse, but does not improve hypovolemia. In addition to decreased SVR, depressed myocardial function, hypovolemia and hypoosmolality due to malnutrition-related hypoalbuminemia may trigger septic shock.

Secondly, hypoxia causes an influx of Ca++ into cells due to either depressed ion pump activity or increased cell permeability (West, 1986). As a result, hypocalcemia may occur.

Thirdly, metabolic (lactic) acidosis due to cellular hypoxia and renal dysfunction will replace respiratory alkalosis due to tachypnea in earlier stages.

Fourth, malnutrition and physiological changes, such as hypoxia, tend to cause three metabolic changes: (a) Impaired glucose utilization; (b) increased proteolysis; and (c) increased lipid utilization for fuel (Kispert & Caldwell, 1990). As a result, hyperglycemia, hypoproteinemia, hypoalbuminemia, elevated free fatty acid (FFA) levels and/or

hypomagnesemia may be seen.

Fifth, the digestive system is extremely sensitive to hypoxia because its high metabolic rate requires a highly vascular structure (O'Neill, 1992). Hypoxia increases mucosal permeability and decreases regenerativity, leading to the breakdown of the mucous barrier and impaired digestive movement. As a result, necrosis, ulceration, bleeding and/or an ileus may occur.

Sixth, polyneuropathy and septic encephalopathy may occur by systemic hypoxia and hypoperfusion. Axonal degeneration of the sensory and motor fibers and denervation atrophy of muscles impair deep tendon reflexes, and cause muscle weakness and wasting (Balk & Bone, 1989). In some cases, this disorder can cause respiratory insufficiency and difficulty in weaning a patient from a ventilator.

It is useful to note that commonly used medications in septic syndrome, such as sedatives, alkalinizing agents and antibiotics also interfere with the normal bacterial flora, enhancing impairment of the gastric mucosal barrier (Border, Rodriguez, Bone, & Babikian, 1990).

Finally, the hospital environment, a ventilator

and/or sedation may impair an individual's sleep pattern, and circadian rhythms which are assumed a main controller of the whole body system (Halberg, 1977).

Function of Ca++ and Regulation of Ca++ Metabolism

Plasma Ca++ exists in three forms: protein-bound Ca++ (mainly albumin); Ca++ complexes; and free ionized Ca++. The free ionized Ca++ can be divided into two portions: active form and electro-statically bound Ca++ (Siggaard-Andersen, Thode, & Fogh-Andersen, 1983). Only the active form of ionized Ca++ has functional physiological activity. Ca++ functions are: (a) cardiac action potential generation, (b) excitation-contraction coupling in muscle, (c) neurotransmission, (d) hormonal release, (e) enzyme activation, (f) cellular messenger, and (g) blood coagulation (Rasmussen, 1986; Zaloga & Chernow, 1987).

Ca++ metabolism is controlled by parathyroid hormone (PTH), vitamin D or calciferols, and calcitonin. These hormones regulate Ca++ metabolism by absorption from the diet, by deposition and absorption from bone, and by reabsorption and excretion from kidney. Hypocalcemia activates PTH production, resulting in activation of calciferols through a series

of conversions in liver and kidney. Then Ca++ absorption from the intestine, bone resorption and reabsorption at the distal part of the nephron are enhanced. The normal parathyroid gland supplies PTH about every six hours (Marx & Bourdeau, 1987). Calcitonin lowers blood Ca++ concentration by opposing bone-resorbing effects of PTH, prostaglandins and calciferols. Specifically calcitonin inhibits osteoclastic activity (Gray, 1990).

Blood pH, plasma albumin, FFA levels, plasma magnesium (Mg++) and phosphate also affect blood Ca++ concentration. Alkalosis decreases the ionized Ca++ level by increasing protein-bound Ca++ (Marx & Bourdeau, 1987). Hypoalbuminemia decreases total Ca++ concentration, but may or may not decrease ionized Ca++ concentration due to less protein-bound Ca++. Increased FFA levels decrease ionized Ca++ concentrations by increasing the number of Ca++-binding sites on the albumin molecule in critically ill patients (Zaloga, Willey, Tomasic, & Chernow, 1987).

Hypomagnesemia decreases ionized Ca++ levels in three ways: (a) Increases PTH resistance in target cells causing the cells to become less responsive to PTH; (b) suppresses PTH secretion; and (c) increases

Ca++ influx into bone (Juan, 1977). Calcium and phosphate have an inverse relation in the plasma. When one goes up, the other will go down. This is an important regulatory system because if both levels go up, calcium phosphate salts will precipitate in the soft tissues of the body (Felver, 1991).

Other humoral factors, such as thyroid hormone, osteoclast-activating factors and growth factors increase ionized Ca++ level, while estrogen decreases ionized Ca++ level (Marx & Bourdeau, 1987). The effects of glucocorticoids on the ionized Ca++ level vary, depending on the doses administered (Marx & Bourdeau, 1987).

Definition of Hypocalcemia and its Incidence in Septic Syndrome Patients

Hypocalcemia is defined as a total serum Ca++ level lower than 9 mg/dl or an ionized Ca++ level below 4.12-4.92 mg/dl of plasma with heparin (Felver, 1991; Tietz, 1990). Thus, even though only the active form of the free ionized Ca++ has functional physiological activity, still the total Ca++ level is often used for definition of hypocalcemia.

Marx and Bourdeau (1987) and Rasmussen (1986)

indicate that the intracellular messenger system is a central role of Ca++. Their statements can be interpreted to indicate that the cellular Ca++ level may be the most meaningful value to evaluate Ca++ function. One issue here is that the measurement of intracellular Ca++ level is not a common practice because it is expensive, complex and an invasive technique like a muscle biopsy would be required. Instead, serum ionized Ca++ levels are commonly used since ionized Ca++ levels are assumed to reflect reliable intracellular Ca++ levels.

However, there are two problems regarding the interpretation of the serum Ca++ levels. First, differences in research methodology make report interpretation difficult. Most clinical laboratories measure plasma total Ca++ levels. The ionized Ca++ levels are then calculated, based on the McLean-Hastings Nomogram (1935) in many facilities. Only 350-400 facilities in the U.S. can measure ionized Ca++ levels since ionized Ca++ levels are a recent innovation (T. Green, personal communication, September 28, 1993). In fact, a secondary hospital in Montana and one of the most modern tertiary Japanese hospitals do not measure it in daily practice.

Some research articles explain the difficulty of this laboratory measurement. Ionized Ca++ is dissolved in plasma, a formidably complex aqueous solution and its complete chemical composition is unknown (Marx & Bourdeau, 1987; Zaloga et al., 1985). In addition to technical difficulty in measuring the ionized Ca++ level, there is disagreement in reporting (Siggaard-Andersen et al., 1983). Either direct measurement level or converted level to pH = 7.4 can be reported as the ionized Ca++ level.

Secondly, calculating the ionized Ca++ level may not reflect the actual ionized Ca++ level. Several investigators have reported the discordance of the McLean-Hastings Nomogram in critically ill patients (Falk, Birken, & Baran, 1988; Fenton, Jones, & Hartford, 1983; Szyfebein, Drop, & Martyn, 1981; Zaloga et al., 1985). Some formulas may not reflect the relevant Ca++ level in critically ill conditions (Zaloga et al., 1985). Other formulas to correct influence of blood acidity and of albumin level are not consistent (Calloway, 1987; Falk et al., 1988).

Considering that the measurements of Ca++ level were valid as reported, Desai et al., (1988) found that 70% of their MICU patients had hypocalcemia, and that

the mortality of the hypocalcemic patients (44%) was significantly higher than the mortality of the normocalcemic patients (17%). In other studies, 20-40% of septic patients had hypocalcemia, and the mortality rate of hypocalcemic patients were higher (Aderka et al., 1987; Boyce, Yates, & Mundy, 1989; Woo et al., 1978; Zaloga & Chernow, 1987). Therefore, hypocalcemia appears to be a mediator or a marker of organ dysfunction and mortality rate during septic syndrome (Aderka et al., 1987; Desai et al., 1988; Zaloga et al., 1988).

Risk Factors for Hypocalcemia in Septic Syndrome Patients

Generally, hypocalcemia is seen in critically ill patients who have septic syndrome, pancreatitis, hypoparathyroidism, hypomagnesemia, renal insufficiency, alkalosis, or massive transfusion of citrated blood (Felver, 1991; Juan, 1979). Within septic syndrome patients, an elevated FFA level, hypoproteinemia, hypomagnesemia, hyperphosphatemia, and alkalosis place them at a high risk for hypocalcemia (Felver, 1991). All these risk factors can be caused by the physiological changes in septic syndrome. In

other words, most septic syndrome patients are at a high risk for hypocalcemia.

Mechanisms for hypocalcemia in septic syndrome have been investigated. In a 1987 study, Zaloga and Chernow concluded that the possible causes of hypocalcemia in their subjects were: (a) acquired parathyroid gland insufficiency; (b) renal 1-alpha-hydroxylase insufficiency; (c) vitamin D deficiency; and (d) acquired calcitriol resistance.

Some researchers focused on the prevalence of hypocalcemia between gram-negative and gram-positive bacteria for septic patients (Aderka et al., 1987; Alberts, Serpick, & Thompson, 1975; cited in Zaloga et al., 1988). This difference in bacterial sources will not be discussed here; rather, hypocalcemia itself will be the focus since the concept of "sepsis" has been changing to the concept of "septic syndrome".

Clinical Manifestations and Treatment of Hypocalcemia in Septic Syndrome Patients

Generally, hypocalcemic signs and symptoms are the manifestations of increased neuromuscular excitability due to increased cell membrane permeability. These manifestations are: paresthesias (digital & perioral),

positive Chvostek's sign, positive Trousseau's sign, grimacing, muscle twitching, cramping, hyperactive reflexes, carpal spasm, pedal spasm, tetany, laryngospasm, seizures, cardiac arrhythmias, cardiac arrest, and an electrocardiogram change (prolonged QT interval) (Felver, 1991). The neurological and cardiac manifestations noted above may be caused by other factors in addition to hypocalcemia. Hypomagnesemia may also cause neuromuscular excitability.

As a general characteristic of the incidence of hypocalcemic signs and symptoms, both Chvostek's and Trousseau's signs may be absent in approximately one-third of hypocalcemic patients. Interestingly, Chvostek's sign is present in 10% of the normal adult population (Juan, 1979). Lack of correlation between the exact level of hypocalcemia and the severity of hypocalcemic manifestations is another aspect (L. Felver, personal communication, April 20, 1993).

With respect to septic patients, only three studies have reported hypocalcemic manifestations. Alberts et al. (1975) noted that 17 of their 18 hypocalcemic septic patients possessed clinical features like a positive Chvostek's sign, disorientation, coma or respiratory insufficiency

(cited in Zaloga & Chernow, 1987). Other reports showed impaired cardiac function as the predominant hypocalcemic signs (Woo et al., 1979; Zaloga & Chernow, 1987). However, the evaluation of impaired cardiac function resulting from hypocalcemia is difficult because the administration of Ca++ supplements seems to be the only definitive diagnostic test.

One possible reason why the typical manifestations of hypocalcemia are not seen in septic syndrome is a slow fall in ionized Ca++ levels (Juan, 1979). However, Zaloga and Chernow (1987) reported that hypocalcemia developed rapidly in their patients. Consequently, a decrease within 24 hours may not be rapid enough to manifest signs and symptoms.

Ca++ administration for the treatment of hypocalcemic condition in septic syndrome is a controversy (Bosson et al., 1986; Malcolm et al., 1989; Steinhorn et al., 1990; Woo et al., 1979; Zaloga & Chernow, 1987). However, when the septic patients recover, their Ca++ levels seem to return to normal with or without Ca++ administration (Zaloga & Chernow, 1987). Thus, Ca++ administration for hypocalcemia in septic syndrome is subject to discussion. More research needs to be done to verify this coexistence

and to establish the protocol for hypocalcemic treatment.

Guidelines for Nursing Assessment

Recently, methodological research for development, validation and evaluation of research tools has become an interesting field for nurse researchers (Polit & Hungler, 1991). Felver developed two protocols for nursing assessment of hypomagnesemia and hypophosphatemia (Felver, 1986a, 1986b); however, no previous assessment tool of hypocalcemia existed.

The procedure for developing a questionnaire by Waltz, Strickland and Lenz (1991) has seven steps. The seven steps are: (a) Determine the information to be sought; (b) Develop the questions or items; (c) Determine the sequence for the questions or items; (d) Subject the questionnaire to review; (e) Draft the questionnaire and cover letter; (f) Pretest the questionnaire; and (g) Administer and score the questionnaire. These seven steps were followed in this study.

Eilers, Berger, and Petersen's study (1988) appears to be fundamental for initial research tool development. They reported their study as a pilot

study with interrater reliability and content validity. Based on their report, this study reports interrater reliability and content validity as well as concurrent validity.

Conceptual Framework/Perspective

As discussed previously, the mechanisms that cause hypocalcemia in septic syndrome are not completely understood. Additionally, the problems discussed regarding serum Ca++ measurement make hypocalcemia research difficult pathophysiologically and technically. It is clear, though, that the occurrence of hypocalcemia during septic syndrome is high and requires awareness of all health care providers.

The facts that only three articles have reported hypocalcemic manifestations in septic patients and that no nursing research report about hypocalcemia was found were strong incentives to explore this topic. The nursing assessment of hypocalcemia in septic syndrome may classify individuals into some commonalities. Finding some commonalities might contribute to earlier therapeutic interventions.

Testing of a developed instrument using a deliberate design is one way to examine its

practicability and to prove reliability and validity. When the instrument is qualified as the protocol, the protocol for nursing assessment of hypocalcemia could contribute to quality patient care, and cost effectiveness. The assessment protocol could serve not only as a convenient and useful skill in any setting, but also as a self-confident and self-reliable skill for nurses. Moreover, nurses may establish an independent role in the selective use of a protocol for hypocalcemia in certain conditions.

Research Question

From the discussion above, the research questions are: (a) What are the clinical signs and symptoms of hypocalcemia in septic syndrome patients; and (b) How valid, reliable and practical to use is a developed instrument for nursing assessment of hypocalcemia in septic syndrome?

Operational definitions

Septic syndrome

The five criteria of septic syndrome (Bone et al., 1987) were modified in terms of clinical evidence of infection, fever and hypoxemia for practical use in the

hospital setting (Erickson & Meyer, in press; Zaloga et al., 1993). The modified five criteria were: (a) Diagnosis of infection; (b) Fever (temperature > 38.1 C, core - pulmonary artery by Swan-Ganz catheter; or > 37.8 C, core mode of CORE-CHECK tympanic thermometer) or hypothermia (temperature < 35.5 C, core - pulmonary artery by Swan-Ganz catheter; or < 35.3 C, core mode of CORE-CHECK tympanic thermometer); (c) Tachycardia (heart rate > 90 beats/min); (d) Tachypnea (respiratory rate > 20 breaths/min while breathing spontaneously); and (e) Impaired organ system function or perfusion, including altered mentation (in relation to patient's base line), hypoxemia (arterial oxygen tension < 75 mmHg while breathing room air, without overt pulmonary disease as a cause; or PaO2/FiO2 $\leq$ 225), elevated plasma lactate (> 2.2 mmol/l), or oliguria (urinary output $\leq$ 30 ml for at least 1 hr).

Hypocalcemia

For the concurrent validity, hypocalcemia was defined as less than 1.14 mmol/l of measured ionized Ca++ level in the laboratory at the study hospital.

Descriptive variables

Age, gender, hypocalcemia, site of infection, oral medication and IV fluid were descriptive variables and

possible independent variables.

Independent variables

Categories of risk factors for hypocalcemia such as chronic poor nutritional intake, pancreatitis, hypoparathyroidism, renal dysfunction, milk allergy, overuse of phosphate-containing laxative and enemas, excess phosphate intake, minimal sunlight exposure, hypomagnesemia, alkalosis, hyperphosphatemia, elevated FFAs, nasogastric suction were independent variables.

Dependent variables

Clinical hypocalcemic signs and symptoms such as cramping, paresthesias, Chvostek's sign, Trousseau's sign, twitching, tremors, grimacing, hyperreflexia, tetany, spasm, loss of consciousness, agitation, seizures, hypotension, electrocardiogram change, cardiac arrhythmia, and cardiac arrest were dependent variables.

CHAPTER 3

Description of Methods

Design

This pilot study used a methodological descriptive approach. An assessment sheet for hypocalcemia in septic syndrome and its evaluation sheet were developed by the primary investigator (PI). Subjects were screened and assessed in terms of demographic data, risk factors, laboratory data, medication and manifestations. The assessment sheet was evaluated by the nurses who participated in assessment.

The research setting was a multi-disciplinary University Hospital with a CCU and three ICUs. The patients in this setting were considered at high risk for septic syndrome due to advanced technology.

Subjects/Participants

This convenience sample study consisted of 15 subjects (12 males and 3 females; one male patient was entered twice) from January 3, 1994 to March 10, 1994. The age range was 22 to 79 with mean of 50.8. Eligibility criteria for the first research question were: (a) septic syndrome patients who met the modified five criteria of septic syndrome; (b) having a

laboratory order for ionized Ca++ level for the following morning; (c) age 18-85; and (d) verbal consent. The exclusion criterion was pregnancy. For the second research question, participants were registered nurses who worked in the setting.

Data Collection Instruments

Nursing Assessment Sheets

Nursing assessment sheets developed by the PI were composed of four parts: screening sheet, clinical assessment sheet, evaluation sheet and the manual for each sheet (See Appendix B). The subject screening sheet included patient's demographic information, checklist for the eligibility criteria, and current diet record. Medication, IV fluid and risk factors were noted, as well.

Several references and research articles were reviewed to meet the project's purpose for assessment sheet development (Felver, 1986a, 1986b, 1991,; Juan 1979). Clarity and readability in wording and format to reflect accurate evaluation by different raters, efficiency and simplicity were the goals for the tool. Then items were consulted with a nurse research expert and reviewed with a nurse electrolyte expert and a

clinical specialist to support the content validity. Items were revised on the basis of their comments. Interrater reliability by the patient's nurse and the PI was examined in the study.

A manual for the screening sheet, risk factors, medications and the assessment sheet described the definition of each category and provided observational technique in order to reduce threats to external validity.

An evaluation sheet was developed by referring to an evaluation research article and opinions from colleagues, and was reviewed with experts (RNs with Ph.Ds and MSs) (Jacobson, 1984). The semantic differential (SD) technique appeared to be one of the most valid measures available for assessing the evaluative connotations of objects (Waltz et al., 1991). Three dimensions of SD scale (information characteristic; usefulness in assessment; and usefulness in nursing action) were used. An SD consisted of pairs of bipolar adjectives separated by blanks assumed to represent a 7-point equal-interval rating scale. The subject's task was to make a circle at the appropriate point on the scale (Polit & Hungler, 1991). Based on the expert advise, NA (unable to

decide) was added to differentiate from a neutral opinion.

At the end of the evaluation sheet, a comment column was prepared to enhance future development of the assessment tool. Page order was arranged for screening and practical use.

Measurement of Ionized Ca++ Level

To establish concurrent validity of the tool, an order for ionized Ca++ level was included in the eligibility criteria. In this study, the relationship between the number or degree of hypocalcemic manifestations and measured ionized Ca++ level was not the focus. Rather, measured ionized Ca++ level was used to establish concurrent validity if manifestations were noted in hypocalcemic patients but not normocalcemic patients.

In the study hospital, quantitative determination of ionized Ca++ concentration was made by Ca++-selective electrodes, Stat 5 Nova (Nova Biomedical Corp., Waltham, MA.). The measurement of ionized Ca++ level required 1 ml of whole blood; serum was not necessary. The machine assayed and reported concentration of solute per specimen both in measured

ionized Ca++ level and its pH, and in converted ionized Ca++ level to pH=7.4. As indicators of precision, standard deviation was 0.01-0.02 mmol/l and coefficient of variation was 1.3-1.6% in January 1994 (N = 300), and 0.01-0.03 mmol/l and 1.7-2.6% in February 1994 (N = 300; C. Ulman, personal communication, April, 6, 1994).

For verification of the laboratory technique, five techniques were employed at the study hospital: (a) External quality control by peer group review; (b) national standard calibrator run; (c) three levels of internal quality control; (d) recovery check after spiking a known concentration; and (e) comparison with clinical status (T. Green, personal communication, September 28, 1993).

With regard to feasibility, measurement of ionized Ca++ level took about 2-4 minutes. The cost of the test was $ 58.20.

The possible sources of error were: (a) anticoagulant therapy; (b) mixture with chelating agent; and (c) abnormal acidity. In other words, there were the same possible errors as with the total calcium measurement from plasma or serum.

Data Collection Procedures

After approval by the Institutional Review Board (IRB), the research project was introduced to the department directors and unit coordinators of the CCU and three ICUs. After their approval of research policy and data collection procedure, the project and assessment procedure were explained to staff nurses at the each unit.

The PI evaluated the patients' conditions daily with the sheets for screening, medication and IV fluid record, and risk factors. Mainly the patients' charts, supplementally direct questions to the patients or their family, and/or general assessment were used.

The five modified criteria were ascertained before or without any medication effects. When the patient was under medication which might affect a criterion, the patient was considered to be qualified in that criterion. When no medication was determined to affect the criterion, then the patient was reevaluated on the criterion and may or may not have been selected as a subject for the following morning.

When a patient met all eligibility criteria, assessment was done once a day between 2:00 and 4:00 a.m. by the patient's nurse and the PI separately. The

maximum duration of participation by any one patient was set at 7 days, since Aderka et al. reported a progressive decrease in corrected Ca++ level with nadir on day 7 from the onset of fever (1987). The evaluation sheet was completed the first day that a subject's nurse took care of the subject.

Blood was drawn every morning around 4 a.m. on the clinical units in the chosen hospital. The time was ideal since the blood drawn at 2 to 4 a.m. was considered the lowest value for total Ca++ (Tietz, 1990). All blood work was drawn from indwelling arterial or venous catheters after 5 ml was discarded.

After pretest (two patients from November 25, 1993 to November 28, 1993), a revision for productivity and consistency was approved by the IRB. In the revision, the PI took a primary role in assessment of signs and symptoms. Assessment items were adjusted for the usage of sedatives and/or paralysis. Also age range was widened from 18-75 to 18-85 to broaden the patient population.

Data Analysis

Data were coded based on a code book developed by the PI and analyzed using Crunch Statistical Package,

Version 4 (Crunch Software Corporation; Oakland, CA). For the first research question, chi-square analysis between Ca++ level (normo- or hypo-calcemia) and other variables was performed based on the assessment by the PI.

Possible threats to internal validity for the first question were personal medical history and past/current treatment. The patients were assessed by physiological measurement; as a result, there should be little or no threat to reactive effect (external validity).

For the second research question, the assessment sheet was evaluated in terms of concurrent validity, interrater reliability and practicability. Concurrent validity of the incidence of observed manifestations in hypocalcemic patients, but not in normocalcemic patients was included in the report of the first research question. Percentage agreement based on data points between the patient's nurse and the PI was used as an interrator reliability. Descriptive statistics were used for practicability based on a three dimensional semantic deferential scale.

Instrumentation could threaten internal validity, and both Hawthorne and novelty effects were considered

to be a threat to external validity for the second question. This tertiary medical center was an educational-oriented hospital, which might threaten external validity of nurses' attitudes, as well.

Protection of Human Subjects

Approval was obtained from the IRB to conduct this study. An informed consent form was waived by the IRB because a pre-existing order for the blood drawn for ionized Ca++ level was included as an eligibility criterion and because no additional invasive procedure was performed for purpose of this study. Instead, obtaining verbal consent was requested by the IRB (See Appendix C).

Each qualifying patient or his/her significant others was given an oral explanation about the nature of the study, that participation would be completely voluntary (could be discontinued at any time) and that their decision would not affect their treatment or care. Participants were assured of complete anonymity.

The PI informed the patients' nurses orally about the nature of the study, that participation would be completely voluntary and that their decision would not affect their evaluation. The nurses were told that

they could discontinue participation at any time and would be assured of complete anonymity. The respondents' willingness to complete the instrument were their indication of consent.

CHAPTER 4

Results

Demographic Data

The sample size of 15 patients, which included 12 men and 3 women from 22 to 79 years of age (mean ± SD = 50.8 ± 15.0), produced 46 data points. One male patient was entered twice because he met all criteria in two admissions. Table 1 reflects characteristics related to this study.

Of 46 observations, 24 data points showed hypocalcemia (52.2%); 22 showed normocalcemia (47.8%). There were no hypercalcemic patients. The incidence of hypocalcemia (on at least one study day) was 80% (12 patients out of 15).

Reflecting the critical care setting, 38 of 46 data points were from patients who were mechanically ventilated (82.6%) and 36 of 46 data points were from patients who were pharmacologically sedated or paralyzed (78.3%). Six out of another 10 data points were from patients who were self-sedated with hepatic encephalopathy.

Table 2 reflects the number of data points between normo- and hypo-calcemia in four age groups. Chi-square analysis showed a significant difference in the

ID	Medical diagnosis	Age/ Sex	Infection site[A]	Complication [B]	Day in the CCU/ICU	Risk factor [C]	# of Hypo-Ca data/ total data	# of S/S data/ total data
1	Respiratory Failure	71/M	R	R,U	9,10	1,4,8	2/2	2/2
2	Infection (post lung transplant)	61/M	R	R,U	2-8	4	0/7	5/7
3	Pulmonary Alveolar Proteinosis	54/M	R,B	R	12	1,11	0/1	1/1
4	Neutropenia (post heart transplant)	58/M	B	U	11-13	4	0/3	3/3
5	Gun shot wound	29/F	B,R,W	R	11,13-16	4,9,11	4/5	2/5
6	Sepsis	33/M	R,B	R,U	4-6	1	3/3	2/3
7	Post abdominal aortic aneurysmectomy	79/M	R,U	U	20	1,2,4	1/1	1/1
8	Liver failure (Hepatic encephalopathy)	41/M	R	U	5-8, 10,13	1,2,4, 11	3/6	2/6
9	Bowel obstruction	72/F	B,U, R,W	U,R	9,10, 12	4,9, 11	3/3	3/3
10	Respiratory, renal & liver failure (Hepatic encephalopathy)	51/M	R	U,R	3,5,6	1,4	2/3	3/3
11	Sepsis, ARDS, Renal failure	48/M	B,R	R,U	4	1,2,4, 8,9	1/1	1/1
12	Infection (post total abdominal hysterectomy)	45/F	U,W	U,R	2,3	1,9	2/2	0/2
13	Gun shot wound	22/M	R,B,W	R,U	31,36	9,11	1/2	0/2
14	Infection (post lung transplant)	61/M	B,R	R,U	6,9,11 12	1,4,8	1/6	0/6
15	Idiopathic dilated cardiomyopathy	56/M	B	U	4	4	1/1	0/1

Note. [A]Infection site: R: Respiratory, B: Blood, W: Wound, U:Urinary
[B]Complication: R: Hypoxemia, U: Oliguria
[C]Risk factor: 1: Poor nutrition, 2: Pancreatitis, 4: Renal dysfunction, 8: Minimal sunlight exposure, 9: Risk factor of hypomagnesemia, 11: Nasogastric suction

Table 2

Number of Data Points between Normo- and Hypo-calcemia in Four Age Groups

Age group	No. of data points	Normocalcemia	Hypocalcemia	% of hypocalcemia
22-33	10	2	8	80%
41-48	9	3	6	66.7%
51-61	21	17	4	19%
71-79	6	0	6	100%
Total	46	22	24	

Note. $X2 = (3, N = 46) = 18.6$, $p = .0003$

number of normo-and hypo-calcemic data points between age groups, (X2 = 18.6, 3df, N = 46, p=.0003). All data from patients over age 70 reflected hypocalcemia. Also the young adult tended to be more hypocalcemic (80%). Because of small sample size, some of the exact p values reported in this study may not be accurate.

Table 3 represents the number of normo- and hypo-calcemic data points between genders. Data points from females showed 90% occurrence of hypocalcemia; data points from males showed 47.2% (X2 = 7.3, 1df, N = 46, p=.0068). However, the appearance of signs and symptoms based on the number of data points among hypocalcemic patients was similar between genders (female = 55.6%, male = 58.9%).

Pre-, and post-admission risk factors were checked on each patient. Chi-square analysis of risk factors did not show a statistical significance. However, pancreatitis (n = 3), minimum sunlight exposure (n = 3) and hypomagnesemic risk factors (n = 5) were noted only for hypocalcemic patients.

Four laboratory results beside ionized calcium were checked (pH, serum albumin, phosphate, & Mg++). Table 4 compares the range and mean values of these four variables between normo- and hypo-calcemia by data

Table 3

Number of Data Points between Normo- and Hypo-calcemia in Gender

Sex	No. of data points	Normocalcemia	Hypocalcemia	% of hypocalcemia
Male	36	21	15	47.2%
Female	10	1	9	90%
Total	46	22	24	52.2%

Note. $X2$ (1, N =46) = 7.3, p=.0068.

Table 4

Range and Mean Values of Five Laboratory Data Between Normo- and Hypo-calcemia by Data Points

	Ca++	pH	Albumin	P	Mg++
HypoCa	1.05(.076)	7.41(.05)	2.0(.60)*	4.68(2.20)**	2.2(.58)
Range	0.85-1.13	7.32-7.51	1.1-3.3	1.1-10.3	1.2-3.5
N	24	24	23	24	22
NormoCa	1.21(.048)	7.41(.05)	2.8(.68)*	3.64(1.38)**	2.6(.60)
Range	1.14-1.29	7.32-7.49	1.2-3.9	1.7-7.6	1.9-3.3
N	22	22	21	21	8
Total	1.12(.104)	7.41(.05)	2.4(.74)	4.19(1.91)	2.3(.60)
N	46	46	44	45	30

Note. ( ) = Standard deviation. N = Number of data points

* t = 4.060, p=.0002. ** t = 1.919, p=.0623.

points. As expected with a septic condition, 98% of the data points showed hypoalbuminemia (Kispert & Caldwell, 1990). Independent groups *t* test showed that mean albumin levels between normo- and hypo-calcemic groups by data points were significantly different (t = 4.060, p=.0002). Also mean phosphate level between normo- and hypo-calcemic groups by data points were close to a significant difference (t = 1.919, p=.0623). Both of the two data points showing hypomagnesemia were from hypocalcemic patients.

In summary, patients over 70, female, with history of pancreatitis, minimal sunlight exposure and hypomagnesemic risk factors tended toward hypocalcemia. Hypoalbuminemia, hyperphosphatemia and hypomagnesemia appeared to be indicators for hypocalcemia.

Research Question 1: Clinical Signs and Symptoms of Hypocalcemia

Chi-square analysis showed no significant difference in signs and symptoms occurrence between normo- and hypo-calcemia by data points. The percentage occurrence of any signs and symptoms on the assessment sheet by data points was 58.3% in hypocalcemia and 50% in normocalcemia.

Table 5 presents Ca++ level, sedatives and signs and symptoms observed for all hypocalcemic data points (N = 24). Twitching (n = 2) and prolonged QT interval (n = 2) were observed only in hypocalcemic patients. Grimacing was observed for 8 data points out of 24.

Table 6 reflects 11 data points from five different normocalcemic patients who had signs and symptoms on the assessment sheet. All of these patients had agitation and/or arrhythmia, except patients 4 and 10. Patient 4 had a positive Chvostek's sign, tremors, grimacing, hypotension beside agitation; patient 10 had grimacing.

Except for one positive Chvostek's sign in a normocalcemic and normomagnesemic patient, Chvostek's and Trousseau's signs were not observed. Since most data points were from patients who were pharmacologically sedated, only five subjective data points were collected. Loss of consciousness was able to be assessed for only three data points due to pharmacologic sedation or preexisting conditions.

Ca++ supplements were used for 36.9% of all data points. Chi-square analysis between normo- and hypocalcemic groups in Ca++ supplement was close to a statistical significance, (X2 = 7.327, 1df, N = 46,

Ca++ level, Sedatives and Signs and Symptoms in Hypocalcemic Data Points 44

ID-Period	Ca++ level	Sedation*	Signs & symptoms
1-1	0.97	-	Hypotension
1-2	1.04	-	ECG change, arrhythmia
5-1	1.06	V,F	Grimacing, agitation
5-3	1.05	V,F	Grimacing
5-4	1.08	V,F	None
5-5	1.07	V	None
6-1	0.85	V,F	Hypotension
6-2	0.85	F	None
6-3	1.10	F	Tremors, agitation
7-1	1.13	V	Agitation, ECG change
8-4	1.04	-	None
8-5	0.97	-	None
8-6	0.94	-	Twitching, tremors, grimacing, agitation
9-1	1.11	MS	Grimacing, arrhythmia
9-2	1.08	MS,V	Grimacing, arrhythmia
9-3	1.09	MS	Twitching, tremors, grimacing, arrhythmia
10-1	1.05	-	Grimacing
10-2	1.02	V	Grimacing, arrhythmia
11-1	1.13	V,F,MS	Agitation
12-1	1.12	P,V,F	None
12-2	1.05	P,V,F	None
13-2	1.08	P,V,F	None
14-5	1.13	F	None
15-1	1.11	V,A	None

Note. *Sedation: V-Versed, F-Fentanyl, MS- Morphine Sulphate, A-Ativan, P-paralysis
N = 24

Table 6

Ca++ Level, Sedatives and Signs and Symptoms of the Assessment Sheet in 11 Normocalcemic Data Points

ID-Period	Ca++ level	Sedatives	Signs & Symptoms
2-3	1.16	V,F	Arrhythmia
2-4	1.17	V,F	Agitation, arrhythmia
2-5	1.18	V,F	Agitation, arrhythmia
2-6	1.21	V,F	Arrhythmia
2-7	1.26	V,F	Arrhythmia
3-1	1.18	V,F	Agitation
4-1	1.26	MS	Tremors, grimacing
4-2	1.25	MS	Positive Chovostek's sign, tremors, grimacing, hypotension
4-3	1.29	MS	Tremors, grimacing, agitation, hypotension
8-1	1.22	-	Arrhythmia
10-3	1.14	V	Grimacing

Note. Sedatives: V-Versed, F-Fentanyl, MS-Morphine Sulphate.

p=.0556), with more Ca++ supplements used in the hypocalcemic group.

Research Question 2: Evaluation of Assessment Sheet

Concurrent validity of the assessment sheet was examined with ionized Ca++ level to determine if the assessment sheet had convergence with a criterion. Chi-square analysis did not demonstrate a significant difference in the occurrence of signs and symptoms between normo- and hypo-calcemia by data points. Detailed results have been discussed in section Research Question 1 above.

Interrater reliability (percent agreement) was 96.2% out of 37 data points. The other nine data points were from subjects whose nurses declined to participate.

For the practicability of the evaluation sheet, 17 out of 24 nurses responded. Three out of 17 nurses responded N/A (unable to answer). The results, including comments, are shown on Table 7 and Figure 1.

The evaluation sheet adopted three dimensions of semantic differential (SD) scale: information characteristics; usefulness in assessment; and usefulness in nursing action (See Appendix B). Each SD

Table 7

Mean Scores of Evaluation Sheet and Comments

	Mean score
A: Information characteristics	5.89
A1: Difficult-Easy	5.58
A2: Disorganized-Organized	5.92
A3: Incomplete-Complete	6.17
B: Usefulness in assessing	4.45
B1: Confusion-Clear	5.08
B2: Impractical-Practical	4.00
B3: Theoretical-Important	3.25
B4: Unsound-Sound	5.18
B5: Waste-Quick	4.75
C: Usefulness in driving action	3.49
C1: Not helpful-Helpful	3.23
C2: Not change my care-Change	3.17
C3: Not applicable-Applicable	4.08

Comments:

A. Parts of writing difficult
Appreciated descriptions page 3-4

B. Too long for assessing one single lab value
Neurological symptoms/cardiac symptoms related to other (many other) possible causes
Assuming a range of subjective answers between staff
Some of the symptoms listed are also symptoms of other things - not conclusive

C. Wouldn't use it because labs drawn frequently enough to tell me exactly what Ca++ level is
We treat

Other. Unable to assess sheet due to patient's condition
12 Blank

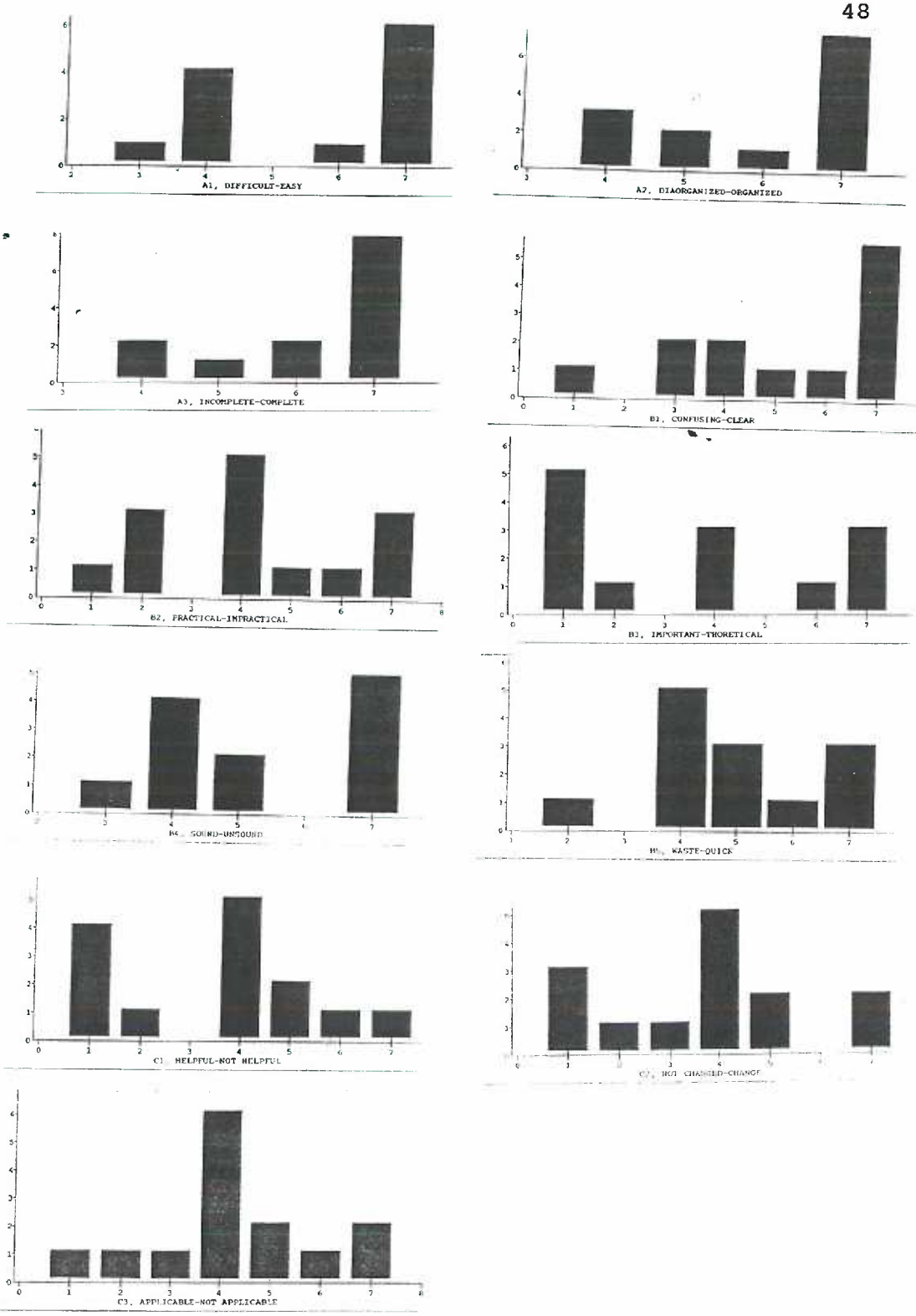

Figure 1. Frequent Distribution of Evaluation Sheet.

represented a 7-point equal-interval rating scale (1 low & 7 high).

After eliminating an outlier, information characteristics had the highest mean value (5.89), with responses from 3-7. Usefulness in assessment had a mean value of 4.45, with responses from 1-7 and usefulness in driving nursing action had the lowest mean value (3.49), with responses from 1-7.

In summary, the assessment sheet was considered to be moderately easy to use and organized. At the same time, it was perceived to be theoretical and not influential. Whether the assessment sheet was practical and applicable had a wide range.

CHAPTER 5

Discussion

Demographic Data

Statistical analysis suggested several trends for hypocalcemia in septic syndrome patients, even though a small sample size might have not provided precisely accurate *p* values. All previous research reports have used individual point for the incidence of hypocalcemia. Hypocalcemic occurrence of 80% in this study was higher than the 70% in MICU patients of Desai et al. study (1988) and 20-40% of other septic patients' studies (Aderka et al. 1987; Boyce et al. 1989; Woo et al., 1978; Zaloga & Chernow, 1987).

All of the patients with age greater than 70 years were hypocalcemic in this study. This finding is consistent with the report that intestinal Ca++ absorption decreases steadily with advancing age (Marx & Bourdeau, 1987). There is no explanation as to why the young adults (age 22-31) tended to have more incidence of hypocalcemia than the middle aged patients (41-61 year old). Mortality or duration of stay in ICU/CCU was unrelated.

Females had a higher occurrence of hypocalcemia in this study. However, the percentage occurrence based

on only 10 data points from 3 females would overestimate the female occurrence of hypocalcemia. These results are in contrast to those of Aderka et al. (1987) who reported that males had a higher occurrence and lower levels of hypocalcemia in gram-negative bacteremia. In general, males over 50 physiologically turn toward hypocalcemia (Tietz, 1990).

Three risk factors, pancreatitis (n = 3), minimal sunlight exposure (n = 3), and risk factors for hypomagnesemia (n = 5) were noted only for hypocalcemic patients. The cause of hypocalcemia in pancreatitis remains unclear (Potts, 1992). However, poor Ca++ intake, disturbed intestinal absorption and increased fecal excretion of Ca++ due to poor digestion of fat are suggested as major contributing factors for hypocalcemia in pancreatitis (Felver & Pendarvis, 1989).

Of those patients who had minimal sunlight exposure, two were transferred from other institutions, and one was home-bound. Minimal sunlight exposure may cause a lack of vitamin D production, which leads to hypocalcemia, especially if oral intake is poor.

The risk factors for hypomagnesemia included: use of diuretics, more than 300 ml of wound exudate and

greater than 300 ml vomiting, in this study. Only 1 data point (ID 12-1) out of 13 data points, among 5 patients at risk for hypomagnesemia, actually demonstrated hypomagnesemia. Another hypomagnesemic data point (ID 1-2) came from a patient who was not at identified risk for hypomagnesemia. No direct relationship between risk factors for hypomagnesemia and hypocalcemia appeared in this study.

Regarding laboratory data, hypoalbuminemia may or may not reduce the ionized Ca++ levels due to low levels of protein-bound Ca++. However, the mean value of serum albumin for the hypocalcemic group (2.04 mmol/l $\pm$ SD 0.59) was significantly lower (t = 4.03, p=.0003) than the mean for the normocalcemic group (2.81 mmol/l $\pm$ SD 0.68). Desai et al. study also reported similar results in which 55 percent of their hypocalcemic patients had a lower mean albumin level than the normocalcemic patients (1988).

Ca++ and phosphate have an inverse relation in the plasma. The mean value of phosphate for the hypocalcemic group (4.68 mg/dl $\pm$ SD 2.20) was higher than the mean for the normocalcemic group (3.64 mg/dl $\pm$ SD 1.38), close to the statistically significant level (t = 1.919, p=.0623). This result is consistent with

the physiological inverse relationship of plasma Ca++ and phosphate.

Hypomagnesemia affects ionized Ca++ level by increasing PTH resistance, suppressing PTH secretion and increasing bone deposition of Ca++ (Juan, 1977). Only two hypomagnesemic data points were found in this study; both patients (ID 1-2 and 12-1) were hypocalcemic. There was no commonality between the two in terms of risk factors, signs and symptoms, and other laboratory levels.

Laboratory data which belonged to the patients who were observed more than three days were graphed. The ionized Ca++ levels were correlated to serum albumin levels strongly in patient 9 and weakly in patients 2 and 4; inversely to pH levels strongly in patients 2, 4 and 5 and weakly in patients 8 and 10; and to Mg++ levels strongly in patient 4. The relation between the ionized Ca++ level and phosphate level was not consistent. They were inversely correlated strongly in patient 8 and weakly in patients 2, 4 and 6. However, they were also directly correlated strongly in patients 10 and 14, and weakly in patient 9.

In summary, the findings of this study suggest that age over 70, history of pancreatitis and minimal

sunlight exposure are indicators of hypocalcemia in septic syndrome. This is consistent with previous studies. Hypoalbuminemia, hyperphosphatemia and hypomagnesemia appear to be additional indicators for hypocalcemia, which is consistent with physiological mechanisms.

Clinical Signs and Symptoms of Hypocalcemia

Three clinical signs of hypocalcemia appear to be of key importance in septic syndrome patients; they are twitching, prolonged QT interval and grimacing.

Twitching is a submaximal response to a single action potential (Murphy, 1993). Only hypocalcemic patients 8-6 and 9-3 (both no Mg++ data) had twitching (Table 5). The sample size of two was too small to be conclusive; however, twitching appeared to be a meaningful assessment for hypocalcemia in this study because no normocalcemic patients showed twitching.

Prolonged QT interval was also observed only in hypocalcemic patients (ID 1-2 & 7). Prolonged QT interval is a precise sign to show the plateau phase of the cardiac action potential (Felver, 1989). Prolonged QT interval in patient 1-2 was likely due to hypocalcemia; however, the prolonged QT interval in

patient 7 might also have been caused by procainamide. This specific sign has an advantage for assessment of hypocalcemic patients since most critical care settings have a cardiac monitoring system. If a patient is not on quinidine, procainamide or phenothiazine, prolonged QT interval might be caused by hypocalcemia.

Grimacing was observed for 12 data points (ID 4, 5-1, & -3, 8-6, 9 & 10). Since medications used on these patients had no possible side effect of grimacing, the possible causes of grimacing in these patients might be noxious situations or hypocalcemia. No hypomagnesemic patient had grimacing. Of those, eight data points were hypocalcemia. Because two hypocalcemic data points with twitching showed also grimacing, and because grimacing (n = 8) was observed on one third of hypocalcemic data points (N = 24), grimacing would be useful as a hypocalcemic sign.

Another four data points (ID 4-1, -2, & -3 and 10-3) were normocalcemic. However, grimacing for data point 10-3 could be considered as due to hypocalcemia (the ionized Ca++ of 1.14 was borderline). The fact that he had grimacing during the proceeding two days when he was hypocalcemic would support this analysis.

On the other hand, agitation and arrhythmia could

not be used as indicators for hypocalcemia. As Table 6 shows, agitation and arrhythmia were observed for various normocalcemic data points (ID 2, 3, 4, & 8). These signs might be also caused by side effects of medications such as amantadine, corticosteroid (Solu-Medrol, Prednisone, & Hydrocortisone), midazolam hydrochloride (Versed) and dobutamine.

Eight data points were from patients who were on sedation but showed agitation at the same time. Of these, four normocalcemic data points might mean that doses of sedation were not sufficient to sedate or that these patients were showing paradoxical excitement, a possible side effect of Versed. Hypocalcemia would be added to these two explanations for another four hypocalcemic data points.

The normocalcemic patient (ID 4-2) who had a positive Chvostek's sign might be one of the 10% of normal adults who have a positive Chvostek's sign (Juan, 1979). If the results of this study were consistent with Juan's report, two-thirds of the hypocalcemic patients (eight patients in this study) should have had either Chvostek's or Trousseau's signs positive. This discrepancy could be attributed to the difference in the hypocalcemic patient population.

Focusing on hypocalcemic patients who did not have signs and symptoms (n = 10), there was high possibility that medications might have masked these signs (Table 8). Since sedatives appear inevitable medications in treatment of septic syndrome patients (78.3% usage by data points), neuromuscular excitability was difficult to assess.

The nominal level of Ca++ supplement information was not sufficient to analyze the effect. More detailed information such as doses, dietary supplements, patient's weight and height would be needed.

Evaluation of Assessment Sheet

An instrument developed for nursing assessment of hypocalcemia in septic syndrome patients was examined in terms of validity, reliability and practicability. With regard to concurrent validity, the 58.3% occurrence of any signs and symptoms for hypocalcemic data points was not much different from the 50.0% occurrence for normocalcemic data points.

With regard to interrater reliability, agreement between the patients' nurses and the primary investigator was 96.2%. Agreement regarding

Table 8

Possible Masked Signs and Symptoms by Medications in Hypocalcemic Data Points

ID #	Ca++ level	Medication	Covered signs/symptoms
5-4	1.08	Imipenem	seizures
		Versed	neuromuscular signs (spasm, seizures, tetany), hypotension,
		Fentanyl	neuromuscular signs
5-5	1.07	same as above	same as above
6-2	0.85	Benedryl	cramping, tetany
		Dopamine	hypotension
		Fentanyl	neuromuscular signs
8-4	1.04	N/A	Hepatic encephalopathy
8-5	0.97	same as above	same as above
12-1	1.12	Vecuronium	neuromuscular signs
		Versed	neuromuscular signs (spasm, seizures, tetany), hypotension
12-2	1.05	same as above	same as above
13-2	1.08	same as above	same as above
14-5	1.13	MS	sedation
		Procardia	arrhythmia
15-1	1.11	Versed	neuromuscular signs (spasm, seizures, tetany), hypotension
		Ativan	

Note. N = 10.

observation of agitation was lowest at 83.3%, except for 80% agreement regarding patient self-report paresthesias for five data points. Three possible reasons for the different results of assessment between the nurses and the PI were: (a) different reading abilities for ECG; (b) different observation time; and (c) different interpretation of the assessment. The latter was a reason for tremors, grimacing and agitation. However, the assessment by the patients' nurses did not alter the findings: Grimacing was of key importance and agitation was not a good indicator in those patients.

With regarding to practicability, the mean score of information characteristics was 5.89 (max. = 7, Table 7). One nurse marked on the description instead of on the numbers; these data were eliminated. Clarity was still a problem for some participants since a comment stated "part of writing difficulty", and since some direct questions were presented to the PI at the evaluation. A different font or letter size might have helped to clarify statements within a single page.

In section B, usefulness in assessing, mean scores greater than 5 in clearness and soundness indicated that the participants knew they checked signs and

symptoms of hypocalcemia. Time to perform the assessment and causes of signs and symptoms assessed were participant concerns. The time required for the assessment was not objectively measured so that the "time" concept might also reflect a participant's feeling, such as "extra work". Concern about causes of signs and symptoms assessed might reflect the slightly "low" evaluation on practical and theoretical questions.

The range of each question in section C, usefulness in driving nursing action, was wide; the mode was neutral; and the mean score was 3.49. One interpretation is that the assessment sheet appeared not to provide valued information to drive nursing action at the moment. The comment on the evaluation sheet supported this interpretation (Table 7). In addition, an interesting finding was that the presence of signs and symptoms was not viewed as important in driving nursing action. Further open questions would be needed to know the reason for this response.

In summary, the evaluation indicated that the assessment sheet was structurally "moderately" acceptable, but that it was not ready to use in practice.

Limitations

There were several limitations to this study. They were the small sample size, low concurrent validity, the lack of precise definition of two assessments, the lack of supplemental information, an inconsistency in data collection and possible misunderstanding of the research question by staff nurses.

The most significant limitation was the small sample size. A maximum of 30 patients, 7 days observation each (total 210 data points) was hoped at the beginning; however, only 15 patients, 46 data points, were entered into the investigation. Low numbers of eligible subjects were enrolled due to a number of situations.

First, an unusually low census occurred during the study (one ICU was closed for 4 days). Secondly, the study criteria limited the number of subjects. For example, evidence of infection in the modified septic syndrome criteria took at least two days to provide a result. Therefore, some patients who met all criteria, except the evidence of infection, were ineligible to

evidence of infection would have increased patient eligibility.

Thirdly, physicians predominately ordered ionized Ca++ levels during the patients' first two days in ICU. Once the evidence of infection was confirmed, fewer physician's ordered ionized Ca++ levels, which blocked many patients' participation. Authorization for the researcher to directly order ionized Ca++ levels would be much more advantageous.

The original age-range criterion, 18 to 75, somewhat limited the accessible sample population. A wider age range, 18 to 85, was approved after the first half of the study, increasing its sample size. Hence, a wider age-range should be included in future studies.

Another limitation of the study was the low concurrent validity of the assessment sheet. Low concurrent validity may be unavoidable because of the indefinite nature of hypocalcemic manifestation, patient's pathophysiological conditions and the treatment of this patient population. Four possible reasons for this low concurrent validity were: (a) slow fall in ionized Ca++ level; (b) no concurrent occurrence of alkalosis and hypocalcemia; (c) high masking rate by medication; and (d) wrong timing of

assessment.

As explained in the Review of Related Literature, the occurrence of signs and symptoms of hypocalcemia may necessitate a rapid fall in ionized Ca++ level. Similarly, the occurrence of tetany may require both alkalosis and hypocalcemia (Edmondson, Brashear & Li, 1975). In the animal study of Edmondson et al. (1975), ionized Ca++ level ranged .65-.95 mmol/l with pH 7.42-7.57 during tetany. Metabolic acidosis rather than alkalosis is more likely to occur in septic syndrome patients except during the early stage. Only patient (ID 8-6) had both hypocalcemia and metabolic alkalosis. If he had not been sedated by hepatic encephalopathy, he might have had tetany.

The high rate of sedative/paralytic usage (78.3%) would mask the neuromuscular excitability which is typical of hypocalcemia. The trough of ionized Ca++ level in circadian rhythm for healthy adults in an ordinary environment was 4:00 to 10:00 p.m. (Markowits, Rotkin & Rosen, 1981) or 10:00 p.m. to 2:00 a.m. (Ishida et al., 1983). Further study would be needed in the critical care setting in order to validate whether the assessment timing of 2:00 to 4:00 a.m. was the best timing or not.

An additional drawback to this study was the lack of precise definition. For example, ECG change (prolonged QT interval) was defined as a measured QT interval more than 0.40 s (Lentner, 1990). This number was based on 60 of HR. Because septic syndrome patients tended to have tachycardia which was a criterion, this study might have excluded some prolonged QT interval during tachycardia. QT interval should have been corrected for heart rate.

Another example of need for more precise definition was revision for sedated patients. The effect of sedatives was highly individual, so that the elimination of some observations might have excluded meaningful data.

Lack of supplemental information limited further analysis of patient conditions related to hypocalcemia. Additional electrolyte levels such as sodium and potassium would have been helpful to analyze each patient's condition; FFA would also have been useful, if available.

Collection of the evaluation sheet was inconsistent. The return rate was low, especially during the first half of the study, since evaluation was done after the primary investigator had left the

unit to reduce experimenter effects. To increase the return rate during the second half of the study, the nurses were asked to submit the evaluation immediately after assessment. Although this might have pushed the nurses toward positive results, the results did not appear to be so influenced.

Finally, misunderstanding by staff nurses of the first research question may have reduced their participation. The study's purpose was to look for indicators of hypocalcemia, not for a detector. Nobody documented any misunderstanding. However, the nurses commented that they had never seen signs and symptoms of hypocalcemia in their practice. Possibly, some had not assessed patients for this condition before. Unfortunately, nine nurses failed to participate, possibly reflecting a misunderstanding.

The primary investigator suspected that participation was low due to variable factors; a high acuity/census, administrative duties, a float nurse in unfamiliar surroundings and/or simply a lack of committed interest to the study. This investigation probably would have been strengthened if only the first research question had been addressed.

Recommendations for Future Study

Replication of this study is justified within the limitations because an increase in the number of subjects would contribute significantly to the statistical power of the study. With the indefinite nature of hypocalcemic manifestations in terms of the incidence and causes, a longitudinal study would explore individuality and circadian rhythm aspects.

Application to different populations, such as crosscultural, and a different setting study could discover another profile since the treatment (including diet) and care system would be different. Use of unseptic controls would give insight into the presence and clinical significance of hypocalcemia in septic syndrome. The difference between the Ca++ supplement and non-supplement groups should be examined with ratio level information. Attention to hemodynamic aspects might identify cardiovascular assessment as well as neuromuscular assessment. The measurement of both ionized and total Ca++ levels should also be considered since the definition of hypocalcemia uses both terms and their correlation is not consistent.

Implications for Nursing Practice

This study demonstrated that muscular twitching, prolonged QT interval and grimacing may be possible key factors in identifying hypocalcemic septic syndrome patients. Additionally, patient over 70 years of age, with a history of pancreatitis and minimal sunlight exposure may be at a higher risk. Hypoalbuminemia, hyperphosphatemia and hypomagnesemia may also be high indicators. On the other hand, agitation and arrhythmia are poor indicators for hypocalcemia in septic syndrome.

High occurrence of hypocalcemia in septic syndrome should alarm nurses to approach these patients with special attention. Nursing assessment is not harmful to patients most of the time. One utilization of this study results could be as a topic of continuing education. This result should draw nurses' attention to hypocalcemia.

In the highly technological hospital in which this study was performed, nurses should ask a physician to order ionized Ca++ level when a patient appears to be septic with high risk of hypocalcemia. At the same time, nurses should assess neuromuscular excitability, especially twitching and grimacing and prolonged QT

interval (corrected for heart rate).

When all patients' data become computerized, the results of this study may help to make a profile for assessment of hypocalcemia. Nurses would enter risk factors and daily laboratory data, then the computer would provide an assessment reminder for the highest risk patients.

In the setting where ionized Ca++ level is not available, these findings could sensitize nurses to the possibility of hypocalcemia in septic patients with high risk. Nurses could identify such a septic patient and assess twitching, grimacing and corrected prolonged QT interval if available. When he/she has observed some of these signs in the patient without sedatives, a nurse should institute seizure precautions and decrease environmental stimuli. Also an endotracheal tube or ventilator should be prepared in case of laryngospasm.

In summary, nurses in high technological settings should take advantages of direct measuring ionized Ca++ levels and of computerized high risk assessment, if possible. Nurses in settings where ionized Ca++ levels are not available should be aware of the risk factors and indicators for hypocalcemia, and be prepared for its incidence.

Summary

Ionized Ca++ plays several important roles physiologically. The high occurrence of hypocalcemia in septic syndrome patients should emphasize the importance of nursing assessment for hypocalcemia. Patient over 70 with histories of pancreatitis and minimal sunlight exposure, and with conditions of hypoalbuminemia, hyperphosphatemia and hypomagnesemia are at high risk for hypocalcemia. Nursing assessment for hypocalcemia does not hurt any patients physically. Twitching, prolonged QT interval and grimacing are good indicators for hypocalcemia. Since appearance of signs and symptoms of hypocalcemia in septic syndrome is highly individual, a nurse should not hesitate to assess these signs and symptoms.

References

Abraham, E., Shoemaker, W. C., Bland, R. D., & Cobo, J. C. (1983). Sequential cardiorespiratory patterns in septic shock. Critical Care Medicine, 11(10), 799-803.

Aderka, D., Schwartz, D., Dan, M., & Levo, Y. (1987). Bacteremic hypocalcemia. A comparison between the calcium levels of bacteremic and nonbacteremic patients with infection. Archives of Internal Medicine, 147(2), 232-236.

Balk, R. A., & Bone, R. C. (1989). The septic syndrome: Definition and clinical implications. Critical Care Clinics, 5(1), 1-8.

Bone, R. C., Fisher, C. J., Clemmer, T. P., Slotman, G. J., Mets, C. A., & Balk, R. A. (1987). A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic chock. The New England Journal of Medicine, 317(11), 653-658.

Border, J. R., Rodriguez, J., Bone L., & Babikian, G. (1990). Role of immediate surgery in prevention of multiple organ failure. In E. A. Deitch (Ed.), Multiple Organ Failure: Pathophysiology and Basic Concepts of Therapy (pp. 261-274). NY: Thieme

Medical Publishers, Inc.

Bosson, S., Kuenzig, M., & Schwartz, S. I. (1986). Increased survival with calcium antagonists in antibiotic-treated bacteremia. Circulatory Shock, 19, 69-74.

Boyce, B. F., Yates, A. J., & Mundy, G. R. (1989). Bolus injections of recombinant human interleukin-1 cause transient hypocalcemia in normal mice. Endocrinology, 125(5), 2780-2783.

Calloway, C. (1987). When the problem involves magnesium, calcium, or phosphate. RN, 50(5), 30-36.

Deitch, E. A. (1990). Gut failure: Its role in the multiple organ failure syndrome. In E. A. Deitch (Ed.), Multiple Organ Failure: Pathophysiology and Basic Concepts of Therapy (pp. 40-59). NY: Thieme Medical Publishers, Inc.

Desai, T. K., Carlson R. W., & Geheb, M. A. (1988). Prevalence and clinical implications of hypocalcemia in acutely ill patients in a medical intensive care setting. American Journal of Medicine, 84(2), 209-214.

Dominioni, L., Dionigi, R., Zanello, M., Monico, R., Cremaschi, R., Dionigi, R., Ballabio, A., Massa,

M., Comelli, M., Dal Ri, P., & Paolo Pisati. (1987). Sepsis score and acute-phase protein response as predictors of outcome in septic surgical patients. Archives of Surgery, 122(2), 141-146.

Edomondson, J. W., Brashear, R. E., & Li, T. (1975). Tetany: quantitative interrelationships between calcium and alkalosis. American Journal of Physiology. 228(4), 1082-1086.

Eilers, J., Berger, A. M., & Petersen, M. C. (1988). Development, testing, and application of the oral assessment guide. Oncology Nursing Forum, 15(3), 325-330.

Elebute, E. A., & Stoner, H. B. (1983). The grading of sepsis. British Journal of Surgery, 70, 29-31.

Erickson, R. S., & Meyer, L. T. (in press). Infrared ear thermometry. American Journal of Critical Care.

Falk, S. A., Birken E. A., & Baran, D. T. (1988). Temporary postthyroidectomy hypocalcemia. Archives of Otolaryngology--Head and Neck Surgery, 114(2), 168-174.

Felver, L. (1986a). A protocol for nursing assessment of hypomagnesemia in chronic alcoholism.

Medicolegal Library: Drugs and Alcohol, 6, 199-202.

Felver, L. (1986b). A protocol for nursing assessment of severe symptomatic hypophosphatemia in hospitalized alcoholics. Medicolegal Library: Drugs and Alcohol, 6, 195-198.

Felver, L. (1989). The effect of electrolyte imbalances on the cardiovascular system. In S. Underhill, S.L. Woods, C.J. Halperny, & E. Sivarajan (Eds), Cardiac Nursing (2nd ed., pp. 988-999). Philadelphia: Lippincott.

Felver, L. (1991). Fluid and electrolyte balances and imbalances. In M. Patrick, S. Woods, R. Craven, J. Rokosky, & P. Bruno (Eds.), Medical-Surgical Nursing: Pathophysiological Concepts (2nd ed., pp. 228-271). Philadelphia: Lippincott.

Felver, L., & Pendarvis, J. H. (1989). Electrolyte imbalances...intraoperative risk factors. AORN-Journal, 49(4), 989, 992-998, 1000

Fenton, J. J., Jones, M., & Hartford, C. E. (1983). Calcium fractions in serum of patients with thermal burns. Journal of Trauma, 23, 863-866.

Halberg, F. (1977). Implications of biologic rhythms for clinical practice. Hospital Practice, 12(1),

139-149.

Harkema, J. M., & Chaudry, I. H. (1990). Oxygen delivery and multiple organ failure. In E. A. Deitch (Ed.), Multiple Organ Failure: Pathophysiology and Basic Concepts of Therapy (pp. 87-103). NY: Thieme Medical Publishers, Inc.

Huddleston, V. B. (1992). Multisystem organ failure: Background and etiology. In V. B. Huddleston (Ed.), Multisystem Organ Failure: Pathophysiology and Clinical Implications (pp. 3-15). St. Louis: Mosby.

Ishida, M., Seino, Y., Yamaoka, K., Tanaka, Y., Satomura, K., Kurose, Y., & Yabunchi, H. (1983). The circadian rhythms of blood ionized calcium in humans. Scandinavian Journal of Clinical Lab Investment, 43(Suppl. 165), 83-86.

Jacobson, S. F. (1984). A semantic differential for external comparison of conceptual nursing models. Advances in Nursing Science, 6, 58-70.

Juan, D. (1979). Hypocalcemia: Differential diagnosis and mechanisms. Arch Intern Medicine, 139(10), 1166-1171.

Kispert, P., & Caldwell, M. D. (1990). Metabolic changes in sepsis and multiple organ failure. In

E. A. Deitch (Ed.), Multiple Organ Failure: Pathophysiology and Basic Concepts of Therapy (pp. 104-125). NY: Thieme Medical Publishers, Inc.

Lentner, C. (Ed.). (1990). Heart and circulation. Geigy Scientific Tables (vol 5). Ciba-Geigy: New Jersey.

Malcolm, D. S., Zaloga, G. P., & Holaday, J. W. (1989). Calcium administration increases the mortality of endotoxic shock in rats. Critical Care Medicine, 17(9), 900-903.

Markowits, M., Rotkin, L., & Rosen, J. F. (1981). Circadian rhythms of blood minerals in human. Science, 213(8), 672-674.

Marx, S. J., & Bourdeau, J. E. (1987). Calcium metabolism. In M. H. Maxwell, C. R. Kleeman, & R. G. Narins (Eds.), Clinical Disorders of Fluid and Electrolyte Metabolism (5th ed., pp.207-244). NY: MaGraw-Hill Book Co.

McLean, F. C., Hastings, A. B. (1935). The state of calcium in fluids of the body. Journal of Biological Chemistry, 108, 285-322.

Murphy, R. A. (1993). Skeletal muscle physiology. In R.M. Berne, & M.N. Levy (Eds.), Physiology (3rd ed., pp. 292-308).St. Louis: C.V.Mosby.

Nespoli, A., Chiara, O., Clement, M. G., Dagnino, G., Bevilacqua, G., & Aguggini, G. (1983). The cardiorespiratory impairment in cirrhosis and sepsis. Circulatory Shock, 10, 15-30.

O'Neill, P. L. (1992). Gastrointestinal system: Target organ and source. In V. B. Huddleston (Ed.), Multisystem Organ Failure: Pathophysiology and Clinical Implications (pp. 158-177). St. Louis: Mosby.

Parker, M. M., & Parrillo, J. E. (1983). Septic shock: Hemodynamics and pathogenesis. JAMA, 250(24), 3324-3327.

Pine, R. W., Wertz, M. J., Lennard, E. S., Dellinger, E. P., Carrico, C. J., & Minshew, B. H. (1985). Determinants of organ malfunction or death in patients with intra-abdominal sepsis: A discriminant analysis. Archives of Surgery, 118(2), 242-249.

Polit, D. F., & Hungler, B. P. (1991). Nursing Research: Principles and Methods (4th ed.). Philadelphia: J.B. Lippincott Company.

Potts, J. T. (1991). Disease of the parathyroid gland and other hyper- and hypocalcemia disorders. In J.D. Wilson, E. Braunwald, K.J. Lsselbacher, R.G.

Petersdorf, J.B. Martin, A.S. Fauci, R.K. Roots (Eds.), Harrison's Principles of Internal Medicine (12th ed., pp. 1902-1921).

Rasmussen H. (1986). The calcium messenger system (part 1). New England Journal of Medicine, 314, 1094-1101.

Rogers, E. M. (1983). Diffusion of Innovations. (3rd ed). NY: Free Press.

Siggaard-Andersen, O., Thode, J., & Fogh-Andersen, N. (1983). What is "ionized Calcium"? Scandinavian Journal of Clinical Lab Investment, 43(Suppl. 165), 11-16.

Skau, T., Nystrom, P., Carlsson, C. (1985). Severity of illness in intra-abdominal infection: A comparison of two indexes. Archives of Surgery, 120(2), 152-158.

Steinhorn, D. M., Sweeney M. F., & Layman, L. K. (1990). Pharmacodynamic response to ionized calcium during acute sepsis. Critical Care Medicine, 18(8), 851-857.

Stevens, L. E. (1983). Gauging the severity of surgical sepsis. Archives of Surgery, 118(10), 1190-1192.

Szyfebein, S. K., Drop, L. J., & Martyn, A. J. (1981).

Persistent ionized hypocalcemia in patients during resuscitation and recovery phases of body burns. Critical Care Medicine, 9, 454-458.

Tietz, N. W. (1990). Clinical Guide to Laboratory Tests (2nd ed). Philadelphia: Saunders.

Walker, J. F., Cumming, A. D., Lindsay, R. M., Solez, K., & Linton, A. L. (1986). The renal response produced by non-hypotensive sepsis in a large animal model. American Journal of Kidney Disease, 8, 88-97.

Waltz, C. F., Strickland, O. L., & Lenz, E. R. (1991). Measurement in Nursing Research (2nd ed). Philadelphia: F. A. Davis Company.

West, C. M. (1986). Ischemia. In V. Carrieri, A. Lindsey, & C. West (Eds.), Pathophysiological Phenomena in Nursing (pp. 13-67). Philadelphia: Saunders.

Woo, P., Carpenter, M. A., & Trunkey, D. (1979). Ionized calcium: The effect of septic shock in the human. Journal of Surgical Research, 26, 605-610.

Zaloga, G. P., & Chernow, B. (1987). The multifactorial basis for hypocalcemia during sepsis: Studies of the parathyroid hormone-vitamin D axis. Annuals of Internal Medicine, 107(1) 36-

41.

Zaloga, G. P., Chernow, B., Cook, D., Snyder, R., Clapper M., & O'Brian, J. T. (1985). Assessment of calcium homeostasis in the critically ill surgical patient: The diagnostic pitfalls of the McLean-Hastings Nomogram. Annuals Surgery, 202(11), 587-594.

Zaloga, G. P., Malcolm, D., Chernow, B., & Holaday, J. (1988). Endotoxin-induced hypocalcemia results in defective calcium mobilization in rats. circulatory Shock, 24(2), 143-148.

Zaloga, G. P., Washburn, D., Black K. W., & Prielipp, R. (1993). Human sepsis increases lymphocyte intracellular calcium. Critical Care Medicine, 21(2), 196-202.

Zaloga, G. P., Willey, S., Tomasic, P., & Chernow, B. (1987). Free fatty acids alter calcium binding: A cause for misinterpretation of serum calcium values and hypocalcemia in critical illness. Journal of Clinical Endocrinology and Metabolism, 64(5), 1010-1014.

Appendix A

Obs	ID	PERIOD	CA	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12	A13	A14	A15	A16	A17
1	1	1	1	0	0	0	0	0	0	0	.	0	0	.	0	0	1	0	0	0
2	1	2	1	0	0	0	0	0	0	0	.	0	0	.	0	0	0	(1)	(1)	0
3	2	1	0	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0	0	0
4	2	2	0	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0	0	0
5	2	3	0	.	.	0	0	.	.	0	0	0	0	.	0	.	.	0	1	0
6	2	4	0	.	.	0	0	.	.	0	0	0	0	.	1	.	.	0	1	0
7	2	5	0	.	.	0	0	.	.	(0)	0	0	0	.	1	.	.	0	1	0
8	2	6	0	.	.	0	0	.	.	0	0	0	0	.	(0)	.	.	0	1	0
9	2	7	0	.	.	0	0	.	.	0	0	0	0	.	(0)	.	.	0	1	0
10	3	1	0	.	.	0	0	.	.	0	0	0	0	.	1	.	.	0	0	0
11	4	1	0	.	.	0	0	.	1	1	0	0	0	.	0	.	0	0	.	0
12	4	2	0	.	.	1	0	.	1	1	(0)	0	(0)	.	(0)	.	1	0	.	0
13	4	3	0	.	.	0	0	.	1	1	0	0	0	.	1	.	1	0	.	0
14	5	1	1	.	.	0	0	.	.	1	0	0	0	.	1	.	0	0	0	0
15	5	2	0	.	.	0	0	.	.	0	0	0	0	.	0	.	0	0	0	0
16	5	3	1	.	.	0	0	.	.	1	0	0	0	.	0	.	0	0	0	0
17	5	4	1	.	.	0	0	.	.	0	0	0	0	.	0	.	0	0	0	0
18	5	5	1	.	.	0	0	.	.	0	0	0	0	.	0	.	0	0	0	0
19	6	1	1	.	.	0	0	.	.	0	0	0	0	.	0	.	1	0	0	0
20	6	2	1	.	.	0	0	.	.	0	0	0	0	.	0	.	0	0	0	0
21	6	3	1	0	(0)	0	0	0	1	0	0	0	0	0	1	0	0	0	(0)	0
22	7	1	1	.	.	0	0	.	.	0	0	0	0	.	1	.	.	1	0	0
23	8	1	0	.	.	0	0	0	(0)	0	0	0	0	.	0	0	0	0	1	0
24	8	2	0	.	.	0	0	0	0	0	0	0	0	.	0	0	0	0	0	0
25	8	3	0	.	.	0	0	0	0	0	0	0	0	.	0	0	0	0	0	0
26	8	4	1	.	.	0	0	0	0	0	0	0	0	.	0	0	0	0	0	0
27	8	5	1	.	.	0	0	0	0	0	0	0	0	.	0	0	0	0	0	0
28	8	6	1	.	.	0	0	1	1	1	0	0	0	.	1	0	0	0	0	0
29	9	1	1	.	.	0	0	.	.	1	0	0	0	.	0	0	0	0	1	0
30	9	2	1	.	.	0	0	.	.	1	0	0	0	.	0	0	0	0	1	0
31	9	3	1	.	.	0	0	1	1	1	0	0	0	.	0	0	0	0	1	0
32	10	1	1	.	.	0	0	0	0	1	0	0	0	.	(0)	.	0	0	0	0
33	10	2	1	.	.	0	0	.	.	1	0	0	0	.	(0)	.	.	0	1	0
34	10	3	0	.	.	0	0	.	.	1	0	0	0	.	0	.	.	0	0	0
35	11	1	1	.	.	0	0	.	.	(0)	0	0	0	.	1	.	.	0	0	0
36	12	1	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0	0	0
37	12	2	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0	0	0
38	13	1	0	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0	0	0
39	13	2	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0	0	0
40	14	1	0	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0	.	0
41	14	2	0	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0	.	0
42	14	3	0	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0	.	0
43	14	4	0	.	.	0	0	.	.	0	0	0	0	.	0	.	.	0	.	0
44	14	5	1	.	.	0	0	.	.	0	0	0	0	.	0	.	.	0	.	0
45	14	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	.	0
46	15	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	.	0	0	0

All Clinical Signs and Symptoms Observed. 1 = presence of signs and symptoms; 0 = absence of signs and symptoms. Circle means discrepancy between observers.

Subject #: _____

Nursing Assessment of Hypocalcemia in Septic Syndrome

Subject Screening Sheet

1. Date: _____
2. Length of stay : ___
3. Age: ___
4. Sex: ___
5. Medical Dx: _____
6. ___ Dx of infection: Site (date) _____
7. ___ T: _____ > 38.1 C / < 35.5 C at core; or > 37.8 C / < 35.5 C core mode of CORE-CHECK tympanic thermometer; Date & Time _____ ___
8. ___ HR: _____ > 90/min; Date & Time _____ ___
9. ___ RR: _____ > 20/min; ventilator/intubation;Date & Time _____ ___
10. ___ LOC: _____; Date & Time _____ ___*
11. ___ PO2: _____ < 75 mmHg @ RA; or PaO2/FiO2 ≤ 225; Date & Time _____ ___*
12. ___ Lactate: _____ > 2.2 mmol/l; Date & Time _____ ___*
13. ___ U/O: _____ ≤ 30 ml for at least 1 hr; Date & Time _____ ___*
14. ___ Order for blood ionized Ca++ level ___
15. ___ Verbal consent obtained
16. Lab value: pH ___; Alb ___; P ___
17. Curreent diet: _____
18. Ca++ supplement: + / -

Subject #: _____

Nursing Assessment of hypocalcemia in Septic Syndrome

Medication, IV Fluid and Diet Record

19. Oral Medication:

20. IV Fluids:

Subject #: _____

Nursing Assessment of hypocalcemia in Septic Syndrome

Risk Factors Assessment

Preadmission Risk Factors:

1. ___ Chronic poor nutritional intake: Hx ___;
   Prot ___ < 6.1; Alb ___ < 3.8; RBC ___ < 4.3; Het ___
   < M 40.5, F 37.0; Hb ___ < 13.5; Skin integrity ___
2. ___ Pancreatitis: Hx ___
3. ___ Hypoparathyroidism: Hx ___; Post-thyroidectomy ___
4. ___ Renal dysfunction: Hx ___; Cr ___ > 1.3; BUN ___ > 23
5. ___ Milk allergy: Hx ___
6. ___ Overuse of phosphate-containing laxative and enemas
7. ___ Excess phosphate intake (oral/intravenous)
8. ___ Minimum sunlight exposure: ≥ a month home-bound, institutionalization, hospitalization

Postadmission Risk Factors:

2. ___ Pancreatitis: Current Dx ___
4. ___ Renal dysfunction: Current Dx ___
7. ___ Excess phosphate intake (oral/intravenous)
9. ___ Hypomagnesemia * Diuretic use: _____
   * Large wound exudate loss: ___
   * Vomiting: Duration _____ Amt _____
10. ___ Elevated free fatty acids: FFAs _____ > .6
11. ___ Nasogastric suction (date initiated _____, Amt. ___)

Ca++: _____; Ca++ (pH=7.4): _____; Mg++: _____ Subject #: _____

Clinical Assessment Sheet for Hypocalcemia in Septic Syndrome

I would like to ask you to please assess the following clinical signs and symptoms of hypocalcemia.
Date & Time that assessment was done: _____
Site blood drawn: A / V / other _____ ; Date & Time blood drawn _____ (If differrent from above)
Please circle the number you are categorized:
1. OHSU Hospital RN; 2. Agency RN

Place a **CHECK** above the line next to the question number when the sings and symptoms are present in the patient and fill in the site as appropriate; leave blank when absent ; write N/A when you cannot apply in the patient. When you are not sure what you should assess, please read instructions of pages 3 & 4.

Neuromuscular: Subjective 1. ___ cramping (site _____)

2. ___ paresthesias (fingers ___, toes ___, at around the mouth ___)

Objective 3. ___ positive Chvostek's sign

4. ___ positive Trousseau's sign

5. ___ twitching (site _____)

6. ___ tremors

7. ___ grimacing

8. ___ reflexion (knee: diminished __; normal __; hyper __ / ankle: diminished __; normal __; hyper __)

9. ___ tetany

10. ___ spasm (carpal ___ / pedal ___ / laryngeal ___)

Neurological: 11. ___ loss of consciousness (disorientation: time ___ / person ___ / place ___; confusion ___, lethargy ___, obtundation ___, coma ___)

12. ___ agitation

13. ___ seizures

Other: 14. ___ hypotension (BP < 100 mmHg or MAP ≤ 55 mmHg for 1 hr)

15. ___ electrocardiogram change (prolonged QT interval; QT > half the preceding RR interval or more than .40 sec)

16. ___ cardiac arrhythmia (Specify _____)

17. ___ cardiac arrest on your shift so far (specify time that cardiac arrest occurred _____)

Subject #: _____

Evaluation of Clinical Assessment Sheet

When you are this patient's assigned nurse and this is your first time to take care of this patient, please fill in evaluation sheet. Or if you do not feel like it, you may mark here.
___ Unwilling to complete.

Next, I would like to ask you to please describe your general impressions about: a) the information on the form; b) the usefulness of the information; and c) the usefulness in patients care. (1 very, 2 moderately, 3 slightly to the left side of description; 4 neutral; 5 slightly, 6 moderately, 7 very to the right side of description; NA cannot decide either)

A. Information Characteristics:

1. Difficult	1	2	3	4	5	6	7	Easy	NA
2. Disorganized	1	2	3	4	5	6	7	Organized	NA
3. Incomplete	1	2	3	4	5	6	7	Complete	NA

B. Usefulness in assessing for hypocalcemia

1. Confusing (obscure)	1	2	3	4	5	6	7	Clear	NA
2. Practical	1	2	3	4	5	6	7	Impractical	NA
3. Important for patient care	1	2	3	4	5	6	7	Theoretical academic exercise	NA
4. Sound	1	2	3	4	5	6	7	Unsound	NA
5. Waste of time	1	2	3	4	5	6	7	quick to be completed	NA

C. Usefulness in driving to nursing action

1. Helpful	1	2	3	4	5	6	7	Not helpful	NA
2. Results would not change my care	1	2	3	4	5	6	7	Results would change my care	NA
3. Applicable to other patients	1	2	3	4	5	6	7	Not applicable to other patients	NA

VI. Comments: (How investigator can improve the assessment sheet? or any)

Your contribution to the success of this project is **GREATLY** appreciated.

Manual for the Nursing Assessment of Hypocalcemia in Septic Syndrome

Subject Screening Sheet

This should be filled in at sampling by principle investigator and/or a charge nurse.

1. Date: Today's date.
2. Length of stay in the unit: 1 means the date on admission
3. Age: Patient's biological age
4. Sex: M(ale) or F(emale)
5. Medical Dx: Primary department the patient belongs to and one or two main Dx(s)
6. Dx of infection or using antibiotics: Infected organ or location clinically evidenced

Check the far right underline in # 7-14 if data is today's.

A patient will be qualified as a subject when the modified five criteria are filled. When the patient is appeared to have medication effects, the criterion will be considered being filled during that medication.

7. T: > 38.1 C or < 35.5 C at core; or > 37.8 C / < 35.5 C core mode of CORE-CHECK tympanic thermometer; The last temperature before medication or some kind of device was used

8. HR: > 90 /min; The last heart rate before medication or some kind of device was used

9. RR: > 20 /min; The last respiratory rate before medication or some kind of device was used such as a ventilator

10. LOC: in relation to the patient's base line
If a patient is full in this category, cross out # 11 on clinical assessment sheet.

11. PO2: < 75 mmHg while breathing room air, without overt pulmonary disease as a cause; or $PaO_2/FiO_2 \leq 225$
12. Lactate: > 2.2 mmol/l
13. U/O: ≤ 30 ml for at least 1 hr

14. Order for blood ionized Ca++ level from physician(s)
15. Verbal concent from the patient or his/her family
16. Lab data: pH, Alb, TP, P
17. Current diet
18. Ca++ supplement

Manual for the Nursing Assessment of Hypocalcemia in Septic Syndrome

Risk Factors Assessment

Pre- and Postadmission **Risk Factors**:

Check if the patient is appropriate condition. Note presence and descriptive or objective degree if possible. Ask the patient directly, get information from the chart and/or assess present condition. Hx means the patient had diagnosed before.

1. Chronic poor nutritional intake: Hx; Protein < 6.1; Albumin < 3.8; RBC < 4.3; Hematocrit < M 40.5, F 37.0; Hemoglobin < 13.5; Skin integrity: hair - easy pluckability, flag sign, dull, dry, sparse hair; nail - dull, lackluster, transverse ridging; skin - flaky, paint dermatosis

2. Pancreatitis: Hx; Current Dx

3. Hypoparathyroidism: Hx; Post-thyroidectomy

4. Renal dysfunction: Hx; Cr > 1.3; BUN > 23.

5. Milk allergy: Hx

6. Overuse of phosphate-containing laxative and enemas

7. Excess phosphate intake (oral/intravenous): high phosphate content food (carbonated beverages, eggs, meat, milk, and processed foods); phosphate supplement + / -

8. minimum sunlight exposure: ≥ a month home-bound; institutionalization; hospitalization

9. Hypomagnesemia
* diuretic use: Thiazide; Loop; K+-sparing; Carbonic anhydrase (Diamox); Osmotic; * large wound exudate loss; * vomiting: Duration; Amount > 300 ml/day

10. Elevated free fatty acids: FFAs _____ > .6

11. Nasogastric suction: date initiated; daily amount > 300 ml

Clinical Assessment Sheet for Hypocalcemia in Septic Syndrome

Assess daily by questioning or examining. Check if present; leave blank if absence; N/A if not applicable.
For sedated patients, ask Q 3,4,7,8,9,10,12,15,16

Neuromuscular:

Subjective: 1. cramping (site): Painful, involuntary contraction of a muscle; caused by spasms of muscle

2. paresthesias (fingers / toes / at around the mouth): unusual sensations such as burning, tingling, numbness, and crawling.

Objective: 3. positive Chvostek's sign: Tap the facial nerve in front of the ear. If the corner of the mouth draws up in a grimace, the sign is positive.

4. positive Trousseau's sign: Occlude arterial flow to the hand with a sphygmomanometer cuff (about 20 mmHg more than SBP) for about 3 minutes. If the hand contorts in a carpal spasm, the sign is positive.

5. twitching (site): rapid irregular movements of overlying skin

6. tremors: rhythmic, purposeless, quivering movements resulting from involuntary alternately contracting and relaxing of opposing muscle groups.

7. grimacing: a contortion of the face expressive of pain, contempt or disgust.

8. reflexion (knee / ankle): a condition in which reflexes are increased above normal; a patient should be seated or supine with the knee slightly flexed;

use the blunt end of the reflex hammer to strike the patellar tendon, located just below the knee; leg extension at the knee is normal

support the foot in a dorsiflexed position; top the achilles tendon above the heel; planter flexion is normal.

9. tetany: spontaneous, intermittent, bilateral painful, irregular repetitive tonic muscle spasm

10. spasm (carpal / pedal / laryngeal): sudden involuntary contraction of a muscle or group of muscles, interfering with normal function of that particular muscle group

Neurological:

When #11 is cross out, skip it since the patient has LOC as a criterion.

11. Loss of Consciousness (LOC): disorientation -
    Time: ask today's date / the day of the week (mistaken of a couple of days is close enough to be correct); time of the day; the season; the last holiday

    Person: ask the patient's name; visitor's name; age; job; address; significant other's name

    Place: ask where the patient is now; the name of the building; the name of the city; this state

confusion: inappropriate response to question; decreased attention and memory

lethargy: drowsy, falls asleep quickly; once aroused, responds appropriately

obtundation: sleeps and makes few spontaneous movement; need shouting or shaking to arouse; less appropriate response

coma: neither awake nor aware; a state of unconsciousness from which the patient cannot be aroused, even by powerful/painful stimulation

12. agitation: fatiguing restlessness with violent motion

13. seizures: episodic, sudden, violent and involuntary contractions of a group of muscles

Other:

14. hypotension: BP < 100 mmHg or mean arterial pressure (MAP) ≤ 55 mmHg for one hour

15. electrocardiogram change (prolonged QT interval: more than half the preceding RR interval or more than .40 sec)

16. cardiac arrhythmia (Specify which arrhythmia)

17. cardiac arrest on your shift so fur (Specify time that cardiac arrest occurred)

Appendix C

OREGON HEALTH SCIENCES UNIVERSITY

Study Explanation for Patients and Families

TITLE: Development and testing of a nursing assessment of hypocalcemia in septic syndrome

PRINCIPAL INVESTIGATOR: YAMASHITA, Yoshiko, B.S.N., R.N.

(503) 494-5397

Advisor: FELVER, Linda, Ph.D., R.N.

This is a nursing study for observing signs of low blood calcium. There will be **no extra charge** and **no extra blood** will be drawn. What the nurse will do is a little more additional observation. The nurse will watch the patient more closely if he or she has signs of low blood calcium. Based on this observation, the nurse may be able to give the patient extra care.

If the patient does not like it, he or she may withdraw from this study at any time.

If you have any questions, please call the investigator, Yoshi at (503) 494-5397.

Thank you very much for your attention.