

## TOTAL PARENTERAL NUTRITION REVIEW

June 27, 2014



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## EXECUTIVE SUMMARY

Total parenteral nutrition, more commonly known as parenteral nutrition (PN), is a high-alert medication<sup>1,2</sup> and a form of nutrition support that involves the delivery of nutrients through an intravenous catheter into a large central vein (e.g., superior vena cava) or peripheral vein on the hand or arm. Patients who receive PN typically have underlying disorders that involve a non-functioning digestive system. Many adults and children who require PN are critically ill, often immunocompromised, and have complex medical disorders or surgical complications. PN admixtures are devised to meet the nutritional needs of individual patients, and contain glucose, amino acids (building blocks of protein), lipids (fat), electrolytes, vitamins, minerals, and trace elements. PN is classified as a high-alert medication because significant patient harm may occur when it is used incorrectly or without regard to accepted leading practice standards.<sup>1,2</sup>

In the pharmacy at the University of Alberta Hospital (UAH), a calculation error occurred in the creation of a recipe that was used to prepare a nutrient additive, which resulted in 186 neonatal and pediatric patients at three Edmonton hospitals<sup>1</sup> receiving an incorrectly prepared PN admixture between December 13, 2012 and April 12, 2013. Families of the patients were notified by Alberta Health Services (AHS) or Covenant Health; there was no evidence of any adverse clinical outcome. AHS initiated its own internal reviews of the adverse event and requested that the Health Quality Council of Alberta (HQCA) conduct an independent review of all PN processes, pursuant to Section 15(2) of the *Health Quality Council of Alberta Act*.<sup>3</sup>

### Purpose, objective, and scope

The objective of the review was to examine the implications for quality and patient safety with respect to the processes of PN in the Edmonton Zone, and to make recommendations for system-level improvements.

The scope<sup>ii</sup> of the review included a truncated version of the PN process in the Edmonton Zone for patients from all age groups (neonate, pediatric, and adult patients):

- Communicating the PN order (a subtask of PN prescribing).
- PN order verification and review.
- PN compounding, labelling, and dispensing.
- PN administration.

The review was not to include:

- Preparation of PN in facilities outside of AHS.
- Preparation of PN in facilities outside of the Edmonton Zone.
- Patient assessment, monitoring, and re-assessment.
- PN prescribing (with the exception of communicating the PN order).
- Identification and benchmarking of leading practices related to process and outcome indicators for these PN processes and applicable patient outcomes.

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<sup>1</sup> The University of Alberta Hospital, Grey Nuns Community Hospital, and Misericordia Community Hospital.

<sup>ii</sup> Modified from the original scope, as is explained in the main report and related appendices. A modified scope was necessary to prioritize other unrelated reviews underway at the HQCA and ensure that all could be accomplished within appropriate timelines.

## Methodology

The review was conducted by the HQCA's Quality Assurance Committee (QAC) in accordance with Section 9 of the *Alberta Evidence Act*.<sup>4</sup> Information to be reviewed was gathered from a number of sources:

- Published literature related to PN.
- Documents provided by AHS related to the PN process (e.g., policies and procedures).
- Findings and recommendations from the AHS quality assurance review (QAR) of the adverse event.
- Findings from the AHS human factors evaluation of the preparation and distribution of PN.
- AHS PN usage reports.
- AHS and external patient safety reporting data.
- Observations from site visits to the UAH, Royal Alexandra Hospital (RAH), Misericordia Community Hospital (MCH), and Grey Nuns (GN) Community Hospital in the Edmonton Zone and to the Central Production Pharmacy (CPP) in the Calgary Zone.
- Interviews with individuals from AHS and other healthcare organizations.

The CPP in Calgary was used as a comparator for PN processes within pharmacy for this review because of its size and similarity in healthcare services provided.<sup>iii</sup>

## Findings

### Parenteral nutrition as a high-alert medication

The American Society for Parenteral and Enteral Nutrition (ASPEN)<sup>iv</sup> and the Institute for Safe Medication Practices (ISMP) acknowledge PN to be a high-alert medication.<sup>1,2,5</sup> Classifying PN as such requires healthcare organizations to develop evidence-based policies and procedures applicable to these medications in order to reduce risk to patients.<sup>6</sup>

The current AHS directive (Edmonton Zone) does not contain an explicit list of high-alert medications, which requires users to take an additional step to locate another document from an external website.<sup>v</sup>

Double checks, and in some instances independent double checks, are an important strategy to mitigate hazards associated with high-alert medications. Double checks and other strategies to mitigate hazards at different stages of the PN process in the Edmonton Zone were noted to be inconsistently applied or ineffective/error prone.

### Communicating parenteral nutrition prescriptions

This review found that the PN ordering templates and processes in use within the Edmonton Zone do not comply with recognized leading practices.<sup>6</sup> PN is prescribed in the Edmonton Zone using one of

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<sup>iii</sup> All PN admixtures for the Calgary Zone are prepared at the CPP, which serves five hospital sites: the Foothills Medical Centre, Rockyview General Hospital, Peter Lougheed Centre, Alberta Children's Hospital, and South Health Campus.

<sup>iv</sup> The American Society for Parenteral and Enteral Nutrition (ASPEN) sets leading practice standards for PN and has defined the roles for each discipline involved in providing PN.

<sup>v</sup> Some nursing policies were noted to classify PN as a high-alert medication and require various mitigation strategies. For example, AHS Patient Care Policy 15.1, specific to the Stollery Children's Hospital, requires performing an independent double check of medication calculations and programming of infusion pumps for high-alert medications, which are specifically listed in the policy and which include PN [see reference 38].

three standardized PN order forms onto which the prescriber handwrites the prescription. The PN order template does not include all of the elements recommended by ASPEN and the order forms all require updating. ASPEN recommends avoiding handwritten orders and using electronic systems instead.<sup>6</sup>

All PN orders across the province are transcribed by Pharmacy into the Abacus system.<sup>vi</sup> Transcribing is subject to human error, and this is amplified in the Edmonton Zone by inconsistencies in the sequence in which ingredients are listed on the PN order form in comparison to the Abacus interface, as well as by inconsistencies in the dosing units of measure.

## Sterile compounding environment

The sterile compounding facilities in the UAH and RAH pharmacies do not comply with sterile compounding standards that have been established to protect admixtures from microbial and particulate contamination.<sup>vii</sup> Licensed pharmacies in Alberta are required to comply with a minimum practice and quality standards for compounded sterile preparations. The current state of the infrastructure at the UAH and RAH limits the possibility of improvements, and a centralized pharmacy for the Edmonton Zone, such as the one in the Calgary Zone, has never reached the approval stage.

## PN knowledge and skills within Pharmacy

There are no explicit knowledge or skill requirements or related training and competency assessment programs for PN pharmacists within AHS. This compromises the ability of the pharmacy to conduct a thorough review and verification of a PN order, develop standardized processes that meet current ASPEN recommendations, and participate effectively in zone and province-wide oversight of PN. No policies or procedures could be found that specify the knowledge and skills required of a PN pharmacist, outline a training process, or provide guidance on expectations of the PN order review and verification process.

## PN reporting and learning within Pharmacy

The Edmonton Zone pharmacy departments are not fully optimizing the good catch and Reporting and Learning systems for improving PN safety.

AHS uses the Reporting and Learning System (RLS) and good catch reporting system to capture data regarding hazards, close calls, and adverse events; both are used provincially. The good catch reporting system was implemented by the AHS Pharmacy Department to detect hazards within pharmacy processes to enable learning from reports submitted by staff. Yet, staff rarely report issues related to PN preparation. Furthermore, data from the good catch reporting system are not combined with data from the RLS. Staff involved with sterile compounding and PN preparation are either not aware of the good catch reporting system, do not believe it applies in certain situations, find the form difficult to use for PN, or find the system time-consuming and inconvenient. The RLS does not list PN within the medication drop-down list. Consequently, reporters need to select all medications included in the PN admixture, or select 'other' and use the free text box. Using the free text box is problematic when searching and analyzing data specific to PN reported in RLS. There is an opportunity to increase Pharmacy staff's awareness of improvement initiatives or changes that have resulted from reporting into RLS and the good catch reporting system.

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<sup>vi</sup> The Abacus system interfaces with the automated compounding device.

<sup>vii</sup> United States Pharmacopeia (USP) Chapter 797[see reference 27] and the ISMP sterile compounding guidelines [see reference 31].

Important information about the context and rationale to support the recommendations made through the AHS PN QAR and human factors evaluation were not widely shared. Pharmacy leadership (managers and above) received a summary of the recommendations as email attachments but discussions did not focus on the findings (including context and rationale), recommendations, and applicability for implementation at other pharmacy sites. At the site where the adverse event occurred, frontline staff are aware of the AHS PN QAR review but not the findings and recommendations from the review; specific recommendations will be shared as changes are implemented.

## Recommendations

The QAC makes recommendations in the five key areas identified in the Findings: (1) PN as a high-alert medication, (2) communicating PN prescriptions, (3) sterile compounding environment, (4) PN knowledge and skills within Pharmacy, and (5) PN reporting and learning within Pharmacy.

### Recommendation 1

Create and maintain an explicit list of high-alert medications that includes PN to ensure that risk-mitigation strategies are applied. Include or reference the list in all applicable policies and procedures across the province.

### Recommendation 2

Standardize pharmacy and nursing PN checking processes across the Edmonton Zone, implementing a true independent double check process to verify:

- Transcription of data before compounding of the PN admixture.
- Calculations and unit of measure conversions before compounding of the PN admixture.
- Alerts required to be overridden.
- Initial daily automated compounding device setup.
- Infusion pump settings before PN infusion begins.

#### Enabling action

- Ensure that independent double check processes are designed with and tested by human factors specialists before implementation.

### Recommendation 3

Ensure provincial use of strategies beyond double checks to mitigate pump set-up and programming hazards during PN preparation and administration.

#### Enabling actions

- Improve visual verification and connection to the correct port on the ExactaMix 2400 by increasing the visibility of the port number labelling (i.e., through more effective use of contrast and number placement) and by applying a second label, with the port number, to the end of the tube near the port.
- Introduce 3-in-1 PN formulations within the Edmonton Zone for applicable patients.



- When lipids have to be administered separately with a 2-in-1 formulation, dispense the lipid from the pharmacy with a patient-specific label containing all the information recommended by *ASPEN PN Safety Consensus Recommendations*.

## Recommendation 4

Eliminate handwritten orders for PN in the Edmonton Zone and in the interim modify the current paper order forms to meet leading practice.

### Enabling actions

- Implement a computerized prescriber order entry (CPOE) system or other electronic format for communicating the PN order that includes clinical decision support (i.e., embedded practice guidelines) and is editable by both prescribers and pharmacy.
- Create a process to routinely update the clinical decision support information relating to PN (e.g., on the back of the PN order form or in CPOE or electronic ordering system) to ensure it reflects current leading practice.
- Plan to establish an interface between the CPOE system and the Abacus system to eliminate the transcription of PN orders within pharmacy. An interface should be considered at all sites in AHS using a CPOE system or planning to implement a CPOE system.
- Modify the PN order template (paper and electronic version) and the Abacus order entry system to comply with the *ASPEN PN Safety Consensus Recommendations* regarding order components, ingredient sequence, and units of measure.

## Recommendation 5

Improve sterile compounding environments in the Edmonton Zone to meet an established standard (e.g., United States Pharmacopeia Chapter 797, Institute for Safe Medication Practices sterile compounding guidelines).

### Enabling action

- Conduct a cost/benefit analysis to compare upgrading the current facilities with the development of a centralized pharmacy with a sterile compounding facility for the Edmonton Zone.

## Recommendation 6

Develop a structured training process with annual competency assessment for PN pharmacists throughout AHS with clearly defined expectations for knowledge and skills related to their role in the PN process as well as specialized qualifications for pharmacists involved in PN oversight.

### Enabling actions

- Training for all PN pharmacists should address both clinical and pharmaceutical aspects of PN therapy and highlight current leading practice standards for all components of the PN process.

- Support a small team of pharmacists to develop specialized practice (for example, Board Certified Nutrition Support Pharmacist designation or equivalent level of expertise) in nutrition support, who would participate in provincial oversight of the PN process.

## Recommendation 7

Develop PN-specific policies and standardized procedures within the Pharmacy Department at the provincial level where possible (and within the Edmonton Zone at a minimum) that address the pharmacy components of the PN process (order verification and review; compounding, labelling, and dispensing).

### Enabling action

- Use the ASPEN *PN Safety Consensus Recommendations* and leading practice recommendations from the Institute for Safe Medication Practices and the Canadian Society of Hospital Pharmacists (currently under development) related to sterile compounding to inform the development of the policies and procedures.

## Recommendation 8

Pharmacy staff (management and frontline) to regularly review and trend site, zone, and provincial data related to sterile compounding and PN from the reporting systems to identify system issues and actions for improvement.

### Enabling actions

- Enhance the structure and process for staff working in the sterile compounding and PN preparation area to more easily report hazards and close calls.
- Include PN as a listed medication in the Reporting and Learning System to make it easier to enter and analyze hazards, close calls, and adverse events.

## Recommendation 9

Share the findings and recommendations from the AHS PN quality assurance review across all AHS pharmacies with the expectation that site leadership implement recommendations as appropriate. Also share the findings and recommendations with frontline staff to increase awareness of hazards related to PN.

## **Supplementary recommendation**

### **PN order verification in the Calgary Zone**

The double check to verify PN order entry at the CPP occurs, in some cases, after the PN admixture is compounded, and potentially after the product has been delivered to the nursing unit. At the acute care sites in Calgary, PN orders are sent to the CPP via computerized prescriber order entry (CPOE; i.e., Sunrise Clinical Manager), are printed, and are then transcribed into Abacus by a pharmacist. The PN label is then printed and used to initiate the PN compounding process. The original order is not used in the checking processes after transcription, though this is recommended by ASPEN. A double check to validate the accuracy of order entry into Abacus is performed by a second pharmacist and, depending on scheduling, may occur after the compounding process has started and potentially after administration to the patient. ASPEN recommends that all PN orders that require transcription be independently double checked before compounding of the PN admixture.<sup>6</sup>

### **Prescribed dosing irregularities**

A memo sent to AHS described dosing irregularities observed on some PN orders during site visits (Appendix V). In response, AHS conducted an internal review (Appendix VI) and solicited feedback from the HQCA (Appendix VII).

### **Recommendation 10**

Verify transcription of the PN order into Abacus by a pharmacist (other than the one who transcribed the order) before compounding the PN admixture at the Central Production Pharmacy.

## PROJECT OVERVIEW

### Background

Total parenteral nutrition, more commonly known as parenteral nutrition (PN), is offered to patients whose digestive systems are not functioning and who need nutrition support. Many adults and children who require PN are critically ill, often immunocompromised, and have complex medical disorders or surgical complications. In the pharmacy at the University of Alberta Hospital (UAH), a calculation error occurred in creating a recipe used to prepare a nutrient additive, which resulted in 186 neonatal and pediatric patients at three Edmonton hospitals receiving an incorrectly prepared PN admixture between December 13, 2012 and April 12, 2013. The PN admixture containing the supplement was administered intravenously to patients at the UAH, the Grey Nuns (GN) Community Hospital, and the Misericordia Community Hospital (MCH).

Families of the patients were notified by Alberta Health Services (AHS) or Covenant Health; there was no evidence of any adverse clinical outcome related to the incorrectly prepared supplement for the patients involved. AHS initiated an internal quality assurance review (QAR) to examine system issues surrounding the adverse event and also conducted an internal human factors evaluation to identify system issues related to the preparation and distribution of PN. AHS requested that the Health Quality Council of Alberta (HQCA) conduct an independent review of all PN processes.

At the time of the event, the UAH compounded PN admixtures for six hospitals (UAH, GN, MCH, Fort Saskatchewan Community Hospital, Leduc Community Hospital, and Sturgeon Community Hospital). The Royal Alexandra Hospital (RAH) compounded its own PN admixtures. Since the event, the RAH assumed compounding PN admixtures for the Sturgeon Community Hospital in August 2013; the UAH assumed compounding PN admixtures for the Cross Cancer Institute in September 2013.

### Purpose, objective, and scope

On April 26, 2013, pursuant to Section 15(2) of the *Health Quality Council of Alberta Act*,<sup>3</sup> the President and Chief Executive Officer (CEO) of AHS asked the HQCA to conduct an independent review of PN processes in the Edmonton Zone (Appendix I).

The objective of the review was to examine the implications for quality and patient safety with respect to the processes of PN in the Edmonton Zone, and to make recommendations for system-level improvements (Appendix II).

Initially, the review was to include all aspects of PN management in the Edmonton Zone including, but not limited to:

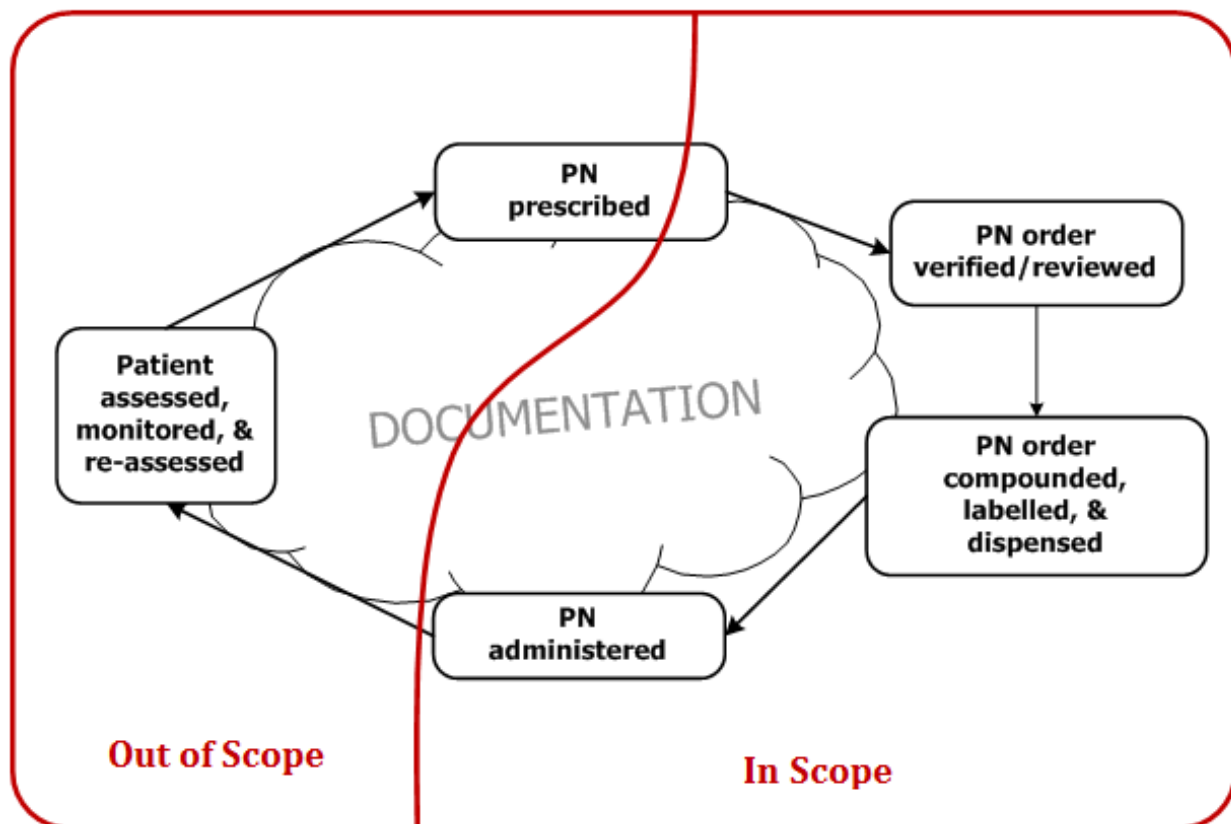
- All age groups (neonate, pediatric, and adult patients).
- Prescribing, ordering, preparing, administering, monitoring, and applicable outcomes in the delivery of PN.
- Identification and benchmarking of leading practices related to process and outcome indicators for these PN processes and applicable patient outcomes.

The review was not to include:

- Preparation of PN in facilities outside of AHS.
- Preparation of PN in facilities outside of the Edmonton Zone.

A number of other, unrelated QARs were underway at the HQCA at the same time as this review. As a result, the scope and timelines of this review were modified (Appendix III). Specifically, the modified scope excluded clinical assessment of the patient, prescribing (but included communication of the PN order), and the monitoring steps in the PN process. It also excluded the identification and benchmarking of leading practices related to process and outcome indicators. A more detailed outline of the PN process is described by Hudson,<sup>7</sup> explained below, and is shown in Figure 1 relative to what was included and excluded under the modified scope.

**Figure 1:** PN process adapted from Hudson<sup>7</sup> also illustrating the modified review scope



The modified scope of the review included a truncated section of the PN process in the Edmonton Zone for patients from all age groups (neonate, pediatric, and adult patients):

- Communicating the PN order (a subtask of PN prescribing).
- PN order verification and review.
- PN compounding, labelling, and dispensing.
- PN administration.

According to the modified scope, the review was not to include:

- Preparation of PN in facilities outside of AHS.
- Preparation of PN in facilities outside of the Edmonton Zone.
- Patient assessment, monitoring, and re-assessment.
- PN prescribing (with the exception of communicating the PN order).
- Identification and benchmarking of leading practices related to process and outcome indicators for these PN processes and applicable patient outcomes.

## Review team

The review was conducted by the HQCA's Quality Assurance Committee (QAC) in accordance with Section 9 of the *Alberta Evidence Act*.<sup>4</sup> The review team included:

- Jonas Shultz, MSc, Human Factors Lead, Review Lead, HQCA
- Dale Wright, BSP, MSc, MDE, Senior Project Lead, HQCA
- Joseph Boullata, PharmD, RPh, BCNSP, FASPEN, Nutrition Support Consultant
- Pauline Darling, BSc, MSc, PhD, RD, Associate Scientist, Li Ka Shing Knowledge Institute of St. Michael's Hospital, Assistant Professor, University of Toronto
- Don Duerksen, MD, FRCPC, Medical Director, Manitoba Home Nutrition Program
- Donna MacFarlane, RN, Patient Safety Lead, HQCA
- Carmella Duchscherer, RRT, BHS(RT), MPA, Quality & Safety Review Team Lead, HQCA
- Rinda LaBranche, RN, BEd, MEd, Patient Safety Lead, HQCA

The following people provided input into the report:

- Christiane Langtry, Administrative Assistant, HQCA
- Lisa Strosher, MSc, Patient Safety Lead, HQCA
- Charlene McBrien-Morrison, RT (CSLT), MBA, Executive Director, HQCA
- Eric Wasylenko, MD, BSc, MHSc (Bioethics), Ethics and End of Life Consultant, HQCA

## APPROACH AND METHODOLOGY

The Health Quality Council of Alberta (HQCA) conducted this review under Section 9 of the *Alberta Evidence Act*<sup>4</sup> to gain insight into the many system factors that may contribute to breakdowns in the parenteral nutrition (PN) process, with the goal of developing system-level recommendations that could help improve the quality and safety of care for patients in the future.

This review was conducted using the *Systematic Systems Analysis: A Practical Approach to Patient Safety Reviews* as a guide.<sup>8</sup> The methodology encourages a systemic view of the healthcare system; that is, “how all parts of the healthcare system play a role”, rather than a focus on “only one particular factor in isolation”.<sup>9</sup> A model of the healthcare system was used, which is made up of five major components: patients, personnel, equipment/environment, organization(s), and regulatory agencies.<sup>9,10</sup> The model also considers the quality assurance fundamentals of structure, process, and outcome.<sup>11</sup>

The following describes the approach taken to collect and analyze information and to develop recommendations and enabling actions. We have provided enabling actions to help guide the implementation of the recommendations.

### Collection and analysis of information

Information was gathered from a number of sources:

- Published literature related to PN.
- Documents provided by Alberta Health Services (AHS) related to the PN process (e.g., policies and procedures).
- Findings and recommendations from the AHS quality assurance review (QAR) of the adverse event.
- Findings from the AHS human factors evaluation of the preparation and distribution of PN.
- AHS PN usage reports.
- AHS and external patient safety reporting data.
- On-site observations.
- Interviews with individuals from AHS and other healthcare organizations.

The Central Production Pharmacy (CPP) in the Calgary Zone was used as a comparator for PN processes within pharmacy for this review because of its size and similarity in healthcare services provided. All PN admixtures for the Calgary Zone are prepared at the CPP, which serves five hospital sites: the Foothills Medical Centre, Rockyview General Hospital, Peter Lougheed Centre, Alberta Children’s Hospital, and South Health Campus.

### Published literature related to PN

A PN literature review of published research and leading practices was undertaken to develop an understanding of the implications for quality and patient safety related to the PN processes defined by the initial scope of the review. The literature reviewed included systematic reviews, meta-analyses, and grey literature from associations, societies, clinical practice guideline developers, and selected journals

in the area of PN (Appendix IV). The review team also reviewed PN leading practice guidelines, recommendations, and standards documents.

### **Documents provided by AHS related to the PN process**

More than 250 documents from the AHS departments of Pharmacy, Nursing, and Nutrition Services were reviewed including policies, procedures, and manuals that were related to the PN process across all patient populations, high-alert medications, and double checks.

### **Findings and recommendations from the AHS PN QAR of the adverse event and human factors evaluation**

The findings and recommendations from the AHS PN QAR were reviewed to gain a better understanding of the background, context, and specific details of the event. The human factors evaluation was used to confirm details of the PN preparation process with the University of Alberta Hospital (UAH) pharmacy.

### **AHS PN usage reports**

Provincial PN usage data included the number of PN admixtures dispensed for each hospital. Data for the Calgary and Edmonton zones were analyzed.

### **AHS and external patient safety reporting data**

Data reviewed included reports from the AHS Reporting and Learning System (RLS) and the AHS Pharmacy good catch reporting system as well as an external safety reporting database (Manufacturer and User Facility Device Experience [MAUDE]).<sup>12</sup> The RLS is an electronic voluntary reporting system that collects detailed information from healthcare providers about patient safety adverse events, close calls, and potential hazards. Reporters may submit reports confidentially. The United States Food and Drug Administration requires manufacturers, importers, and device user facilities in the United States to report to the MAUDE database when marketed medical devices may have caused or contributed to the death or serious injury of a patient.<sup>12</sup> Healthcare professionals, patients, and consumers can voluntarily report on such outcomes through MAUDE and reports are publicly searchable. Reports specific to the automated compounding device (ACD) used in AHS to compound PN admixtures were reviewed.

### **On-site observations**

Site visits were made to the UAH, Royal Alexandra Hospital (RAH), Misericordia Community Hospital (MCH), and Grey Nuns (GN) Community Hospital in the Edmonton Zone. A task analysis was performed during the site visits and later translated into a flow map to accurately capture the PN processes as observed at each site. The task analysis and subsequent flow maps included the processes of communicating the PN order, order verification and review, as well as compounding, labelling, dispensing, and administering PN. The flow maps were validated with frontline pharmacists and pharmacy technicians at each site and were modified as needed to most accurately capture PN processes. The task analysis and flow maps were used to identify process variation between sites. PN experts on the review team compared the flow maps of the current PN processes to known leading practices and standards. As a comparator, site visits, task analysis, flow mapping, and validation of the pharmacy PN processes were conducted at the CPP in the Calgary Zone.

A second round of site visits occurred to conduct an observational human factors assessment at four sites – UAH, RAH, MCH, and CPP – to focus specifically on how the environment, technology, forms, and labels are used and the extent to which their design helps or hinders PN processes. A third round of site



visits occurred at three of the sites – UAH, RAH, and CPP – to allow one of the PN experts on the review team to conduct a more focused assessment of each pharmacy’s compliance with guidelines for sterile preparation as well as with recommended PN practice standards. Information collected during the site visits were used to identify hazards within the PN processes as per the scope of this review and to generate system-level recommendations for improvement.

### **Interviews with individuals from AHS and other healthcare organizations**

Semi-structured interviews were conducted with 49 individuals, including frontline staff and management at various levels within AHS in the Edmonton and Calgary zones as well as representatives of other healthcare organizations in Canada and the United States. Interviews were primarily conducted face-to-face, and some by conference call. Interviews focused on gathering information about PN processes and quality management, the roles of leadership, as well as the history and future directions of PN oversight within Alberta. Some interview questions targeted perceptions of PN as a high-alert medication and associated risk-mitigation strategies, availability of PN expertise within Pharmacy, reporting culture for adverse events, close calls and hazards, dissemination of recommendations from the AHS PN QAR, as well as recognition and compliance with known leading practices in PN.

To better understand strategies that are used in other organizations to eliminate transcription of PN orders, interviews were conducted with individuals at Sunnybrook Health Sciences Centre in Toronto, Canada, the University of Pennsylvania Health System in Philadelphia in the United States, as well as a vendor for a computerized prescriber order entry (CPOE) system for PN. Regulatory standards in Alberta regarding sterile compounding in licensed pharmacies were discussed with a representative of the Alberta College of Pharmacists.

## INTRODUCTION

### Parenteral nutrition

Parenteral nutrition (PN) is a high-alert medication (one that bears a heightened risk of causing significant patient harm when used incorrectly)<sup>1,2</sup> and a form of nutrition support. It involves the delivery of nutrients through an intravenous catheter into a large central vein (e.g., superior vena cava) or peripheral vein on the hand or arm. Patients who receive PN typically have underlying disorders that involve a non-functioning digestive system. These patients are not able to ingest or absorb food or specialized nutritional products taken by mouth or administered directly into other parts of the gastrointestinal tract using a feeding tube (enteral route). Some patients may be otherwise well nourished but have not been able to eat for seven to 10 days prior to starting PN; others may have pre-existing malnutrition requiring nutrition repletion. Infants who are born very prematurely require PN as the principal source of nutrition in the first days or weeks of life, depending on their medical condition. The most recent European<sup>13</sup> and American<sup>14</sup> guidelines for feeding premature infants recommend early initiation of PN with amino acids on the first day of life and lipids on the first or second day of life in order to improve the cumulative energy and protein deficit, promote postnatal growth, and improve neurologic outcomes. Many adults and children who require PN are critically ill, often immunocompromised, and have complex medical disorders or surgical complications. Specific indications for using PN are described below for neonate (Table 1), pediatric (Table 2), and adult (Table 3) patients. Appropriate and judicious use of PN is important given that it is invasive and associated with significant complications.

**Table 1:** Indications for PN in neonate patients<sup>15</sup>

<ul style="list-style-type: none"> <li>▪ Any infant requiring major surgery before the establishment of milk feeds and as soon as possible after surgery.</li> <li>▪ Gastrointestinal anomalies requiring surgery – gastroschisis, omphalocele, intestinal atresias, necrotizing enterocolitis, ileus, pseudo obstruction, or Hirschsprungs.</li> <li>▪ Malabsorption – short gut, intractable diarrhea, villous atrophy, dysmotility syndrome.</li> <li>▪ GI perfusion compromised by conditions such as cardiovascular or respiratory instability, congenital heart disease, and use of certain medications.</li> <li>▪ PN should be considered within 24 hours if an infant is expected to have a delay in reaching full volume enteral feeds beyond 3–4 days.</li> </ul>
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**Table 2:** Indications for PN in pediatric patients<sup>16,17</sup>

<p><b>Partially functional gastrointestinal tract</b></p> <ul style="list-style-type: none"> <li>▪ Cannot meet nutrient requirements after maximizing enteral support.</li> <li>▪ Gastrointestinal fistula.</li> <li>▪ Multi-organ failure.</li> <li>▪ Malabsorption, e.g., short-bowel syndrome, intractable diarrhea, villous atrophy, or dysmotility syndromes.</li> <li>▪ Risk of aspiration when small bowel feedings are not possible.</li> <li>▪ Malnutrition with hypoproteinemia.</li> <li>▪ Upper gastrointestinal bleed.</li> </ul> <p><b>Non-functional gastrointestinal tract</b></p> <ul style="list-style-type: none"> <li>▪ Paralytic ileus.</li> <li>▪ Bowel obstruction.</li> <li>▪ Chronic intractable vomiting or diarrhea.</li> <li>▪ Small bowel ischemia.</li> <li>▪ Peritonitis.</li> <li>▪ Necrotising enterocolitis.</li> <li>▪ Gastrointestinal surgery (gastroschisis, omphalocele, multiple intestinal atresias, etc.) until the enteral route is accessible.</li> <li>▪ Severe inflammatory bowel disease with impending surgery.</li> </ul>
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**Table 3:** Indications for PN in adult patients<sup>18</sup>

<ul style="list-style-type: none"> <li>▪ Inflammatory bowel disease where enteral nutrition has failed to prevent or reverse malnutrition (i.e., severe malabsorption).</li> <li>▪ Patients with multi-organ failure where nutritional requirements cannot be met by the enteral route alone.</li> <li>▪ Intestinal atresia.</li> <li>▪ Radiation enteritis.</li> <li>▪ Severe mucositis following chemotherapy.</li> <li>▪ Motility disorders such as scleroderma or chronic idiopathic intestinal pseudo-obstruction syndromes.</li> <li>▪ Extreme short-bowel syndrome (e.g., thrombogenic), trauma, resection due to tumour.</li> <li>▪ High-output stoma (&gt;1000 mL).</li> <li>▪ Enterocutaneous fistulas.</li> <li>▪ Inborn error of the bowel surface.</li> <li>▪ Motility disorders.</li> <li>▪ Malnourished dialysis patients (interdialytic PN).</li> <li>▪ GI tract obstruction.</li> <li>▪ Prolonged post-operative ileus.</li> </ul>
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PN admixtures are devised to meet the nutritional needs of individual patients, and contain glucose, amino acids (building blocks of protein), lipids (fat), electrolytes, vitamins, minerals, and trace elements. Management of PN is complex and involves supplying nutrients to meet a patient's needs without exceeding the metabolic capacity for handling glucose, fat, or energy, and maintaining electrolyte and mineral balance while addressing PN-associated clinical complications that may arise.

PN is classified as a high-alert medication because significant patient harm may occur when it is used incorrectly or without regard to accepted leading practice standards.<sup>1,2</sup> Safety concerns relate to the product, the route of administration, and the vulnerability of the patients for whom it is prescribed. It is a complex compound that contains multiple medication ingredients, and it creates a growth medium in which infectious agents can thrive. PN is administered intravenously to patients who are often immunocompromised or otherwise prone to infection. PN administration is associated with complications including catheter-related sepsis<sup>19</sup> and thrombosis.<sup>20</sup> Metabolic complications for the patient include disordered fat metabolism, impaired glucose metabolism,<sup>21</sup> acid base disorders, and electrolyte (e.g., sodium, potassium) and mineral (e.g., magnesium, phosphate) imbalances. It may also cause liver toxicity.

## Parenteral nutrition process

The PN process typically involves inter-professional collaboration between dietitians, physicians, pharmacists, and nurses to provide effective and safe nutrition care.<sup>6</sup> Good communication and standardization of processes across all steps is an important risk-management strategy.<sup>7</sup> Each discipline contributes unique expertise to provide safe and appropriate PN therapy to patients who are unable to maintain their nutrition status enterally. Ideally each step within the PN process should follow accepted guidelines and standards of practice with nutrition support specialists in each discipline. Expertise in PN is required to optimize therapeutic outcomes and minimize complications that can result when PN is prescribed inappropriately (or incorrectly), prepared incorrectly, or administered inappropriately, or when patients are not adequately monitored, including monitoring for complications that can arise from administering PN. The American Society for Parenteral and Enteral Nutrition (ASPEN) is an international organization that sets leading practice standards for PN and has defined the roles for each discipline involved in providing PN.<sup>22,23,24,25</sup> A recent ASPEN practice management task force concluded that "it is clear that dietitians, pharmacists, physicians, and nurses each play important roles in improving the nutrition status of patients, but the safety and efficacy of care are enhanced when they collaborate as a team".<sup>26</sup>

The PN process includes a number of critical patient-focused steps (Figure 1).<sup>2,7</sup>

*Patient assessment:* a comprehensive nutritional assessment of the patient, by the nutrition support service or dietitian, is based on subjective and objective data to determine if PN is appropriate and if malnutrition is present. It also guides developing the plan of care including the amount of energy, macronutrients, minerals, vitamins, fluid, and electrolytes required, as well as the need for non-nutrient medications and monitoring parameters.

*Prescribing:* this plan is then communicated to the physician or designate who orders the PN by prescription.

*Verification and review:* the PN prescription is then verified and reviewed by a pharmacist to assess appropriateness of the many PN ingredients for patient-specific dosing, compatibility, and stability.

*Compounding, labelling, and dispensing:* a PN order deemed appropriate will be prepared (i.e., compounded, labelled, and dispensed) in a pharmacy adhering to stringent guidelines for sterile compounding.<sup>6,27,28,29,30</sup>

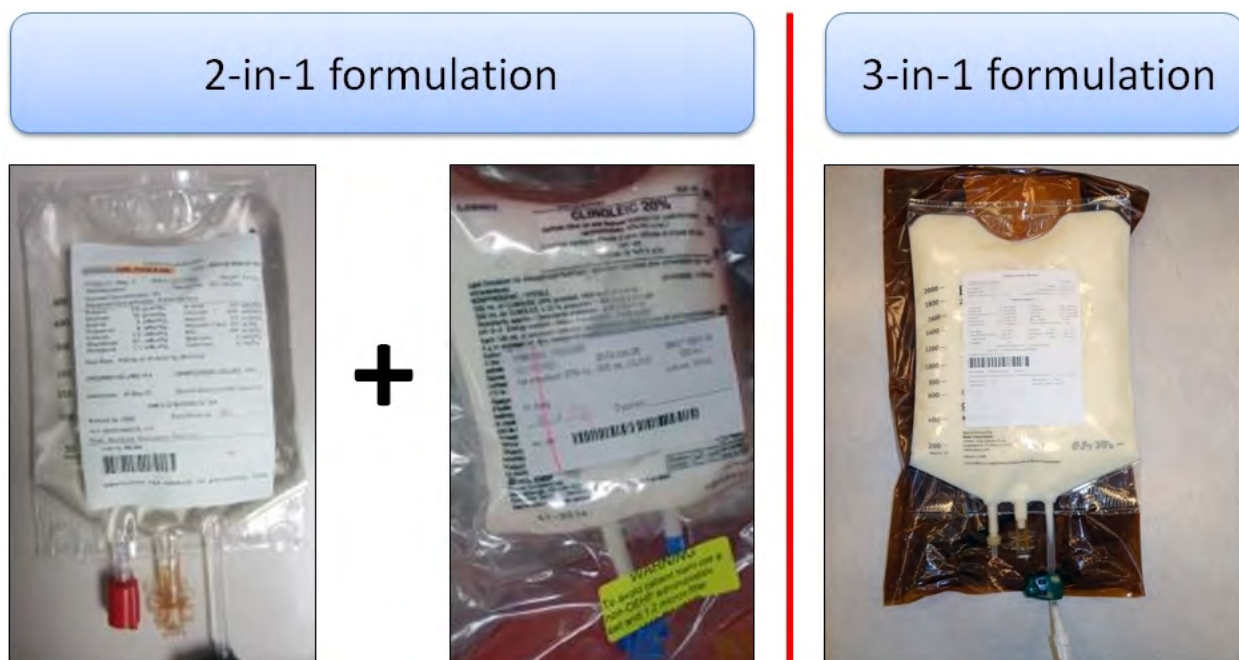
*Administration:* the prepared PN is sent to the patient care unit for administration to the patient.

*Monitoring and reassessment:* following administration, monitoring, and reassessment of the patient by the nutrition support service completes the loop.

Documentation should take place at each step of the PN process.<sup>6</sup> This includes documentation of the nutrition support service or dietitian's assessment and plan, the prescriber's order, the pharmacist's review with all clarifications and interventions, all calculations that are performed, steps of the compounding process, the nurse's assessment and administration of PN to the patient, as well as documentation of independent double checks that are required at any point of the PN process. All documentation should be readily retrievable from the patient's medical record or associated information system(s) for audit of all components of the PN process.<sup>6,27,31</sup>

PN can be administered as either a 2-in-1 or 3-in-1 formulation, which refers to the number of macronutrients combined with micronutrients in the same infusion container. A 2-in-1 formulation combines dextrose and amino acids in a single bag (at left in Figure 2). The lipid is provided in a separate bag or syringe (at centre in Figure 2) that is typically administered by a second pump through tubing that joins the PN tubing at the Y-site closest to the patient. A 3-in-1 formulation, also known as a total nutrient admixture, includes amino acids, dextrose, and lipid in a single bag (at right in Figure 2). By mixing all nutrients in one bag, only a single pump is used. Therefore, only one administration set is required and only one pump is programmed to administer the admixture, which reduces line manipulation and potential pump programming error.

**Figure 2:** PN as either a 2-in-1 or a 3-in-1 formulation



The 3-in-1 PN formulation includes the exact amount of lipid prescribed in the bag as stability allows, thus eliminating overfill wastage and inadvertent overdosing of the lipid. The potential destabilizing effect of other PN ingredients on the lipid emulsion, however, means that only certain admixtures can be formulated as a 3-in-1. When a 3-in-1 formulation is ordered, a pharmacist reviews the prescribed ingredients and determines if it is suitable for a 3-in-1 formulation or if a traditional 2-in-1 formulation must be used with the lipid administered separately by Y-site.<sup>32</sup>

## FINDINGS

### Parenteral nutrition as a high-alert medication

High-alert medications can be defined as those medications that bear a heightened risk of causing significant patient harm when they are used incorrectly.<sup>1</sup> The American Society for Parenteral and Enteral Nutrition (ASPEN) and the Institute for Safe Medication Practices (ISMP) acknowledge parenteral nutrition (PN) to be a high-alert medication.<sup>1,2,5</sup> Classifying PN as such requires healthcare organizations to develop evidence-based policies and procedures applicable to these medications in order to reduce risk to patients who rely on PN support as part of their care.<sup>6</sup> A number of strategies have been recommended by the ISMP to mitigate hazards associated with high-alert medications, such as standardizing processes for their ordering, storage, preparation, and administration; improving access to information about these medications; limiting access to the medications; using auxiliary labels and automated alerts; and employing redundancies, such as automated or independent double checks when necessary.<sup>1</sup> Independent double checks should be used to verify any calculations and unit of measure conversions as well as pump programming prior to administration.<sup>6</sup>

Among Alberta Health Services (AHS) policies related to high-alert medications provided to the review team, some do not include PN and some indirectly identify PN as a high-alert medication. For example, the Pharmacy high-alert medication list does not include PN.<sup>33</sup> The current Edmonton Zone high-alert medication directive, which was in place at the time of the PN incident, adopts the ISMP high-alert medication list by reference only and requires users to view an external website to identify the high-alert medications.<sup>34</sup> The Edmonton Zone directive suggests establishing a minimum of one risk-avoidance strategy for each high-alert medication such as:

- “limiting access to the medication,
- using auxiliary labels and automated alerts,
- standardizing ordering, preparation and administration of the medication,
- employing automated or independent double checks when necessary.”<sup>34</sup>

Although not in place at the time of the adverse event, a province-wide policy<sup>35</sup> and procedure<sup>36</sup> related to the management of high-alert medications as well as a guideline that outlines the process for completing independent double checks is currently being developed by AHS.<sup>37</sup> The draft high-alert medication policy and procedure provided to the review team did not include an explicit list of medications considered to be high alert so it was not possible to determine if PN will be included on the list in the future. The independent double check guideline states it applies to high-risk medications, but does not reference an explicit list of medications considered to be high risk.

Some nursing policies were noted to classify PN as a high-alert medication and require various mitigation strategies. For example, AHS Patient Care Policy 15.1, specific to the Stollery Children’s Hospital, requires performing an independent double check of medication calculations and programming of infusion pumps for high-alert medications, which are specifically listed in the policy and which includes PN.<sup>38</sup>

Interviewees indicated significant variation both within and among healthcare professions and management in their perceptions about the level of risk associated with PN. In interviews, pharmacy staff identified compounding PN as a high-alert process, yet many did not consider PN a high-alert

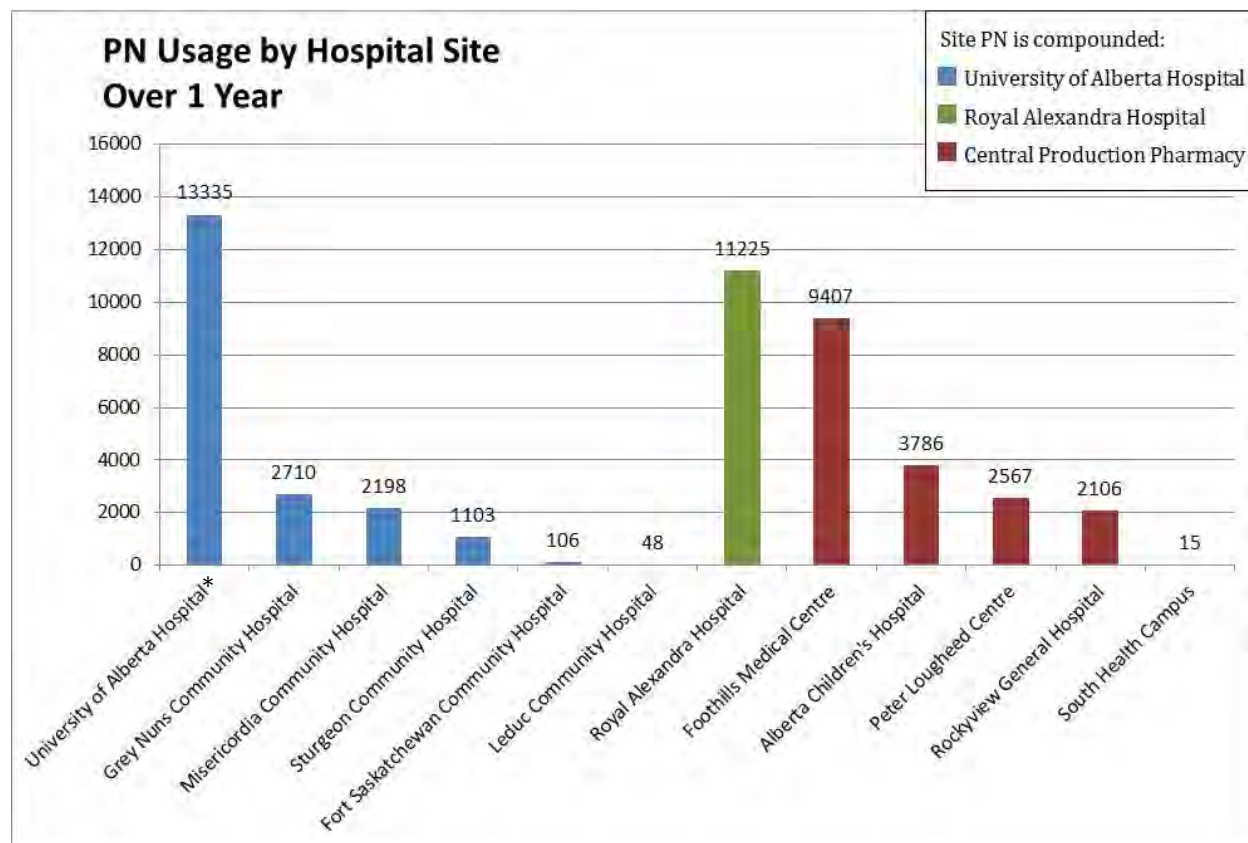
medication; some did not consider PN to be a medication, instead referring to it as a food or supplement. Mitigation strategies for high-alert medications were noted to be either inconsistently applied (e.g., no double check of pharmacist order entry at one site, checking processes vary between sites, independent double checks are not truly independent, final product is not always checked against the original order) or ineffective/error prone (e.g., syringe pullback method of checking after manual additives have been completed). Hazard-mitigation strategies for sterile compounding intended to reduce harm from microbial and particulate contamination varied widely between sites (e.g., sterile room design, sterile compounding processes), and rarely conformed to leading practice recommendations.

## **Parenteral nutrition usage**

Data were provided by AHS indicating the number of PN admixtures dispensed by each hospital across the province. Figure 3 summarizes data for the Edmonton and Calgary zones from October 1, 2012 to September 30, 2013. The Edmonton Zone dispensed 30,725 PN admixtures, which included 19,500 PN admixtures compounded at the University of Alberta Hospital (UAH – blue bars) as well as 11,225 PN admixtures compounded at the Royal Alexandra Hospital (RAH – green bars). All PN in the Edmonton Zone is dispensed as a 2-in-1 formulation. In comparison, the Calgary Zone dispensed 17,881 PN admixtures, which were compounded at the Central Production Pharmacy (CPP – red bars). Most PN in the Calgary Zone is dispensed as a 3-in-1 formulation. Three noteworthy changes have occurred since the dates shown in this data. Changes include: (1) PN for the Sturgeon Community Hospital, as of August 2013, is being compounded at the RAH instead of the UAH; (2) PN for the Cross Cancer Institute, as of September 2013, is being compounded at the UAH; and (3) PN for the South Health Campus in Calgary, as of June 2013 for adult patients and September 2013 for neonate and pediatric patients, is being compounded at the CPP.



**Figure 3: PN admixtures dispensed by hospital**

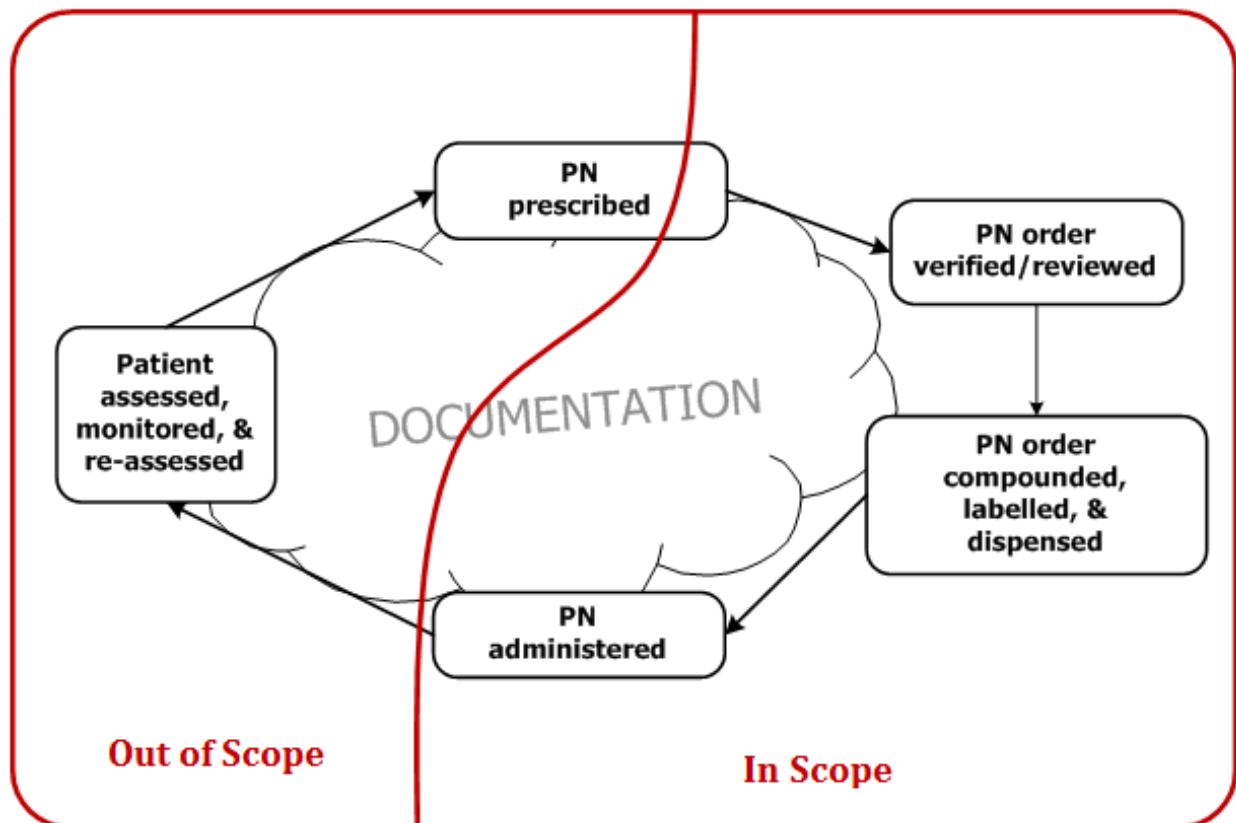


\*Data include the Stollery Children's Hospital.

## Parenteral nutrition process

The findings presented within this section review each of the components of the PN process (Figure 4) that are within the scope of this review (communicating the PN order; verification and review; compounding, labelling, and dispensing; and administration). They summarize the analysis of information gathered from all information sources.

**Figure 4:** PN process adapted from Hudson<sup>7</sup> also illustrating the modified review scope



**Table 4:** Required components for PN orders and preferred sequence from Ayers<sup>6</sup>

Components for the PN Order	
Patient Information	
Patient identifiers (patient name, medical record number or other unique identifiers, birth date/age, patient location)	
Patient location (home address for home PN patients)	
Allergies and reactions	
Height and dosing weight (metric)	
Diagnosis(es)/indication(s) for PN	
Vascular access device/location	
Administration date/time	
PN Ingredients (should match PN label)	
Amino acids	
Dextrose	
IVFE (lipids)	
Sodium phosphate	
Sodium chloride	
Sodium acetate	
Potassium phosphate	
Potassium chloride	
Potassium acetate	
Magnesium sulfate or magnesium chloride	
Calcium gluconate	
Multivitamins	
Trace elements	
Additives (e.g., cysteine, regular insulin) as clinically appropriate and compatible	
PN Instructions	
Total volume, infusion rate, start and stop times, cycle information	
Prescriber and contact information	

The gold standard to prescribe PN, as recommended by ASPEN, is a standardized electronic PN order with embedded clinical decision support, ideally through the use of a computerized prescriber order entry (CPOE) system.<sup>6</sup> Where this is not possible, ASPEN recommends using an editable electronic document; the use of handwritten orders is discouraged. One study estimated that using a CPOE system to order medications reduced medication error rates by 48 per cent.<sup>40</sup> In one survey conducted in the United States, one-third of healthcare organizations that responded use a CPOE system for PN.<sup>41</sup> One of the primary benefits that CPOE systems provide is eliminating handwritten orders and ultimately

enabling use of an interface to eliminate the transcription of orders between prescribers and pharmacy<sup>42</sup> although a number of other benefits have been noted.<sup>2</sup>

As noted during site visits, PN orders in the Edmonton Zone were usually handwritten onto one of three paper PN order forms (neonate, pediatric, or adult) standardized across the zone. If the order was written by a dietitian, a physician co-signed the order. A telephone order from the dietitian would be accepted for continuation of the previous day's PN when there were no changes to the components, and for discontinuation of PN. In the Calgary Zone, on the other hand, all PN orders were entered by the physician or dietitian into Sunrise Clinical Manager, a CPOE system.

The Edmonton Zone PN order forms, including the PN product-related information provided on the reverse of the form, were last revised between 1998 and 2008. In addition, deviations from the ASPEN recommendations for order form components were noted for one or more order form templates in terms of the following:

- Prescriber contact information.
- Prescription cut-off times to accommodate pharmacy processing.
- Allergies and reactions.
- Patient height.
- Type and location of the venous access device.
- PN indication.
- PN ingredients in amount (g, mg, mcg, mmol) per day (or amount per kg per day in pediatrics).
- Vitamin K ordered weekly or biweekly rather than daily as recommended.

Leading practice guidelines suggest that verbal or telephone orders should not be used for PN.<sup>6</sup> Most current policies within AHS permit verbal or telephone orders of medications; however, PN is not specifically addressed in the policies. No specific guidelines related to communicating the PN order were found in the document review.

In the Edmonton Zone, one copy of the PN order generally went into the patient chart immediately after being written. The RAH, however, followed a different protocol for new neonatal orders. There, both copies of the order were sent to pharmacy due to the increased likelihood that modifications would be made during the order verification and review by pharmacy. Having both copies in pharmacy made it possible to simultaneously update both copies when adjustments were made by pharmacy. The chart copy of the original order was then sent back to the unit with the PN admixture. The mechanism used to send the order to pharmacy varied between sites and included scanning and electronically sending the order, faxing the order, walking the order to the pharmacy department, or sending via pneumatic tube. In the Calgary Zone, the order was automatically sent to the CPP electronically via the CPOE system.

At all sites visited, pharmacy printed the PN orders as they were received. The printed orders were then sorted to assist with manual order entry (transcription) into the Abacus system, which interfaces with the automated compounding device (ACD).

## PN order verified and reviewed

### *Pharmacist order review*

Review and verification of a PN order by a pharmacist is recognized as a critical step in the PN process.<sup>6</sup> The review process should include both a patient-focused clinical review (indications, dose of macro and micronutrients) and a product-focused pharmaceutical review (stability, compatibility, correct product selection).<sup>6</sup> This review should take place in an environment without distractions.<sup>6</sup>

Review of existing AHS pharmacy policies found no requirement for clinical and pharmaceutical review of PN orders received in pharmacy. At all sites, the observed pharmacy review process involved comparing the current PN order to the PN order from the previous day for that patient and clarifying any issues. In addition, the pharmacist used embedded decision support tools within Abacus to check incompatibilities, calcium-phosphate solubility<sup>viii</sup>, and some dosing limit warnings. At the CPP in Calgary, the pharmacist had access to patient profiles in Sunrise Clinical Manager (SCM) to check other medications and laboratory results for the patient if available. When potential issues were detected, the pharmacist would then contact the appropriate prescriber to discuss; at the CPP the pharmacist could make PN order changes directly in SCM as applicable, whereas in the Edmonton Zone the prescriber was generally required to adjust the original order form in the patient's chart on the unit. Documenting the identification and resolution of potential issues varied between sites and zones.

### *Order transcription and verification*

A safer system is one in which PN is ordered using a CPOE system fully integrated with the pharmacy's ACD to eliminate the need for transcription of PN orders into the pharmacy system (an error-prone step). Transcribing PN orders has resulted in adverse events causing patient harm.<sup>43,44,45</sup> When transcription of the PN order into the pharmacy compounding system is undertaken, an independent double check using the original order is needed to verify the accuracy of the transcription.<sup>6,46</sup>

Discussions with a PN CPOE vendor, and with two healthcare organizations that have eliminated the transcription step, highlight three approaches to eliminate the transcription of PN orders.

Web-based CPOE applications exist in which prescribers enter electronic PN orders for neonate, pediatric, and adult patients. TPN Assistant is one example of a commercial software product that interfaces directly with the ACD in the pharmacy to eliminate the transcription of PN orders and provides alerts when prescribing (e.g., calcium-phosphate solubility).

Sunnybrook Health Sciences Centre in Toronto, Canada has a 40-bed NICU. A number of changes have been made over time to enhance patient safety. For example the NICU moved away from handwritten PN orders in the fall of 2011 and introduced Abacus software onto the unit for direct order entry. The NICU has several dietitians who provide coverage during the day, 365 days per year. Dietitians are available to create daily PN orders directly into the software after collaboration with the inter-professional team, thus avoiding a need for standing orders. The PN admixture is compounded on the unit in the NICU-dedicated satellite pharmacy. This model eliminates the PN order transcription process that previously occurred when using the handwritten orders. The electronic order, as entered into Abacus, is then available for verification and review by the NICU pharmacist and for co-signature by the physician or nurse practitioner. The safety features of using the Abacus software in the NICU include:

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<sup>viii</sup> Calcium-phosphate is an insoluble compound that can form a precipitate in PN admixtures if the total dose of calcium and phosphate in the admixture exceeds a critical value.

- Elimination of transcription error by order entry directly into the software.
- Informed clinical decision-making by system alerts provided through the software regarding compatibilities, osmolarities, and dosing limits.
- Generation of an order-specific barcode that communicates directly with the compounder, which eliminates human error when PN is manufactured.
- Generation of a PN order that is visually verified by the medical team prior to co-signature.
- Generation of an order-specific serial number on the PN order and the PN bag that are visually checked by the nurse before administration to ensure the correct order matches the correct infant and the correct PN bag.

The University of Pennsylvania Health System in Philadelphia, U.S.A. has three sites that developed technology to eliminate the transcription of PN orders. At these sites, PN is recommended by a dietitian, prescribed by a physician, verified and reviewed by a pharmacist, and then compounded by an off-site vendor. To eliminate the PN order transcription step and potential transcription errors, a file transfer protocol was developed. This allowed PN orders to be entered into the Sunrise clinical information system, where alerts can be provided to prescribers, and then verified by a pharmacist in Sunrise before sending the electronic files to the off-site vendor.

In all pharmacies in the Edmonton and Calgary zones, all PN orders were transcribed into a PN order entry system (Abacus) either by a pharmacist or a pharmacy technician. In the Edmonton Zone, the hazard of transcription is amplified by inconsistencies between the sequence in which ingredients are listed on the PN order form and the sequence in which they are listed in the Abacus system. Specifically, if the dosage numbers from the order form were transcribed from top to bottom in the same order into the Abacus system, then four ingredients could be entered incorrectly. This is shown in Figure 5. The red lines indicate which ingredients are listed in a different order when comparing the adult PN order form (right) with the Abacus order entry system (left).

**Figure 5:** Comparison of the adult PN order form with the Abacus order entry screen

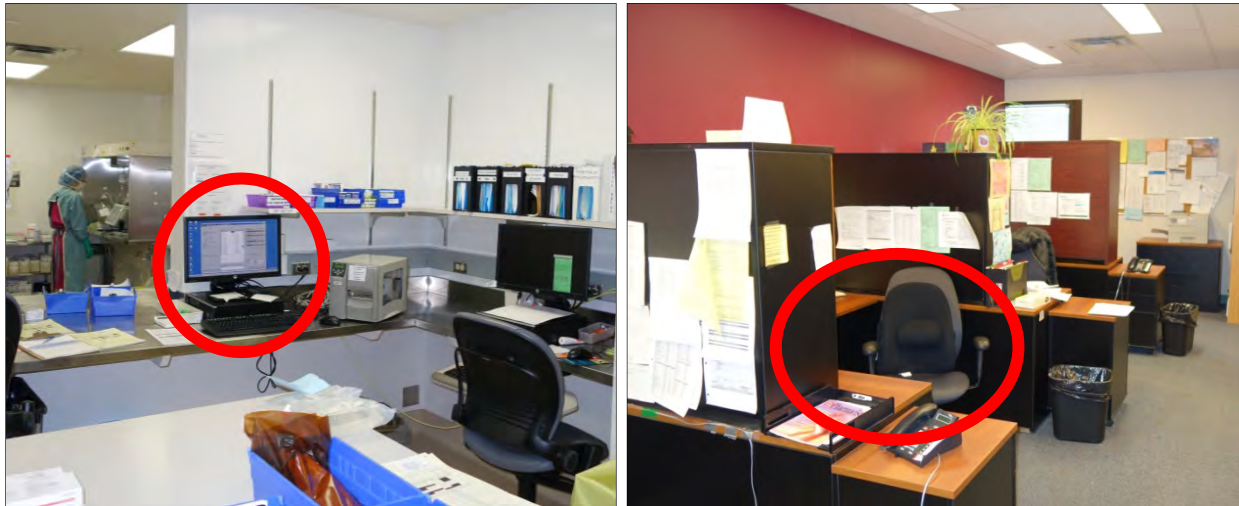
Src	Substance	Value	Num	Denom	Rule	Additives	Recommended Requirements	Total 24 hour Intake
U	Travasol 10%		gram	/day		Sodium <sup>1</sup>	1 - 2 mmol / kg / day	mmol / day
U	Dextrose 70%		gram	/day		Potassium <sup>1</sup>	1 - 2 mmol / kg / day	mmol / day
U	Sodium		mMol	/day		Calcium	10 - 15 mmol / day	mmol / day
T	Potassium		mMol	/day		Magnesium	8 - 20 mmol / day	mmol / day
T	Calcium		mMol	/day		Phosphate	20 - 40 mmol / day	mmol / day
U	Magnesium		mMol	/day		Acetate (mmol)	as required	mmol / day
T	Phosphate		mMol	/day		Multiple Vitamin Solution	10 mL / day	mL / day
U	Acetate		mMol	/day		Vitamin K <sup>2</sup>	10 mg / week <sup>2</sup>	mg / week
T	Chloride		mMol	/day		Trace Element Solution	1 mL / day	mL / day
T	Adult Multivitamin		mL	/day		Heparin	1 unit / mL	units / day
U	Vitamin K		mg	/day		Zinc	as required	mg / day
U	M.T.E.-5 Conc		mL	/day		Folic Acid	as required	mg / day
T	M.T.E.-6 Conc		mL	/day		Famotidine	as required	mg / day
T	Zinc Sulfate		mg	/day		Insulin (units) <sup>3</sup>	as required <sup>3</sup>	units / day
U	Folic Acid		mg	/day		Hydrocortisone sodium succinate	5 mg / L	/ day
T	Famotidine		mg	/day		Other (specify)		/ day
T	Heparin 1000 units/mL		units	/day				
T	Insulin R. Novo		units	/day				
T	Hydrocortisone		mg	/day				

Generally, in the Edmonton Zone, a double check was performed to validate order entry accuracy, although only Covenant Health has a policy that specifically addresses verification of orders transcribed into the pharmacy system by comparing them with the original order.<sup>47</sup> The checking process varied between sites, and at one site did not always occur. Pharmacists at Misericordia Community Hospital (MCH) and the Grey Nuns (GN) Community Hospital performed the order entry task and a different pharmacist performed the double check to validate the order entry. Because PN admixtures are not compounded on site at the MCH or GN, the verified PN orders entered into Abacus were exported electronically by the MCH and GN pharmacists to the UAH pharmacy. The UAH did not receive a copy of the original PN order from the MCH or GN. At the RAH, both pharmacists and PN-trained pharmacy technicians entered PN orders; if entered by a pharmacist, the entry was not double checked. Different sources of information between sites were used to perform the order entry double check (computer screen versus printed PN label). Whether and how individuals communicated the completion of this double check also varied. Pharmacists at the UAH initialled the paper order and the paper label. Pharmacists at the MCH initialled the tracking form. At the RAH, completion of the double check, when one was performed, was communicated by adding the verified PN label to the pile of labels waiting to be compounded. Pharmacists at the RAH did not provide written confirmation to indicate completion of the double check.

Site visits during this review identified environmental factors with the potential to compromise quality and safety during order transcription and review. At the RAH, the order entry computer was located next to the sterile compounding area, as shown at left in Figure 6. At the MCH, the order entry computer was located next to the pharmacy pickup and drop-off window. At the UAH, the order entry computer was in a room just outside the anteroom to the sterile compounding room but the PN pharmacist had other duties in addition to PN review and order entry. Frequent interruptions were observed during PN order entry at all sites in the Edmonton Zone. In contrast, a designated room at the CPP is used for order entry, as shown at right in Figure 6. This room is physically separate from other pharmacy processes and observed to be far less prone to interruptions and distractions.



**Figure 6:** Order entry and verification environment at the RAH (left) and the CPP (right)



Once the orders are entered into Abacus and double checked (at sites where the double check occurs), the PN labels were automatically printed at the site that compounded PN for that facility (UAH, RAH, or CPP). The MCH pharmacists (and pharmacists at other sites that do not compound PN) would then phone the UAH pharmacy to ensure that the number of orders sent was equal to the number of PN labels printed. This was to ensure that no orders were missed when transmitting them to the UAH. The PN labels were then sent to the sterile compounding room to start compounding.

### PN order compounded, labelled, and dispensed

PN can be compounded as a custom admixture for each individual patient, in either a 2-in-1 or 3-in-1 formulation as described previously. Alternatively, standardized admixtures that contain predetermined concentrations of dextrose and amino acids with or without electrolytes can also be used. These are either compounded within the pharmacy or purchased as a commercial product in double (for 2-in-1 formulations) or triple (for 3-in-1 formulations) chamber bags. Standardized solutions still require some patient-specific customization with electrolytes, vitamins, trace elements, and other medications such as insulin added within the pharmacy. However they offer some safety advantages over custom-compounded solutions because the compounding process is less complex, misinterpretation of orders and calculation errors are minimized, and standardization facilitates decision-making to prescribers.<sup>48</sup> Additives are added manually but the compounding time is typically less than that for custom-compounded solutions.<sup>48</sup> There are concerns, however, that these solutions do not meet the clinical needs of all patients, particularly related to protein requirements, and careful patient selection is critical.<sup>49</sup> Currently within the Edmonton Zone, PN is custom compounded as a 2-in-1 formulation for all patients, with lipid provided separately. The introduction of standardized PN admixtures is being considered within the Edmonton Zone.

Organizations compounding PN admixtures should have well-defined policies and procedures that guide each step of PN preparation.<sup>6,31</sup> Both the environment and the personnel are critical to the quality of compounded sterile preparations. The ACD (ExactaMix 2400) and the Abacus system are tools for preparing custom compounded PN, thereby serving only as an extension of the compounding personnel. Compounding of PN should be performed by qualified, certified staff who are required to undergo



annual competency assessments.<sup>6</sup> Leading practice for safe preparation includes several measures: following aseptic techniques; using an ACD that has activated hard and soft dosing limits; conducting independent double checks on initial daily setup of the ACD (preferably using a checklist) as well as at other points during the compounding process; and separating preparation of adult from pediatric or neonatal PN by time or location.<sup>6,31</sup> The compounding environment should adhere to stringent guidelines for sterile preparation to reduce the risk for microbial and particulate contamination as well as the many potential problems that can arise with ingredient dosing and interaction.<sup>6,27, 28,31</sup> Compounding should take place in an ISO Class 5 environment such as a laminar airflow hood, surrounded by a buffer zone meeting ISO Class 7 standards. For ISO Class 5 areas, leading practice guidelines recommend cleaning with 70 per cent isopropanol using low-shed wipes at least every 30 minutes.

Both the UAH and RAH use a suitable laminar airflow hood for PN compounding. No information was available on the air exchange within the rooms to determine whether the environment meets ISO Class 7 standards. Concerns with the sterile compounding environment include:

- At the RAH, the sterile compounding room had no windows, was open to the order entry area, and the door was left open for ventilation.
- At the RAH, a printer and other high-particulate-matter material were located next to one of the laminar airflow hoods. This presents an opportunity for particulate contamination and was a concern for manual additives to PN that required the PN bag to be transferred out of one laminar airflow hood to another. Furthermore, the PN bag was not wiped with a disinfecting solution during the transfer.
- At the UAH, there appeared to be non-sterile activities taking place within the sterile compounding room. The many personnel and material moving constantly throughout the compounding room suggests a design that is not environmentally controlled to minimize airborne contamination.
- At the UAH and RAH, the room surfaces did not meet all United States Pharmacopeia (USP) criteria.
- At the UAH and RAH pharmacies, compounded PN admixtures were not refrigerated.
- Cleaning and disinfecting of the ACD and immediate compounding area did not occur during the site visits.

Province-wide pharmacy policies, education, and certification requirements are in place for aseptic technique and sterile compounding (e.g., AHS Regional Pharmacy Policy 15.01.01.01).<sup>50</sup> Written standard operating procedures for PN compounding were not available at either the UAH or RAH. Edmonton Zone policies that were reviewed do not address an education and certification requirement for staff who use the ACD to compound PN. AHS Regional Pharmacy Policy 15.01.01.01 also specifies the need to check daily the ACD setup, although it does not specify the need to trace tubing sets from source containers to ports. Most notably, this policy permits the use of the pullback method to verify volumes in syringes used for manual additives; this contradicts recommendations from both the ISMP<sup>31,51</sup> and ASPEN.<sup>6</sup> Although the concept of ‘checking’ is included in a number of steps in the sterile compounding process, the requirement for ‘independent double checks’ is not evident.

It was unclear whether a compounding record was maintained for each PN admixture prepared (including names of all ingredients, sources, lot numbers, expiration dates, names of individuals involved in preparation and checking, assigned beyond-use date, results of quality control, and documentation of any quality control issues). Additionally there was no readily available documentation related to ongoing monitoring of air quality (e.g., environmental sampling testing) or personnel practices (e.g., media-fill tests).

In interviews, Pharmacy leadership acknowledged the deficiencies in the sterile compounding environment but see no possibility of improvement with the current state of the infrastructure at the UAH and RAH sites. Through interviews, it was noted that a centralized pharmacy for the Edmonton Zone has repeatedly been a top funding priority for AHS but has never reached the approval stage.

#### *Automated compounding device set-up*

At all sites, pharmacy technicians started their shift by gathering all ingredients required to compound PN admixtures. Some ingredients required special preparation (i.e., reconstitution or creating a larger volume solution) for use with an ACD, specifically the Exacta-Mix 2400 (EM 2400; Figure 7). Depending on the site, a pharmacist or pharmacy technician performed a double check of these preparations. The pharmacy technician then set up the EM 2400. The EM 2400 allows up to 24 ingredients to be connected to the compounder; each ingredient was connected with a tube to a port on the EM 2400. Site differences in the use of UV-protectant bags for light-sensitive ingredients were observed as ingredients were connected to the EM 2400. At the CPP, light-sensitive ingredients were covered with UV-protectant bags, whereas in the Edmonton Zone this was not done.

To prevent connecting the tube to the wrong ingredient, barcode technology was used. Specifically, barcoded labels were affixed on each tube near the point of connection to the ingredient. This label and the barcode on the ingredient were scanned for comparison during set-up and when changing depleted vials to verify that the correct ingredient was selected. Similar barcode technology was not used to verify that the tube was connected to the correct port on the EM 2400. The EM 2400 is not able to detect if a tube is connected to the wrong port.

**Figure 7:** Automated compounding device set-up for PN



At all sites, an independent double check was performed by a second technician to verify the accuracy of the EM 2400 set-up. The EM 2400 tracks who set up and who double checked the set-up. Ensuring that each ingredient tube was connected to the correct port required both technicians to follow the tube from the ingredient container to the port. Furthermore, the manufacturer recommends that users be trained to physically hold the inlet that is being primed to verify visually that the tube with fluid flowing through it is attached to the correct port.

As shown in Figure 8, half of the port numbers were not visible to the user because they were obscured by the ports, caps, or tubes. Legibility of the port numbers within the users' line of sight were compromised by poor contrast between the number and the clear plastic background into which the number was embossed.

**Figure 8:** The EM 2400 port set-up



During an observational assessment undertaken for this review, a tube was observed to be connected to the incorrect port. This was caught during the double check. During the observational assessment, pharmacy technicians indicated that misconnection errors had occurred previously but were not caught during the double check. Instead the error was caught when one of the ingredients was depleted and the technician, while replacing the vial, was prompted to replace a partially full vial. This led to the discovery of the tube connection error and the re-compounding of affected PN admixtures. None of the incorrectly prepared bags were released from pharmacy. Of note, this was only tracked to account for waste but was not reported in the Reporting and Learning System (RLS) or the good catch reporting system.

Four tube connection errors with the EM 2400 occurred in other healthcare organizations and were reported in the Manufacturer and User Facility Device Experience (MAUDE) database.<sup>52,53,54,55</sup> These events occurred between 2009 and 2012. All tube connection errors, where specified, involved ports that were located directly next to each other.

### *Automated compounding device usage*

The EM 2400 interfaces with the Abacus system, which allows for automated compounding of customized PN admixtures using a scan of the barcoded PN label. At all sites, the PN labels were given to the pharmacy technician who then selected the appropriate PN bag, affixed or flagged the barcoded PN label to the bag, connected the bag to the EM 2400, and scanned the PN label. The EM 2400 then pumped the ingredients into the PN bag to reflect the order as entered into the Abacus system. While compounding, the pharmacy technician also replaced ingredient vials as needed and scanned the barcode on the vial and the barcode on the tube label. The EM 2400 then compared the two barcodes to ensure the correct vial was replaced. Once compounded, the filled PN bag weight was checked to ensure that the expected and actual weights did not differ by more than three per cent for adult patients and more than two per cent for neonatal and pediatric patients. A MixCheck report from the EM 2400 was also printed. This report outlines the ingredients and volumes (but not ordered doses) used to make the PN admixture; ingredients and volumes that need to be added manually; percentage difference between the expected and measured weight of the PN admixture; as well as any issues (e.g., bubbles in the tube, etc.) that may have been detected by the EM 2400 during the compounding process.



### *Manual additions to the PN admixture*

Ingredients were added manually to the PN admixture (as opposed to being added by the EM 2400) when the volume required was less than 0.2 mL, or if the ingredient was on back order to minimize waste of ingredients that remain in the tubes. In the Edmonton Zone, when ingredients were added manually, the partially compounded PN admixture was transferred into a second laminar airflow hood and a pharmacy technician drew up the required ingredients into syringes. Technicians at the UAH marked a line on the syringe to indicate the volume of the ingredient drawn up into the syringe and affixed onto the syringe a preprinted label showing the ingredient name and handwritten volume. Technicians at the RAH did not mark the line on the syringe but instead hand wrote the ingredient name and volume on the syringe. A double check was performed to verify patient identifiers, ingredients, concentrations, volume, and expiration dates before injection into the PN bag. Manual additions for as many as three different PN admixtures could be checked at one time. At the CPP in the Calgary Zone, manual additions were done in the same hood they were prepared in with the EM 2400, and manual additions were checked for only one PN admixture at a time. After completing the manual additives, a tamper-evident closure was used to seal the additive injection port at the RAH and CPP to deter access to the additive port; the additive port was left uncovered at the UAH.

### *Final check*

The labelled PN admixture, MixCheck report, syringes (if ingredients were manually added), and formula label were placed into a tray for a final check. The final check involved reviewing and comparing the MixCheck report to the PN label and syringes (as applicable) as well as adding any warning labels or filters. Those who conducted the final check varied among sites (pharmacist at the UAH; pharmacist or pharmacy technician at the RAH; pharmacy technician at the CPP). At only the RAH was the PN label compared to the original PN order during the final check.

### *PN dispensed*

Once compounded, the PN admixtures must be refrigerated for sterility and stability. According to the USP Chapter 797,<sup>27</sup> medium-risk-level compounded sterile products (such as PN) are allowed no more than 30 hours at controlled room temperature (including duration of infusion), and should otherwise be stored at refrigeration temperature (2–8°C). ASPEN states more generally that the “PN admixture should be kept refrigerated and protected from light exposure between the times it is dispensed until just before infusion”.<sup>6</sup>

At all sites, PN admixtures were stored on a counter in the pharmacy after being compounded and until packaged for dispensing. The admixtures were first refrigerated either when they were placed in a shipping box with ice (if shipped to another site, but not all sites ship in refrigerated boxes) or upon delivery to the nursing unit and refrigerated there. It was estimated that some PN admixtures would sit at room temperature on the pharmacy counter for up to six hours. Sites varied in the degree to which they protected PN admixtures from light. Staff at all three PN compounding sites (UAH, RAH, CPP) placed neonate PN admixtures in UV bags, but staff at only the CPP placed adult PN admixtures in UV bags.

Current safety guidelines recommend that lipid be dispensed from the pharmacy labelled as a patient-specific medication.<sup>6</sup> The process of providing lipids for patients was observed to vary among sites. Lipids were stored as ward stock on the nursing units at the UAH; staff at other sites (MCH, GN, and CPP)

dispensed lipids labelled as a patient-specific product; and unlabelled lipids were sent with the PN admixture when it was dispensed at the RAH.

## PN administered

According to ASPEN, safe administration of PN includes use of an appropriate in-line filter, independent double checks of the PN compared to the original order as well as of pump programming, the use of SMART pumps, and a requirement for line labelling and line tracing prior to administration of PN.<sup>6</sup>

Human factors research suggests that not all verification processes are created equal, nor are they equally effective in catching different types of errors. Specifically, independent double check processes are more likely to catch pump programming errors than inappropriate orders.<sup>56</sup> To ensure independent double check processes are user friendly, specific design features should be incorporated and tested through an iterative design approach using simulated scenarios that mimic actual workflow. This should be accomplished by an inter-professional team (i.e., unit manager and/or educator, frontline nurse, and human factors expert) that determines what should be checked. To assist and standardize the checking process for infusion pump programming, a checklist should be developed. The sequencing and grouping of information on the checklist should be consistent with the sequencing of information programmed into the pump and the order of information on PN labels and the order form.<sup>57</sup> Wording used on the checklist should be specific (i.e., indicate what and where information should be checked) to enhance the likelihood of detecting errors.<sup>58</sup> For example, rather than stating 'check rate', it should read 'compare PN rate on order to rate entered into pump'. Having both users initial the checklist, and including a place for this on the form, signals that the double check is complete.

Of the Edmonton Zone site policies provided by AHS, only the Stollery Children's Hospital has a specific policy<sup>15</sup> and procedure<sup>59</sup> related to PN administration. The NICU PN Policy outlines the frequency for line changes and the need for aseptic technique when changing tubing; there is no requirement for independent double checks or line labelling and line tracing.<sup>15</sup> The Stollery Children's Hospital Patient Care Procedure 4.5 Total Parenteral Nutrition does not indicate the need for independent double checks of PN admixtures, lines, or pump programming.<sup>59</sup>

Most policies and procedures provided by AHS related to intravenous medication administration do not require nurses to have the administration set connection and pump programming double checked by another nurse.<sup>59,60,61,62,63</sup> Exceptions include the Stollery Children's Hospital policy<sup>38</sup> and the interim Calgary Zone Medication Administration Policy.<sup>64</sup>

Observations of the PN administration process were conducted at three sites in the Edmonton Zone (UAH, RAH, MCH). Just before administering the PN, nurses selected the PN and lipid. Nurses compared ingredient doses and the ordered volume, as well as patient name and medical record number, unit, date, bag number, weight, and osmolarity on the PN label to the original order. Two of the sites (RAH and MCH) had a second nurse double check that the PN label (including ingredient doses) matched the order. The first nurse then hung the patient's PN and the lipid, and programmed the infusion pump. Nurses at only one site (MCH), and on only some of the units at that site, performed a double check to verify that the pump was correctly programmed. Nurses at only one of the three sites (MCH) added line labels to help verify the correct connections to the infusion pumps.

An analysis of the RLS reports from January 1 to June 30, 2013 indicated that of the 105 reports related to PN, nearly half (n = 48) involved administering the wrong dose or quantity of PN or lipid. Of these 48

instances, the wrong rate being entered into the infusion pump was reported 34 times, including 12 cases where the PN and lipid rates were switched when entered.

## **Parenteral nutrition oversight**

PN requires an institutional inter-professional system of oversight by health professionals with specialized expertise in nutrition support. This system ensures development and ongoing monitoring of adherence to policies, procedures, and practices that are consistent with published leading practice standards and guidelines across all departments involved in the PN process.<sup>2,6,30</sup> In addition, this oversight system should include an ongoing, systematic review of all PN-related adverse events, close calls, and hazards to identify deviations from leading practices or standards of care, in order to continually improve the safety of the institution's PN processes for patients.

Provincial PN oversight is provided by the AHS PN committee and led by a recently created Provincial Medical Advisor for Nutrition role funded through Nutrition Services. Decisions regarding the management of PN processes are generally guided by Nutrition Services with respect to what products are stocked and available to prescribers as well as the development of policies, procedures, and a nutrition support manual to support the PN process. At the zone and provincial level there are physicians and dietitians involved in developing patient-focused clinical practice guidelines for PN, while pharmacists provide information more focused on products used in PN. Enhancing inter-professional engagement is valuable for developing all the policies and procedures that oversee the PN process beyond the important clinical guidelines.<sup>6</sup>

AHS has developed some provincial procedures related to PN. The Nutrition Support Manual – Pediatric<sup>17</sup> provides clinical guidelines for prescribing and monitoring PN in pediatric patients. A similar manual is under development for neonates. During an interview it was noted that the Nutrition Support Manual – Adult<sup>65</sup> from the Edmonton Zone requires updating before it can be used province wide.

The nutrition support manuals do not address pharmacy PN processes or administration of PN by Nursing. Within the Pharmacy Department, provincial-level procedures related to aseptic technique and sterile compounding exist. Most of the policies and procedures that relate to PN processes within Pharmacy are legacy policies from health regions prior to the formation of AHS in 2008; PN-specific policies and procedures within Pharmacy could not be found. Consequently, policies, procedures, and processes pertaining to PN within Pharmacy vary across the province. There are no provincial PN standards currently in place within Pharmacy. Administration of PN within the Edmonton Zone is guided by zone-specific medication-related policies and procedures; there are no provincial policies or procedures currently in place for administration of PN.

Component shortages are an ongoing issue in PN and current safety recommendations suggest establishing organization-wide procedures to respond to shortages.<sup>6</sup> Interviews with Pharmacy staff indicate that processes are in place to manage product shortages; however, no PN-specific procedures have been developed at a zone or provincial level.

## **Parenteral nutrition knowledge and skills within Pharmacy**

Within AHS, there are pockets of significant expertise regarding PN. The Edmonton Zone, for example, has two qualified physician nutrition specialists who lead the weekly PN rounds. They have been recognized as national and international leaders in nutrition support, one of whom was the founding president of the Canadian Nutrition Society. The presence of physician nutrition specialists is limited in

other parts of Canada with major centres typically having only one physician nutrition specialist or none at all. Nutrition support expertise in Alberta is evidenced by the annual 'Western Canada Nutrition Days', a two-day educational event hosted by AHS Nutrition Services that includes the latest updates on PN practice, including safety.

Leading practice standards for PN safety recommend that pharmacists complete both a clinical (patient-focused) and pharmaceutical (product-focused) review of a PN order.<sup>6</sup> This requires specialized knowledge of both the clinical aspects of PN (indications, dosing of macro and micronutrients, complications) and the pharmaceutical aspects of PN (stability, compatibility, product selection for specific patient needs).<sup>6</sup> It is recommended that pharmacists be trained through a structured education program with annual competency assessments to demonstrate knowledge and skills.<sup>6</sup> The Board of Pharmacy Specialties (BPS) offers internationally recognized certification in Nutrition Support Pharmacy to address the care of patients who receive specialized nutrition support, including parenteral and enteral nutrition.<sup>66</sup>

In Canada, pharmacist involvement in the clinical aspects of PN (e.g., prescribing, patient monitoring, and inter-professional oversight of the PN process) is limited. There are only five pharmacists in Canada who are BPS-certified nutrition support pharmacists and none in Alberta. Interviews with pharmacists in both Edmonton and Calgary zones suggest that informal on-the-job training is used to introduce pharmacists to the role of PN pharmacist. There is no expectation to develop specialized knowledge of PN outside of what is learned by shadowing a more experienced pharmacist.

## **PN reporting and learning within Pharmacy**

A safety culture is often described as including five elements: an informed culture, a reporting culture, a learning culture, a just culture, and a flexible culture.<sup>67</sup> An *informed culture* involves collecting and analyzing relevant data regarding factors that affect the safety of a system. A *reporting culture* involves cultivating an atmosphere where people feel comfortable to report safety concerns and use safety reporting systems. A *learning culture* describes the degree to which an organization is willing and able to learn from mistakes and make changes as needed. Everyone has an important role to play in identifying, reporting, and addressing concerns or issues about the health system or organizational processes, and to share what is learned in support of ongoing safety and quality improvement.

AHS uses the RLS and good catch reporting system to capture data regarding hazards, close calls, and adverse events. Both systems are used provincially and allow electronic reporting. The RLS also allows for telephone reporting and the good catch reporting system allows for paper-based reporting. The good catch reporting system was implemented by the AHS Pharmacy Department in July 2012 to provide a means of capturing hazards and close calls that are detected before the product leaves the pharmacy. After the product leaves the pharmacy, staff would then report into the RLS. The RLS and good catch reports related to medications are collated, categorized, and then reviewed by the site and zone pharmacy management teams; data from the two systems are not merged.

Although 17,186 good catch reports were submitted into the good catch reporting system between July 2012 and March 2014, only 23 of these pertained to PN and of these, five were reported from the Edmonton Zone. This is much lower than expected given published error rates of 22 to 37 per cent related to compounding complex preparations such as PN.<sup>68</sup> This published error rate does not include close calls identified in the verification and review process, or the steps of labelling and dispensing from pharmacy.



Interviews with some staff involved with sterile compounding and PN preparation identified difficulties in reporting within both systems. Specifically, the RLS does not include PN in the medication drop-down list. Consequently, reporters need to select all medications included in the PN admixture, or select 'other' and use the free text box. Using the free text box is problematic when searching and analyzing data specific to PN. A number of terms were used to refer to PN in the RLS (e.g., parenteral nutrition, PN, total parenteral nutrition, TPN, peripheral parenteral nutrition, PPN, total nutrient admixture, TNA, amino acid dextrose solution, AADS) and this can be further complicated by potential spelling errors and abbreviations. When asked about the good catch reporting system, interviewees indicated they:

- Are not aware of the good catch reporting system.
- Do not believe it applies in certain situations (e.g., irregularities caught during order review do not need to be recorded; errors that are caught and fixed right away do not need to be recorded).
- Find the form difficult to use for PN.
- Find the system inconvenient (e.g., submitting reports while gowned and gloved for a sterile environment).
- Find the system time consuming.
- Are reluctant to report as it is viewed as "telling on one another".
- Will not report something that will otherwise go undetected.

Staff indicated during interviews that they were unaware of improvement initiatives or changes resulting from the good catch reports.

The adverse event that prompted this Health Quality Council of Alberta (HQCA) review of the AHS PN process also prompted other activities to learn from the event, including an internal AHS quality assurance review (QAR) and human factors evaluation. It also prompted Pharmacy to request that an independent double check of all master compounding recipes be completed provincially. At the site where the adverse event occurred, interviewees indicated that the frontline staff are aware of the AHS PN QAR review but to date the findings and recommendations from the review have not been shared with them; specific recommendations will be shared as changes are implemented. The Pharmacy leadership team (managers and above) received a presentation on the adverse event and the AHS response, focusing on the disclosure to patients and families and support offered to staff at the UAH. Although these elements are important, interviewees indicated there was little discussion about the findings (including context and rationale) and the recommendations that came from the AHS PN QAR and human factors evaluation as well as the applicability of the findings and recommendations to other pharmacy sites.

## ISSUES, ANALYSIS, RECOMMENDATIONS, AND ENABLING ACTIONS

### Parenteral nutrition as a high-alert medication

#### Issue

Parenteral nutrition (PN) is generally not acknowledged to be a high-alert medication in the Edmonton Zone pharmacy.

#### Analysis

A commonly expressed view during interviews with pharmacy staff across all sites was that compounding PN is complex and involves high-alert medication ingredients such as concentrated electrolytes, heparin, and insulin. Yet, there was a perception among many people interviewed that PN is not a high-alert medication or even a medication at all; some referred to it simply as a form of nutrition.

Current Alberta Health Services (AHS) policies may contribute to the confusion about whether PN is a high-alert medication; some do not include PN on the list (e.g., Pharmacy high-alert medication list)<sup>33</sup> and some indirectly identify PN as a high-alert medication through reference to the Institute for Safe Medication Practices (ISMP) high-alert medication list (e.g., Edmonton Zone high-alert medication directive).<sup>34</sup> It is insufficient to simply reference a list on an external website within a policy document because it then requires users to take the additional step of locating another document for the information they need.

Some nursing policies were noted to classify PN as a high-alert medication and require various mitigation strategies. For example, AHS Patient Care Policy 15.1, specific to the Stollery Children's Hospital, requires performing an independent double check of medication calculations and programming of infusion pumps for high-alert medications, which are specifically listed in the policy and which includes PN.<sup>38</sup>

Double checks, and in some instances independent double checks, are an important strategy to mitigate hazards associated with high-alert medications. Within pharmacy processes, the American Society for Parenteral and Enteral Nutrition (ASPEN) recommends a double check occur after entering PN orders, before manually injecting additives, and once the PN has been compounded. Furthermore, independent double checks should be performed following all calculations and unit of measure conversions as well as after a PN order is transcribed.<sup>6</sup> Double checks in the Edmonton Zone pharmacies' PN processes were noted to be either absent (e.g., no pharmacist verification of macro and micronutrient doses prescribed for patients, no double check of order transcription when entered by a pharmacist at one site), inconsistently applied (e.g., checking processes and information sources vary between sites, independent double checks are not truly independent, final product is not always checked against the original order) or ineffective/error prone (e.g., syringe pullback method of checking after preparation). Other double checking issues within PN preparation were noted:

- While independent double checks and line tracing are used during the ExactaMix 2400 (EM 2400) set-up, misconnection errors between the tube and the EM 2400 port have been missed.
- Manual additives for up to three PN bags can be in a laminar airflow hood simultaneously for the double check by a second technician in the Edmonton Zone; the ISMP recommends that only one compounded sterile preparation be prepared at a time to reduce the risk of mix-ups.<sup>31</sup>

- Variability in the final product check included who conducted the check (pharmacist versus pharmacy technician) and whether the original PN order was used as part of the check; only the Royal Alexandra Hospital (RAH) staff used the original PN order form. The ISMP<sup>46</sup> and ASPEN<sup>6</sup> recommend that the original order should be used in the final check.

Pump programming errors related to PN administration were frequently reported in the AHS Reporting and Learning System (RLS). Strategies to mitigate hazards associated with PN administration include independent double checks, line labelling and tracing, as well as simplified PN administration. Independent double checks are recommended for pump programming before administering high-alert medications but this strategy was rarely used in the Edmonton Zone, even at the Stollery Children's Hospital where it is required by policy.<sup>38</sup> Double checks comparing the PN label to the original order varied between sites. Line labelling and tracing was used in only one of three sites in the Edmonton Zone. PN administration in the Edmonton Zone involved 2-in-1 PN formulations, instead of the 3-in-1 PN formulations, for which only one administration set is required and only one pump is programmed to administer the PN admixture.

### Recommendation 1

Create and maintain an explicit list of high-alert medications that includes PN to ensure that risk-mitigation strategies are applied. Include or reference the list in all applicable policies and procedures across the province.

### Recommendation 2

Standardize pharmacy and nursing PN checking processes across the Edmonton Zone, implementing a true independent double check process to verify:

- Transcription of data before compounding of the PN admixture.
- Calculations and unit of measure conversions before compounding of the PN admixture.
- Alerts required to be overridden.
- Initial daily automated compounding device setup.
- Infusion pump settings before PN infusion begins.

#### Enabling action

- Ensure that independent double check processes are designed with and tested by human factors specialists before implementation.

### Recommendation 3

Ensure provincial use of strategies beyond double checks to mitigate pump set-up and programming hazards during PN preparation and administration.

#### Enabling actions

- Improve visual verification and connection to the correct port on the ExactaMix 2400 by increasing the visibility of the port number labelling (i.e., through more effective use of contrast

and number placement) and by applying a second label, with the port number, to the end of the tube near the port.

- Introduce 3-in-1 PN formulations within the Edmonton Zone for applicable patients.
- When lipids have to be administered separately with a 2-in-1 formulation, dispense the lipid from the pharmacy with a patient-specific label containing all the information recommended by *ASPEN PN Safety Consensus Recommendations*.

## Communicating parenteral nutrition prescriptions

### Issue

The PN ordering templates and processes in use within the Edmonton Zone do not comply with recognized leading practices.<sup>6</sup>

### Analysis

PN is prescribed in the Edmonton Zone using one of three standardized PN order forms onto which the prescriber handwrites the prescription. The order forms were last revised between 1998 and 2008 and both the order template and information provided on the back of the form require updating. The PN order template does not include all of the elements recommended by ASPEN (Table 4). Furthermore, ASPEN recommends avoiding handwritten orders; computerized prescriber order entry (CPOE) or an editable electronic document where CPOE is not possible are recommended.<sup>6</sup>

All PN orders across the province are transcribed by pharmacy into the Abacus system. Transcribing information is subject to human error. This hazard is amplified in the Edmonton Zone by inconsistencies in the sequence in which ingredients are listed on the PN order form in comparison to the Abacus interface, as well as inconsistencies in the dosing units of measure.

## Recommendation 4

Eliminate handwritten orders for PN in the Edmonton Zone and in the interim modify the current paper order forms to meet leading practice.

### Enabling actions

- Implement a computerized prescriber order entry (CPOE) system or other electronic format for communicating the PN order that includes clinical decision support (i.e., embedded practice guidelines) and is editable by both prescribers and pharmacy.
- Create a process to routinely update the clinical decision support information relating to PN (e.g., on the back of the PN order form or in CPOE or electronic ordering system) to ensure it reflects current leading practice.
- Plan to establish an interface between the CPOE system and the Abacus system to eliminate the transcription of PN orders within pharmacy. An interface should be considered at all sites in AHS using a CPOE system or planning to implement a CPOE system.
- Modify the PN order template (paper and electronic version) and the Abacus order entry system to comply with the *ASPEN PN Safety Consensus Recommendations* regarding order components, ingredient sequence, and units of measure.

## **Sterile compounding environment**

### **Issue**

The sterile compounding facilities in the pharmacies at the University of Alberta Hospital (UAH) and RAH do not comply with sterile compounding standards (i.e., United States Pharmacopeia [USP] Chapter 797<sup>27</sup> and the ISMP sterile compounding guidelines<sup>31</sup>) that have been established to protect admixtures from microbial and particulate contamination.

### **Analysis**

Licensed pharmacies in Alberta, including the RAH, are required to comply with a minimum practice and quality standards for compounded sterile preparations (e.g., USP Chapter 797<sup>27</sup> or comparable standard). Deficiencies in the sterile compounding environments exist at both the UAH and RAH and include being open to adjacent areas, the presence of high-particulate matter next to laminar airflow hoods, and room surfaces that do not comply with standards. Furthermore, the current state of the infrastructure at those sites limits the possibility of improvements, and a centralized pharmacy for the Edmonton Zone has never reached the approval stage.

### **Recommendation 5**

Improve sterile compounding environments in the Edmonton Zone to meet an established standard (e.g., United States Pharmacopeia Chapter 797, Institute for Safe Medication Practices sterile compounding guidelines).

### **Enabling action**

- Conduct a cost/benefit analysis to compare upgrading the current facilities with the development of a centralized pharmacy with a sterile compounding facility for the Edmonton Zone.

## **Parenteral nutrition knowledge and skills within Pharmacy**

### **Issue**

There are no explicit knowledge or skill requirements or related training and competency assessment programs for PN pharmacists within AHS. This compromises the ability of the pharmacy to conduct a thorough review and verification of a PN order, develop standardized processes that meet current ASPEN recommendations, and participate effectively in zone and province-wide oversight of PN.

### **Analysis**

Pharmacists in both Edmonton and Calgary were introduced to their role through an informal, on-the-job training process in which knowledge of PN was gained mainly through their daily activities unless pharmacists took an interest in learning more on their own. This training process results in variable knowledge and skills related to PN among pharmacists. Pharmacists in the Edmonton Zone described their role as primarily reviewing stability and compatibility issues with the PN order, particularly focusing on calcium phosphate solubility (pharmaceutical review), and not clinical (patient-focused) aspects of PN therapy unless unusual discrepancies were noted from the previous day's order. No policies or procedures could be found that specify the knowledge and skills required of a PN pharmacist,

outline a training process, or provide guidance on expectations of the PN order review and verification process.

The variable level of pharmacist knowledge and skills in PN limits aspects of PN support beyond order review and verification. This contributes to variability in PN preparation procedures within the Edmonton Zone and throughout the province. In the Edmonton Zone, variability was observed in (1) which tasks are performed by pharmacists versus pharmacy technicians; (2) processes used to calculate and create recipes following medication shortages; (3) separation in time or space when preparing neonate, pediatric, and adult PN admixtures; (4) the use of tamper-proof closures to protect injection sites after manually adding ingredients; (5) use of the original PN order as part of the final check; and (6) whether PN admixtures are protected from light or are refrigerated.

Pharmacy currently has a limited role in oversight decision-making related to PN. The variable level of pharmacist knowledge and skills in PN limits the role that pharmacy plays in PN oversight. Overall, limited specialized expertise in PN, as observed in the Edmonton Zone, is common across hospital pharmacy practice in Canada. Pharmacy brings a unique pharmaceutical perspective to the team but this requires a broader understanding of the clinical aspects of PN therapy to contribute fully to decision-making regarding product selection and development of policies and standardized procedures. Recently, Pharmacy was well represented in the Ad Hoc Nutrition Working Group that reviewed intravenous fat emulsion products for the AHS Formulary, and there is an opportunity to build on this level of pharmacy involvement in PN.

## Recommendation 6

Develop a structured training process with annual competency assessment for PN pharmacists throughout AHS with clearly defined expectations for knowledge and skills related to their role in the PN process as well as specialized qualifications for pharmacists involved in PN oversight.

### Enabling actions

- Training for all PN pharmacists should address both clinical and pharmaceutical aspects of PN therapy and highlight current leading practice standards for all components of the PN process.
- Support a small team of pharmacists to develop specialized practice (for example, Board Certified Nutrition Support Pharmacist designation or equivalent level of expertise) in nutrition support, who would participate in provincial oversight of the PN process.

## Recommendation 7

Develop PN-specific policies and standardized procedures within the Pharmacy Department at the provincial level where possible (and within the Edmonton Zone at a minimum) that address the pharmacy components of the PN process (order verification and review; compounding, labelling, and dispensing).

### Enabling action

- Use the ASPEN *PN Safety Consensus Recommendations* and leading practice recommendations from the Institute for Safe Medication Practices and the Canadian Society of Hospital Pharmacists (currently under development) related to sterile compounding to inform the development of the policies and procedures.

## PN reporting and learning within Pharmacy

### Issue

The Edmonton Zone pharmacy departments are not fully optimizing the good catch and Reporting and Learning systems for improving PN safety.

### Analysis

A safety culture is often described as including five elements: an informed culture, a reporting culture, a learning culture, a just culture, and a flexible culture.<sup>67</sup> In terms of an informed, a reporting and a learning culture, AHS has an electronic provincial reporting system to capture data regarding hazards, close calls, and adverse events. The Pharmacy Department has also developed a good catch reporting system to detect hazards within pharmacy processes at all sites in the province. However, very few good catch reports are related to PN. Feedback gathered from some pharmacy staff about good catch reporting indicated they:

- Are not aware of the good catch reporting system.
- Do not believe it applies in certain situations (e.g., irregularities caught during order review do not need to be recorded; errors that are caught and fixed right away do not need to be recorded).
- Find the form difficult to use for PN.
- Find the system inconvenient (e.g., submitting reports while gowned and gloved for a sterile environment).
- Find the system time consuming.
- Are reluctant to report as it is viewed as “telling on one another”.
- Will not report something that will otherwise go undetected.

The RLS does not include PN in the medication drop-down list. Consequently, reporters need to select all of the medications included in the PN admixture, or select ‘other’ and use the free text box. Using the free text box is problematic when searching and analyzing data specific to PN reported in these systems. Data from the two systems are not combined for aggregated analysis.

Information about the AHS PN quality assurance review (QAR) and the human factors evaluation was not widely distributed. Pharmacy leadership (managers and above) received a presentation on the adverse event and AHS response, but there was little discussion about the findings (including context and rationale), recommendations, and applicability for implementation at other pharmacy sites. At the site where the adverse event occurred, the review team heard frontline staff were aware that an internal review was done but the staff were not aware of the findings and recommendations. Limited or lack of understanding of the context and rationale for recommendations often becomes a barrier to organizational learning and the acceptance and transfer of recommendations into practice.<sup>69</sup> Feedback to staff is important for validating the usefulness of reporting and to share learnings from reporting and from quality assurance reviews.

### Recommendation 8

Pharmacy staff (management and frontline) to regularly review and trend site, zone, and provincial data related to sterile compounding and PN from the reporting systems to identify system issues and actions for improvement.

## Enabling actions

- Enhance the structure and process for staff working in the sterile compounding and PN preparation area to more easily report hazards and close calls.
- Include PN as a listed medication in the Reporting and Learning System to make it easier to enter and analyze hazards, close calls, and adverse events.

## Recommendation 9

Share the findings and recommendations from the AHS PN quality assurance review across all AHS pharmacies with the expectation that site leadership implement recommendations as appropriate. Also share the findings and recommendations with frontline staff to increase awareness of hazards related to PN.



## SUPPLEMENTARY RECOMMENDATION

### Parenteral nutrition order verification in the Calgary Zone

#### Issue

The double check to verify parenteral nutrition (PN) order entry at the Central Production Pharmacy (CPP) occurs, in some cases, after the PN admixture is compounded, and potentially after the product has been delivered to the nursing unit.

#### Analysis

At the acute care sites in Calgary, PN orders are sent to the CPP via computerized prescriber order entry (CPOE; i.e., Sunrise Clinical Manager), printed, and then transcribed into Abacus by a pharmacist. After order entry into Abacus, the PN label is printed and used to initiate the PN compounding process. The original order is not used in the checking processes after transcription, though this is recommended by the American Society for Parenteral and Enteral Nutrition (ASPEN). A double check to validate the accuracy of order entry into Abacus is performed by a second pharmacist, and depending on scheduling may occur after the compounding process has started and potentially after administration. If issues are detected during the double check, the pharmacist has to call a series of people within the CPP to see (1) if the label was sent into the compounding area, (2) if the admixture was compounded, and (3) if the final product check occurred and the PN admixture was shipped. If the PN admixture was shipped, then the pharmacist has to call the receiving pharmacy, and potentially the nursing unit, to advise them of the product recall and inform them that a new PN admixture will be sent (assuming PN compounding had not finished for the day). ASPEN recommends that all PN orders that require transcription are independently double checked prior to compounding the PN admixture.<sup>6</sup>

#### Recommendation 10

Verify transcription of the PN order into Abacus by a pharmacist (other than the one who transcribed the order) before compounding the PN admixture at the Central Production Pharmacy.

#### Prescribed dosing irregularities

A memo sent to Alberta Health Services (AHS) described dosing irregularities observed on some PN orders during site visits (Appendix V). In response, AHS conducted an internal review (Appendix VI) and solicited feedback from the Health Quality Council of Alberta (HQCA; Appendix VII).

## APPENDICES

## Appendix I: Alberta Health Services request letter



Our File: E1304171

April 26, 2013

Dr. John Cowell  
Chief Executive Officer  
Health Quality Council of Alberta  
210-811 14 Street NW  
Calgary Alberta T2N 2A4

Dear Dr. Cowell:

**Re: Request for HQCA Quality Assurance Review – Total Parenteral Nutrition**

Based on information provided to Dr. Yiu, Executive Vice President, Quality & Medical Affairs and I, I am requesting that the Health Quality Council of Alberta conduct an independent review, under section 15 of its Act .

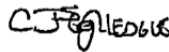
The review will encompass the AHS processes related to the prescribing, ordering, preparing, checking, administering, monitoring and applicable outcomes for delivery of Total Parenteral Nutrition (TPN) in all age groups (neonates, paediatrics and adults) within the Edmonton Zone. Practices and procedures in the Edmonton Zone will be used to inform the HQCA understanding of current state.

A more detailed Terms of Reference for the review will be developed by representatives of our organizations without delay; with a project completion date no later than November 29, 2013.

A joint AHS/Covenant Health Quality Assurance Review has already been launched to review the specific circumstances of recent TPN dose calculation errors. A copy of their report will be provided to the Chair of HQCA Quality Assurance Committee assigned to this review for information purposes.

Thank you for your collaboration in improving the quality and safety of Albertans.

Yours truly,



Chris Eagle, MD, MBA, FRCPC  
President and Chief Executive Officer

Copy: Dr. Verna Yiu, Executive Vice President, Quality & Medical Affairs, Alberta Health Services

---

14th Floor North Tower • Seventh Street Plaza

10030 107 Street NW, Edmonton AB T5J 3E4 Tel: 780-342-2000 Fax: 780-342-2060 [www.albertahealthservices.ca](http://www.albertahealthservices.ca)

## Appendix II: Terms of reference



### HQCA Total Parenteral Nutrition Review

#### Terms of Reference

##### Purpose

Pursuant to section 3 (1), 6 (2), 15 (2), 16 (1) of the *Health Quality Council of Alberta Act*, the HQCA will conduct an independent review of the AHS processes related to all aspects of Total Parenteral Nutrition (TPN) in the Edmonton Zone.

##### Objectives

The HQCA will, through a quality assurance committee under section 9 of the *Alberta Evidence Act*, conduct a review of the implications for quality and patient safety with respect to the processes of TPN preparation in the Edmonton Zone that includes but is not limited to:

- All age groups (neonates, pediatrics and adults)
- Prescribing, ordering, preparing, administering, monitoring and applicable outcomes in the delivery of TPN
- Identifying and benchmarking leading practices related to process and outcome indicators for these TPN processes and applicable patient outcomes

In order to ensure the quality and safety of the preparation and delivery of TPN in Alberta, and based on the findings and analysis of the investigation, the HQCA will make recommendations about the implications for quality and patient safety with respect to the above.

##### Scope

This review will not include:

- Preparation of TPN in facilities outside of Alberta Health Services
- Preparation of TPN in facilities outside of the Edmonton zone

##### Stakeholders

Stakeholders that may be engaged in the review process include but are not limited to:

- Alberta Health Services
- Alberta Health
- Healthcare professional colleges
- Patients
- Physicians

##### Deliverables and Timelines

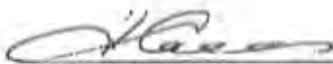
- A full report of the findings and up to five highest priority recommendations will be presented to the Alberta Health Services CEO by January 31<sup>st</sup>, 2014, and will be made public.



- Prompt reporting of any factual irregularities that may immediately affect patient safety will be provided to Dr. Verna Yiu, EVP/CMO, Quality and Medical Affairs.
- Recommended cost of the review is not to exceed \$150,000.

Regular updates on the status of the review will be provided by the Health Quality Council of Alberta to Alberta Health Services.

Approved by:



John W. F. Cowell M.Sc., MD, CCFP, FRCPC  
Chief Executive Officer  
HQCA

MAY 31, 2013  
Date



Dr. Chris Eagle MD, MBA, FRCPC  
President and Chief Executive Officer  
Alberta Health Services

3 June 2013  
Date

## Appendix III: Letter of scope change



Promoting and improving patient safety and health service quality across Alberta

FILE COPY

February 24, 2014

Verna Yiu,  
VP Quality & Chief Medical Officer  
Alberta Health Services  
Seventh Street Plaza, North Tower, 14-030  
10030 - 107 St.  
Edmonton, AB T5J 3E4

Dear Dr. Yiu

**Re: Total Parenteral Nutrition Review**

As per our verbal discussion of January 30, 2014, HQCA will submit the abbreviated TPN Report to AHS by April 30, 2014. Basically, the Report will include the detailed process mapping of the ordering, preparing and administration processes, as well as information gathered from the literature. The Report will also include recommendations on ordering, preparation and administration of TPN.

We will also include a short list of further work, including: an analysis and recommendations on the aspects of prescribing, monitoring and applicable outcomes of TPN, the identification and benchmarking of process and outcome indicators of TPN, per the TOR's, that could be completed to broaden the Report.

AHS will then review and may choose to ask HQCA to provide the further analysis and information if considered value add and/or not a duplication of work previously undertaken by AHS.

Yours sincerely,



Patricia Pelton  
Acting CEO, HQCA  
Chair, HQCA Quality Assurance Committee

## **Appendix IV: Literature review**



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# **PARENTERAL NUTRITION LITERATURE REVIEW**

Prepared for  
**Health Quality Council of Alberta**

October, 2013



## Parenteral Nutrition Literature Review

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## 1.0 Executive Summary

Since its inception in the late 1960s, parenteral nutrition therapy has been widely adopted with significant clinical benefits. Despite a valuable role in patient care, it has been recognized to be an invasive therapy with serious potential for complications, adverse events and even death.

Through clinical studies, enteral nutrition has evolved as the preferred route by which people receive nutrition. While parenteral therapy continues to be a valued and lifesaving option for patients who otherwise could not be fed through the gastrointestinal tract, this research has led to refinement in decision making regarding patients who are appropriate to receive parenteral nutrition, improvement in parenteral nutrition formulations and development of protocols for safe and effective prescribing, ordering, preparation and administration of parenteral nutrition.

The purpose of this review was to document information from the literature regarding the implications for quality and patient safety with respect to the processes of parenteral nutrition including:

- All age groups (neonates, pediatrics and adults)
- Prescribing, preparing, administering, monitoring and applicable outcomes in the delivery of parenteral nutrition
- Identifying and benchmarking leading practices related to process and outcome indicators for these parenteral nutrition processes and applicable patient outcomes.

Systematic reviews and meta analyses done over the past 5 years as well as grey literature from associations, societies, clinical practice guideline developers and selected journals in the area of parenteral nutrition were included in the literature review.

Subjects addressed in this report include current views on and applications for the clinical use of parenteral nutrition, complications of parenteral nutrition, and methods and safe practices of parenteral nutrition. Other issues and considerations, such as shortages of nutrition product and inappropriate use of parenteral nutrition are addressed. The vital need for caregiver expertise in the area of parenteral nutrition is emphasized.

The American Society for Parenteral and Enteral Nutrition (ASPEN) has published extensive literature and practice guidelines related to parenteral nutrition and is referenced widely in this report.

## Abbreviations

ASPEN	American Society for Parenteral and Enteral Nutrition
BPD	Bronchopulmonary dysplasia
CRBSI	Catheter related blood stream infection
CVC	Central venous catheter
DEHP	Diethyl-hexyl-phthalate
EFA	Essential fatty acid
EFAD	Essential fatty acid deficiency
EN	Enteral nutrition
ESPEN	European Society for Clinical Nutrition and Metabolism
GI	Gastrointestinal
HPN	Home parenteral nutrition
ICU	Intensive care unit
IVFE	Intravenous fat emulsion
NEC	Necrotizing enterocolitis
NST	Nutrition support team
PICU	Pediatric intensive care unit
PN	Parenteral nutrition
PNAC	Parenteral nutrition associated cholestasis
PNALD	Parenteral nutrition associated liver disease
RDS	Respiratory distress syndrome
SBS	Short bowel syndrome
SNS	Specialized nutrition support
TNA	Total nutrition admixture
VAD	Venous access device



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## Definitions

**2-in-1 formulations** - Parenteral nutrition formulations that contain 2 macronutrients (amino acids, dextrose) in 1 bag or chamber (no intravenous fat emulsions included)

**3-in-1 formulations** - Parenteral nutrition formulations that contain all 3 macronutrients (amino acids, dextrose and intravenous fat emulsions) in 1 bag or chamber

**Automated compounding device** - A device used in the preparation of parenteral nutrition that automates the transfer of dextrose, amino acids, fat emulsion and sterile water as well as smaller volume injectables such as electrolytes and minerals to the final PN container

**Central parenteral nutrition** - Parenteral nutrition delivered into a high flow (ie. central) vein, usually the superior vena cava adjacent to the right atrium

**Catheter related sepsis** - Clinical picture of spiking fever and chills attributed to the passage of microorganisms. "Touch contamination" includes contamination of the infusion fluid, infusion bag, administration set, and all connections. The source of microorganisms include touch contamination (along inner aspect of catheter) and hematogenous spread (from other site in the body), as well as the major source skin colonization (along outer aspect of catheter).

**Diethyl-hexyl-phthalate** - A plasticizer used in various intravenous administration sets or plastic infusion bags

**Dosing weight** - The weight used by the clinician in determining nutrient doses

**Enteral nutrition** - The non-volitional delivery of nutrients by feeding tube into the gastrointestinal tract

**Expiration date** - The date established from scientific studies to meet regulatory requirements for commercially manufactured products beyond which the product should not be used

**Hang time** - The prescribed period of time beginning with the flow of a fluid through an administration set and catheter or feeding tube and ending with the completion of the infusion

**Hyperalimentation** - An outdated term referring to parenteral nutrition (PN) which no longer aims to overprescribe calories for a patient's needs

**Parenteral nutrition** - The administration of nutrients intravenously

**Peripheral parenteral nutrition** - Parenteral nutrition delivered into a peripheral vein, usually of the hand or forearm

**Specialized nutrition support** - The provision of nutrients orally, enterally or parenterally with therapeutic intent

**Total nutrient admixture** - A parenteral nutrition formulation containing IVFE as well as the other components of PN (carbohydrate, amino acids, vitamins, minerals, trace elements, water and other additives) in a single container; synonymous with "3-in-1" formulations/admixtures

**Venous access devices** - Catheters placed directly into the venous system for infusion therapy and/or phlebotomy

## 2.0 Introduction

### Terminology

Parenteral nutrition means ‘administration of nutrients intravenously’. Enteral nutrition means ‘delivery of nutrients by tube into the gastrointestinal tract’. Both parenteral and enteral nutrition are considered means of ‘artificial nutrition’ as they replace, in full or in part, the normal means of nutrition taken by mouth. Some patients may receive nutrition by both routes at the same time (eg, during periods of transition).

Parenteral nutrition may be administered centrally or peripherally. Central parenteral nutrition is delivered intravenously into a high flow vein, usually the superior vena cava adjacent to the right atrium. Peripheral parenteral nutrition is delivered into a peripheral vein, usually of the hand or forearm. Central venous access is generally required to provide nutrients at greater concentrations than is possible through peripheral veins.

### Background

Parenteral therapy has been available clinically since the late 1960s. With its inception, patients who previously could not be fed were able to receive essential nutrients. It has always been recognized that there were risks associated with PN; more recently the balance of risk versus benefit has been better managed. These risks and mitigation practices are addressed in this report.

The purpose of this literature review was to document information from the literature regarding the implications for quality and patient safety with respect to the processes of parenteral nutrition including:

- All age groups (neonates, pediatrics and adults)
- Prescribing, order review, preparing, administering, monitoring and applicable outcomes in the delivery of parenteral nutrition
- Identifying and benchmarking leading practices related to process and outcome indicators for these parenteral nutrition processes and applicable patient outcomes.



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### 3.0 Project Methods

#### 3.1 Literature Review

##### Literature Search Methodology

Comprehensive search strategies were developed by an information specialist (TD) using a combination of subject headings and keywords and adapted for 3 electronic bibliographic databases. Searches were conducted in the following electronic databases: MEDLINE (Ovid, 1946 to July Week 4 2013), EMBASE (Ovid, 1980 to 2013 Week 30), and EBM Reviews - Cochrane Database of Systematic Reviews 2005 to July 2013 (Ovid). For the search strategies, a combination of subject headings and keywords were developed for each electronic resource using the following terms: total parenteral nutrition and TPN. The search was limited by study design and publication status to systematic reviews and meta analyses in English and covered 2008 to August 4, 2013. References were managed using Reference Manager, Version 11 bibliographic software (Thomson ISI ResearchSoft, Carlsbad, CA).

##### Study Selection

A two-step process for screening of the systematic reviews and meta analyses was used. First, one reviewer (TD) screened the titles and abstracts (when available) to determine if a systematic review or meta analysis met the general inclusion criteria. General inclusion criteria included parenteral nutrition (PN) and prescribing, ordering, preparing, administering, monitoring, or any outcomes in the delivery of PN. Each systematic review or meta analyses that was determined to be either unclear or included by TD, was then further screened by a second reviewer (JA). Full text of articles that were screened as included or unclear by JA were retrieved for formal review.

A Reference Manager database was constructed from all the articles from the reference lists of the included systematic reviews and meta analyses. This database was then limited to English articles published between 2008 and 2013. These articles were then screened by TD for the requested topics of: prescribing, ordering, preparing, administering, monitoring, or any outcomes in the delivery of PN. Each article that was determined to be either unclear or included by TD, was then further screened by a second reviewer (JA). Full text of articles that were screened as included or unclear by JA were retrieved for formal review.

Grey literature (associations, societies and clinical practice guideline developers) and selected journals were searched for guidelines, clinical practice guidelines, CPGs, best practices, protocols, position statement, consensus statements, statements, or care guidelines that addressed prescribing, ordering, preparing, and administering PN.

#### 3.2 Search Findings

The majority of the articles from the systematic review and meta analyses search were found to be clinically oriented, largely addressing clinical applications for PN and clinical complication of using PN. Very few articles were identified that addressed care processes, particularly related to best practices and potential considerations in prescribing, ordering, preparing, and administering PN. In consultation with the client, the HQCA, the search was broadened to include a focused grey literature search of



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## Parenteral Nutrition Literature Review

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associations, societies, clinical practice guideline developers, and selected journals in the area of parenteral nutrition. A search for guidelines was also run in MEDLINE (Ovid, 1946 to August Week 3, 2013) and CINAHL Plus with Full Text (Cumulative Index to Nursing & Allied Health Literature [EBSCOhost]).

Electronic search strategies are presented in Appendix 1.

Grey literature websites are presented in Appendix 1.



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## 4.0 Results

### 4.1 Clinical Use of Parenteral Nutrition

#### Importance of Nutrition to Critically Ill Patients

The significance of nutrition in the hospital setting, particularly in intensive care, is well documented in the literature. Delivering early nutrition support therapy is described as a proactive therapeutic strategy with important benefits including reduction in disease severity, diminished complications, decrease in length of stay in the intensive care unit (ICU) and otherwise favorable impact on patient outcome.<sup>1</sup>

The European Society for Clinical Nutrition & Metabolism (ESPEN) recommends that patients should be fed because 'starvation or underfeeding in ICU patients is associated with increased morbidity and mortality'.<sup>2</sup>

Since its inception and over the past four decades, parenteral nutrition (PN) has become an important primary and adjunctive therapy for a number of disease states. It provides benefit for patients who have significant disruption in gastrointestinal (GI) function. To patients who have permanent loss of the GI tract, PN offers a lifeline.<sup>3</sup>

#### Enteral Nutrition as the Preferred Route of Feeding

In recent years, the literature has emphasized that enteral nutrition is the preferred route of feeding for critically ill patients who require nutrition support therapy and that parenteral nutrition should be reserved for those who are malnourished and unable to be safely fed through enteral means<sup>4</sup>. Only if there is a clear contraindication to enteral feeding should parenteral nutrition be used, and then only until enteral feeding can meet the patient's needs.<sup>5</sup> A number of studies<sup>6</sup> reported that patients receiving PN may experience an increase in all infections, in catheter related blood stream infections and in hospital length of stay.

For these reasons, as well as other metabolic and mechanical issues, PN has been shown to carry inherent risks and should be considered only in patients with inability to receive enteral nutrition.<sup>6</sup> As well, in patients stabilized on PN, efforts should be made periodically to reinstitute EN. As tolerance improves and the volume of EN calories delivered increases, the volume of PN can be reduced.<sup>1</sup>

The basic indication for using PN is to provide nutrition when the gastrointestinal tract is not functioning or is inaccessible. The general guideline is that PN is required if an individual cannot meet their nutritional and/or fluid requirements by mouth or via an enteral feeding tube.<sup>7</sup>

The American Society for Parenteral and Enteral Nutrition's (ASPEN) published indications for Nutrition Support Therapy<sup>8</sup> are as follows:

- Specialized nutrition support (SNS) should be used in patients who cannot meet their nutrient requirement by oral intake.
- When SNS is required, EN should generally be used in preference to PN.
- When SNS is indicated, PN should be used when the GI tract is not functional or cannot be accessed and in patients who cannot be adequately nourished by oral diets or EN.

- SNS should be initiated in patients with inadequate oral intake for 7-14 days or in patients in whom inadequate oral intake is expected over a 7-14 day period.

#### Use of Parenteral Nutrition in Adults

With new knowledge and technology, patient selection for PN therapy has improved. The ASPEN provided the following guidelines for provision of specialized nutrition support to adult critically ill patients:<sup>1</sup>

- If early enteral nutrition is not feasible or available the first 7 days following admission to the ICU, no nutrition support therapy should be provided. In the patient who was previously healthy prior to critical illness with no evidence of protein-calorie malnutrition, use of PN should be reserved and initiated only after the first 7 days of hospitalization (when EN is not available).
- If there is evidence of protein-calorie malnutrition on admission and EN is not feasible, it is appropriate to initiate PN as soon as possible following admission and adequate resuscitation.

The ESPEN guideline is that patients who are not expected to be on normal nutrition within 3 days should receive parenteral nutrition within 24 to 48 hours if enteral nutrition is contraindicated or if they cannot tolerate enteral nutrition.<sup>2</sup>

Some individuals will manage to take some nutrition by mouth and therefore only require supplementary PN. The ESPEN recommends that all patients receiving less than their targeted enteral feeding after 2 days should be considered for supplementary parenteral nutrition.<sup>2</sup>

#### Use of Parenteral Nutrition in Children and Neonates

The ASPEN's Nutrition Support Guideline Recommendations for critically ill pediatric patients are as follows:<sup>3</sup>

- Children admitted with critical illnesses should undergo nutrition screening to identify those with existing malnutrition and those who are nutritionally at risk. A formal nutrition assessment with the development of a nutrition care plan should be required, especially in those children with premorbid malnutrition.
- Energy expenditure should be assessed throughout the course of illness to determine the energy needs of critically ill children. Estimates of energy expenditure using available standard equations are often unreliable.
- There are insufficient data to make evidence based recommendations for macronutrient intake in critically ill children. After determination of energy needs for the critically ill child, the rational partitioning of the major substrates should be based upon understanding of protein metabolism and carbohydrate and lipid handling during critical illness.
- In critically ill children with a functioning gastrointestinal tract, enteral nutrition should be the preferred mode of nutrient provision if tolerated.
- Based on available pediatric data, the routine use of immunonutrition or immune enhancing diets/nutrients in critically ill children is not recommended.
- A specialized nutrition support team in the pediatric intensive care unit (PICU) and aggressive feeding protocols may enhance the overall delivery of nutrition with shorter time to goal nutrition, increased delivery of EN and decreased use of parenteral nutrition.

Toronto's Sick Kids Hospital guidelines for use of PN<sup>10</sup> recommend that children unable to ingest or absorb oral or enterally delivered nutrients for a significant period are candidates for PN. They include infants who have gone 2 to 3 days without adequate intake and older children who have gone 4 to 5 days. Although the GI tract should be used whenever possible, parenteral nutrition may be used as a primary source of nutrition, providing full nutrition support or as a partial source, providing nutrition repletion or augmentation in patients unable to tolerate full enteral nutrition.

Nutrition for premature infants is evolving and has been advanced with the introduction of PN. There is now recognition of the need to nourish very preterm infants from the time they are born<sup>11</sup>. In the small preterm infant, starvation for just one day may be detrimental and, where it is clear that enteral feeds will not be tolerated soon, PN should be instituted shortly after birth.<sup>12</sup>

For extremely small premature infants, due to immaturity of the gut, achieving enteral feeding in a timely fashion may not be possible. The ability of PN to meet a premature infant's nutritional needs has improved steadily over the past number of years. The major complication of parenteral nutrition, PN associated cholestasis, is ultimately treated by advancing enteral feeds as early as possible.

Manipulating nutrient dosing and specific ingredients such as with the newer lipid preparations shows some promise in reversing the hepatic damage of prolonged PN.<sup>13</sup>

King Edward Memorial Hospital in Perth, Western Australia published the following indicators for use of PN for infants:<sup>14</sup>

- Prematurity <32 weeks gestation and/or <1500 g
- Infants <35 weeks who are unlikely to achieve full enteral feeds by day 5
- Necrotizing enterocolitis
- Surgically correctable gastrointestinal tract anomalies
- Prolonged nil by mouth due to other surgery
- Short bowel syndrome

The Neonatal Total Parenteral Nutrition Clinical Practice Guideline from Credit Valley Hospital in Mississauga, Ontario, states the following clinical considerations for use of PN in infants:<sup>15</sup>

- Infants <1500 g should be started on PN by 48 hours of age unless they are expected to be tolerating full feeds within 24-48 hours.
- Infants >1500 g should be started on PN by 72 hours of age if they are not expected to be enterally fed by day 5.

Selection criteria for those infants to receive PN at Credit Valley Hospital are:<sup>15</sup>

- Infants with respiratory distress syndrome (RDS) or bronchopulmonary dysplasia (BPD) or gastrointestinal malformations or necrotizing enterocolitis (NEC) who are unable to tolerate feedings
- Infants <1500 g who cannot be maintained entirely on feedings because of GI tract hypomotility, low gastric capacity and other aspects of prematurity
- Infants with absorption problems, short bowel syndrome, or intractable diarrhea.

### Evolution in Use of Parenteral Nutrition

With the introduction of PN in the late 1960s, for the first time, any sick patient who was unable to eat could be artificially fed intravenously. As a consequence, most patients in ICU were given PN if they remained unable to eat after 3-5 days of critical illness. Experience soon showed that this feeding technique was associated with serious septic and metabolic complications having potential to worsen patients' outcomes<sup>16</sup>. With this realization, controversy and debate arose around the use of PN.

Subsequently, new knowledge and technology have improved patient selection for PN therapy. Refinement of PN will continue to make it a useful therapy in the management of patients with dysfunctional GI tracts.<sup>3</sup>

### Clinical Applications of Parenteral Nutrition

The literature provides a significant amount of information regarding the efficacy of clinical applications of parenteral therapy. The ASPEN has published information regarding the preferred nutrition support options for a number of diagnostic categories.<sup>4</sup>

#### *Short Bowel Syndrome*

There is general agreement that the introduction of PN in the last 60s dramatically improved the management and outcomes of patients with Short Bowel Syndrome (SBS). Today, SBS is an indication for the use of PN. Attention is given to intestinal rehabilitation through nutritional, pharmacologic and surgical approaches to achieve the ultimate goal of enteral nutrition.<sup>17</sup>

#### *Severe Acute Pancreatitis*

Review of studies comparing the safety of enteral and parenteral nutrition among patients with severe acute pancreatitis showed that enteral nutrition was associated with a significantly lower risk of infections, pancreas related complications, organ failure and mortality in patients. There was no significant difference in the overall risk of artificial nutrition-related complications and non-pancreas-related complications. The conclusion was that enteral nutrition appears safer than PN in nutrition support of patients with severe acute pancreatitis.<sup>18</sup>

The ASPEN recommends that patients with severe acute pancreatitis be provided with early enteral therapy, stating that EN compared to PN reduces infectious morbidity, hospital length of stay, need for surgical intervention multiple organ failure and mortality.<sup>4</sup>

#### *Major Upper Gastrointestinal Surgery*

Systematic reviews of studies into enteral versus parenteral nutrition following major upper gastrointestinal surgery demonstrated enteral nutrition to be associated with shorter hospital stay, lower incidence of severe or infectious conditions, lower severity of complications and decreased cost as compared to parenteral nutrition. For patients undergoing elective major upper gastrointestinal surgery requiring post-operative nutritional support, enteral feeding should be considered as the most desirable form of post-operative feeding.<sup>19</sup> Early enteral nutrition can be safely given in the immediate postoperative period after major digestive surgery, and should be considered superior to PN barring exceptional clinical scenarios.<sup>20</sup>



### *Enterocutaneous fistulas*

In absence of definitive studies, there is little evidence of benefit of PN in healing of intestinal mucosa and spontaneous closure of fistulae. In view of the many potentially adverse effects of PN, the general view is that enteral nutrition is the preferred route of administration of nutrition to all patients unless there is a clear contraindication to enteral feeding. There is currently no evidence that this principal should not also apply to enterocutaneous fistula patients.<sup>3</sup>

### *Crohn's Disease & Ulcerative Colitis*

In patients with Crohn's disease and ulcerative colitis, parenteral nutrition is indicated when enteral nutrition is not possible or should be avoided for medical reasons. PN should only be used in complicated cases when ileus is present or probable.<sup>21</sup>

### *Bone Marrow Transplant*

Bone marrow transplant patients can experience prolonged poor appetite with vomiting and diarrhea which could result in malnutrition. Where possible, use of intravenous fluids and oral diet should be considered in preference to parenteral nutrition. If a patient suffers with severe gastrointestinal failure even with a trial of enteral feeding, PN with the addition of glutamine could be considered. Caution in the routine use of PN is required because of the increased risk of infection.<sup>22</sup>

### *Anorexia Nervosa*

Before initiating artificial nutrition, the degree of collaboration of the patient with anorexia nervosa must be assessed and an attempt must always be made to convince him/her of the benefits of natural oral feeding. Parenteral nutrition should not be used for patients with anorexia nervosa unless the patient refuses nasogastric feeding and/or presents gastrointestinal dysfunction.<sup>23</sup>

### Home Parenteral Therapy

When patients receive parenteral therapy in hospital, they are sometimes required to continue the therapy following discharge at home because of inability to be fed enterally or to tolerate sufficient enteral calories to provide their nutrition requirements. Although discharge to home parenteral nutrition (HPN) is complex and can be associated with both immediate and long term complications, it can be successfully achieved. An optimal HPN discharge requires communication with home care providers, development of guidelines, protocols and policies for HPN, and development of educational materials for patients and caregivers. An appropriate mechanism for follow-up and monitoring in the home should be established for all HPN patients.<sup>24</sup>

## 4.2 Clinical Complications of Parenteral Nutrition

Complications related to the usual clinical use of parenteral nutrition have been identified and addressed in the literature. These fall into 3 broad categories: those related to catheter placement (eg, malposition), those related to line care (eg, infection), and metabolic complications (acute and long term).

### 1. Catheter Malposition

Catheter malposition can potentially lead to the fatal complication of pericardial tamponade from a line in the right atrium and subsequent pericardial effusion of PN. Measurement of the estimated distance of insertion of central lines and X-ray before infusion commences is essential. Lines should aspirate blood freely at the length inserted to ensure the line is sitting in a large vessel.<sup>14</sup>

Catheter tip misplacement during insertion of CVCs is not infrequent. The use of fluoroscopy during catheter insertion allows immediate repositioning of the catheter tip into its correct location in the SVC. A chest radiograph should be obtained after the insertion procedure to document catheter placement and rule out a pneumothorax.<sup>25</sup>

### 2. Sepsis

The most frequent complication for patients receiving long term PN via a central venous catheter is of catheter related infection/sepsis.<sup>7</sup> Infections related to central venous catheters are an important cause of morbidity and mortality for hospitalized patients. The National Nosocomial Infections Surveillance System reported a rate of catheter-related bloodstream infection (CRBSI) of five per 1000 central catheter-days.<sup>26</sup> Catheter-related sepsis also contributes to increased medical costs.<sup>25</sup>

Management of Central Venous Line related infection is extremely important. Signs and symptoms of infection include fever, malaise, inflammation and discharge at the exit/subcutaneous pocket/tunnel or vein insertion site<sup>10</sup>. The risk of nosocomial infections can be reduced by proper aseptic technique in placing the catheter and following proper dressing care techniques<sup>13</sup>. Strict sterility of the line during and after insertion must be maintained.<sup>14</sup>

Strategies to decrease risk of catheter associated sepsis are:<sup>25</sup>

- Use of full barrier precautions during catheter insertion (mask, cap, sterile gloves, long sleeve gowns, sheet drapes) reduces the incidence of catheter related infections compared with the use of only sterile gloves and small drapes alone.
- Skin preparation with chlorhexidine results in a lower incidence of microbial colonization of catheters than with povidone iodine.

The treatment of catheter-related sepsis involves catheter removal and appropriate antibiotic coverage although success in managing catheter infection with antibiotics alone has been reported.<sup>25</sup>

In a systematic review addressing the effect of anti-infective treated central venous catheters on catheter related bloodstream infection (CRBSI) in patients who received a central venous

catheter for PN or chemotherapy, sufficient evidence was not found to recommend their use. The recommendation of the Centers for Disease Control and Prevention to use antibiotic or antiseptic impregnated central venous catheters, when the risk for CRBSI is high despite good hygienic practice, should therefore be limited to patients in the intensive care/perioperative setting.<sup>26</sup>

### 3. Thrombosis

Clinically relevant catheter-related thrombosis is a late complication of long term use of central venous catheters. Heparin-bonded catheters and prophylactic use of anticoagulants have been associated with a reduction in thrombosis related to long term catheters.<sup>25</sup>

### 4. Metabolic complications

The potential for development of serious metabolic complications requires that patients receiving parenteral therapy be closely monitored and managed to maximize the benefit of the PN while reducing the risks. The incidence of metabolic complications has been reduced by improvements in parenteral solutions.<sup>17</sup>

#### Cholestasis and liver disease

- The advent of parenteral nutrition resulted in a dramatic improvement in life expectancy for patients suffering intestinal failure. However, long term parenteral nutrition may be responsible for various complications. Liver disease was rapidly identified as one of the limiting factors of long term intestinal failure management. Despite improvements in surgical procedure, ICU management, involvement of nutrition support teams, as well as in the type and mode of delivery of parenteral nutrition, the incidence of end-stage liver disease remains high with special concern in young infants.<sup>27</sup>
- The most serious and significant life-threatening complication present in 40-60% of patients on long term PN continues to be parenteral nutrition associated cholestasis (PNAC) and in children will progress to parenteral nutrition associated liver disease (PNALD). This complication bears a high mortality rate.<sup>17</sup>
- 8 to 50% of extremely low birth weight infants show signs of biochemical cholestasis after 2 weeks of PN therapy; approaching 90% for more than 90 days.<sup>13</sup>
- PN induced cholestasis should be suspected in all patients treated with hospital and home parenteral nutrition. In most patients, elevated bilirubin values are observed after the first two weeks of PN, although they also may develop some months later. The incidence of PN induced cholestasis is higher in children than in adults. A prolonged PN regimen in these adult and pediatric patients may trigger cholestasis, fibrosis, cirrhosis and even may cause liver failure.<sup>28</sup>
- Prevention of PN induced cholestasis includes administration of an adequate amount of energy (ie, <25 kcal/kg/d), a complete mixed-fuel system including lipids, a cycled PN schedule especially in long term patients, and initiation of enteral nutrition as soon as possible.<sup>28</sup>



### Hyperglycemia

- PN presents a greater risk of overfeeding than does enteral nutrition. Large quantities of dextrose, easily and continuously administered via PN, can put critically ill, insulin-resistant patients at high risk for life-threatening hyperglycemia. To address the risk of overfeeding, a standard, weight based regimen for caloric intake in ICU patients is required.<sup>4</sup>

### Refeeding syndrome

- Refeeding syndrome is defined as the acute development of electrolyte depletion, fluid retention and disruption of glucose homeostasis that occurs upon administration of oral, enteral, or intravenous nutrition to malnourished patients.<sup>29</sup> While current recommendations would prohibit aggressive initial refeeding regimens used in the past, fragments of the syndrome, particularly hypophosphatemia, may be observed in at-risk patients. Patients potentially at risk include those with anorexia nervosa, cancer cachexia, chronic GI illness, prolonged fasting especially in presence of stress, and chronic alcoholics. Not all clinics and institutions have nutrition support teams, so it is still important to educate health care practitioners regarding the potential danger of too aggressively refeeding a chronically malnourished patient.<sup>30</sup>
- Onset of refeeding syndrome can occur 12-72 hours after commencement of the feed. Symptoms include irregular pulse, lethargy and muscle weakness and shortness of breath, cardiac arrest and death.<sup>7</sup>
- The oncology population often possesses numerous risk factors for developing refeeding syndrome including poor oral intake due to anorexia, mucositis and chemotherapy-related nausea and vomiting. Unrecognized refeeding syndrome can lead to significant morbidity and occasional mortality, typically due to cardiac arrhythmia or respiratory failure.<sup>29</sup>

### Other metabolic considerations

- **Phenylketonuria**  
 The frequency of phenylketonuria (PKU) in North America may be as high as one in 10,000 births. When on PN, phenylalanine levels in newborns diagnosed with PKU rose five times faster than in orally fed infants with PKU. As a precaution, when PN is used in the early newborn period, it is suggested that neonatologists collect the initial newborn screening sample 12 to 24 hours after starting infusions.<sup>31</sup>
- **Metabolic syndrome**  
 Changing patient demographics with increased prevalence of metabolic syndrome and obesity require extra caution in administration of nutrition support.<sup>4</sup>

### 4.3 Parenteral Nutrition Supplementation

#### Glutamine supplementation

The use of intravenous glutamine supplementation in critically ill patients on PN is currently the standard of care. The evidence clearly points to a survival advantage for patients receiving intravenous glutamine supplementation. The safety of intravenous glutamine administration using glutamine-containing dipeptides has been well documented.<sup>32</sup>

#### Micronutrients

Patients relying on PN receive most of their nutrients in the form of amino acids, glucose and lipid. For the optimal utilization of these nutrients, other substances called micronutrients are necessary. These substances are required in minute quantities. These micronutrients are of two types: trace elements and vitamins. 7 elements – iron, zinc, copper, chromium, selenium, iodine and cobalt – are necessary for human health.<sup>33</sup>

Because zinc is widely distributed in food, people consuming regular diets generally do not experience dietary zinc deficiency. The use of PN creates a unique situation in which it was possible to feed individuals with purified diets specifically deficient in trace elements such as zinc. Zinc is an essential trace element and must be added to all PN mixtures.<sup>33</sup>

Vitamins and trace elements should be added from the beginning of artificial nutrition and provided every day for its entire duration. The deficiency of micronutrients reverses the benefits of parenteral nutrition and makes it potentially dangerous because the micronutrient deficit prevents the correct progress of the intermediate metabolism after the macronutrients have been injected.<sup>34</sup>

The correct prescription of parenteral nutrition requires proper knowledge of the patient's nutritional needs. In a review of ready to use PN mixtures, it was observed that the omission of trace element and vitamin supplementation occurred more often when parenteral nutrition was prescribed by inadequately prepared staff. Further, if PN is provided in premixed bags by medical staff who are not adequately prepared in the nutritional field, there is a risk of incomplete parenteral nutrition, as premixed bags do not include vitamins and trace elements which therefore must be added before administration.<sup>34</sup>

### 4.4 Methods of Parenteral Nutrition Administration

#### Parenteral Access

Regarding route of delivery for PN, the ASPEN states that:<sup>25</sup>

- PN administration requires central venous access in order to provide nutrients at greater concentrations than is possible through peripheral veins. Selection of the most appropriate parenteral access device is based on the patient's vascular access history, venous anatomy, coagulation status, the anticipated duration of PN, the care setting and the nature of the underlying disease.
- Percutaneously inserted catheters advanced into the superior vena cava (SVC) are the route of choice for the delivery of PN. Catheters inserted through the femoral veins are associated with

higher risk of venous thrombosis and catheter related sepsis and are not recommended for PN. Access to the SVC can be gained through the internal jugular vein, the subclavian vein or through peripheral veins in the arm.

The ASPEN's Practice Guidelines for Parenteral Access follow:<sup>25</sup>

1. Parenteral nutrition should be delivered through a catheter located with its distal tip in the superior vena cava or right atrium.
2. A chest X-ray should be obtained after catheter insertion unless internal jugular or upper extremity IV access is obtained by interventional radiology techniques.
3. Full-barrier precautions should be used during the insertion of central lines.
4. Skin preparation before catheter insertion should be performed using chlorhexidine.
5. Catheter hubs and sampling ports should be disinfected before access for medication administration and blood drawing.
6. Central catheters should not be exchanged routinely over guide wires.
7. The use of antimicrobial-impregnated catheters is recommended in high risk patients and high risk care settings.
8. Specialized nursing teams should care for venous access devices in patients receiving PN.

The ESPEN states that a central venous access device is often required to administer the high osmolarity PN mixture designed to cover the nutritional needs fully. Peripheral venous access devices may be considered for low osmolarity mixtures designed to cover a proportion of the nutritional needs and to mitigate negative energy balance. If peripherally administered PN does not allow full provision of the patient's needs then PN should be centrally administered.<sup>2</sup>

At Toronto's Sick Kids Hospital, guidelines for selecting peripheral or central PN routes of administration for children at Sick Kids are:<sup>10</sup>

- Choose peripheral PN when:
  - The patient is not fluid-restricted
  - Nutrient needs can be met and
  - Central PN is not feasible
- Choose central PN when:
  - The patient is fluid restricted
  - Peripheral access is limited and
  - Nutritional needs cannot be met by peripheral PN

All central lines should be placed under full aseptic conditions, preferably in the operating room or in the Diagnostic Imaging Department by a surgeon or an interventional radiologist. The skin site for the catheter should be located in an area that can be easily and meticulously cleaned. Following the placement of a percutaneous central line, a chest x-ray (upright if possible) should be taken to check catheter position, possible pneumothorax, and extravasation of fluid.<sup>10</sup>

Care of the PN system and the catheter should be performed by nurses and doctors competent in central venous line skills. All central venous lines must be accessed and dressed in a sterile fashion according to the appropriate nursing procedure.<sup>10</sup>

In the event of suspected sepsis, blood must be drawn from each lumen as well as a peripheral site and specimens labeled clearly. If the catheter is removed for sepsis, the tip must be sent for semi-quantitative culture.<sup>10</sup>

#### All in One Bag versus Separate Containers

Total Nutrient Admixtures (TNA) or 3-in-1 solutions are PN solutions in which the lipid emulsion has been mixed with the other ingredients to form one solution. The '3' refers to amino acid, dextrose and lipid. A TNA provides the PN admixture in a single bag as opposed to the traditional system, in which a bag or syringe of lipid is administered via a separate line that is 'Y'd with the amino acid/dextrose solution near the patient. Since everything is in one bag, only a single pump and tubing set is required to administer the admixture with reduced line manipulation. The exact amount of lipid prescribed is added to the bag as stability allows, thus eliminating overfill wastage. The major benefit is that it is a safer system. However, the destabilizing effects of the PN constituents on the lipid emulsion mean that only certain recipes can be formulated as TNAs. If higher concentrations are required, then the traditional 2-in-1 system must be used.<sup>10</sup>

The ESPEN recommends that PN admixtures should be administered as a complete all-in-one bag. PN regimens contain more than 40 different components, including water, macronutrients, electrolytes, micronutrients and other additives. They can be administered either using separate containers or from an 'all-in-one bag' system prepared in the hospital pharmacy or by industry. The separate containers approach requires numerous IV line manipulations associated with an increased risk of administration errors as well as of septic and metabolic complications.<sup>2</sup>

A concern observed about PN in premixed bags is the risk of incomplete parenteral nutrition because of inadequate activation of the multichamber bag and because premixed bags do not include vitamins and trace elements which, therefore, need to be added before dispensing. This might be a particular concern when PN is prescribed by personnel who are not adequately prepared in the nutritional field.<sup>34</sup>

#### **4.5 Safe Practices for Parenteral Nutrition**

Parenteral nutrition is an intravenous therapy requiring expert preparation using commercially available injectable products. 'High alert medications' describe drugs that can place patients at risk for significant harm when used in error. PN is classified among the high alert medications with good reason as it is arguably one of the most complex prescription drug preparations available for routine patient care. A single patient PN admixture contains macronutrients and micronutrients that total nearly 50 individual active pharmaceutical ingredients not including solubilizers, preservatives and other excipients. As such, PN requires special safeguards to minimize error risk.<sup>35</sup>

Parenteral nutrition is one of the most complex medications administered to hospitalized and ambulatory patients. 40 or more individual components may be incorporated into a PN formulation, including amino acids, dextrose, lipid emulsions, electrolytes, vitamins, trace elements, insulin and other medications. Despite the successful clinical use of PN for over several decades, adverse events continue to occur, resulting in serious morbidity or even mortality.<sup>37</sup>



Key components of the PN 'system of care' include assessment, the order, order review, preparation, delivery, administration, monitoring; also procurement, and nutrition care planning.<sup>38</sup> The process is interdisciplinary, involving the physician, dietitian, prescriber (both physician and non-physician), pharmacist, nurse, and/or caregiver.<sup>38</sup>

There are multiple points within the PN process for errors to occur. At each of these points, errors may be committed by any of the healthcare practitioners involved in the PN process. Incorrect dosing calculations, wrong formulation preparation, order entry problems with automated technology (ie, automated compounding devices), and incorrect infusion practices are some of the errors unique to PN that have been reported.<sup>37</sup> Unfortunately most organizations do not routinely document and collect or perhaps even recognize PN-related medication errors.<sup>39</sup>

PN errors or issues of safety can adversely affect outcomes from therapy<sup>38</sup>. Protective measures may include a number of strategies such as standardizing the processes of ordering, preparation, storage and administration.<sup>36</sup> The practices and safeguards surrounding this process are critical to maintaining safety for patients.<sup>35</sup>

The ASPEN advocates a standardized process for delivery of PN. A safe PN system is necessary to minimize procedural incidents and maximize the ability to meet individual patient requirements.<sup>39,40</sup>

#### Screening and referral

Careful selection of patients is required to ensure that parenteral nutrition is not provided to those who can be fed by other means. Patients unable to meet their requirements through oral or enteral means, or who have non-functioning or inaccessible GI tract should be referred for consideration of PN to nutrition experts, such as a Nutrition Support Team. A Nutrition Support Team is a multidisciplinary team established to offer access to comprehensive assessment of highly complex nutrition support cases.<sup>7</sup>

#### Prescribing

The ASPEN's practice guidelines for prescribing parenteral nutrient requirements are:<sup>3</sup>

1. Determination of protein, calorie, fluid electrolyte, vitamin and trace element components of a PN formulation should be based on standard nutrient requirements. The dose of each nutrient should fall within the accepted age-based standard range except when warranted by specific clinical situations.
2. Intravenous Fat Emulsion (IVFE) in a dose sufficient to prevent Essential Fatty Acid Deficiency (EFAD) should be provided to adult and pediatric patients who are receiving nothing by mouth. Adults who fail to receive EFAs for 20 days are at risk for development of EFAD. In the absence of (Essential Fatty Acids) EFAs, children can develop EFAD over a shorter period of time, with neonates at risk of EFAD within 2 days of initiating lipid-free PN.
3. All patients receiving PN should receive a parenteral vitamin preparation on a daily basis.
4. Health care providers should choose PN components with the lowest aluminum content when possible to minimize parenteral aluminum exposure.

5. When the use of commercially available multiple trace element combination product results in or increases the risk of trace element toxicity or deficiency states, the use of individual trace element products is warranted.
6. Parenteral iron shall not be routinely supplemented in patients receiving PN therapy. It should be limited to conditions of iron deficiency when oral iron supplementation fails and followed closely in an ongoing monitoring plan.

Use of a standardized PN ordering process, including order forms whether paper or electronic, can reduce prescribing errors. A majority of PN orders are still being handwritten and, in some cases, non-standardized forms are being used despite expert guidelines addressing the need for a standardized PN order form.<sup>36</sup>

Standardized order writing processes reduce prescription errors in that they:<sup>3</sup>

- Incorporate more precise guidelines for PN prescribing
- Provide physician education especially important for clinicians unfamiliar with PN therapy
- Allow comprehensive nursing and dietary care of the patient by reducing nursing order interpretation problems and improving documentation of each bag administered.

The ASPEN recommends that standardized order forms (or order entry screens) be developed and designed for adult and pediatric PN formulations to aid prescribers in meeting the patients estimated daily nutrition requirements and improve order clarity.<sup>3</sup>

The ASPEN recommendations for components of PN order forms are as follows:<sup>3</sup>

- Mandatory components of the PN order form:
  - Clarity of the form
    - Clearly written and understandable to anyone who might use it
    - Organized and easy to scan for completeness
    - Compete enough to address anticipated institution specific concerns
    - Ingredients listed in same order as PN label
    - Decimals and percent concentrations avoided
    - All components ordered in grams/milligrams/milliequivalents/millimoles per day or kg per day
  - Contact information for person writing the order
  - Contact information for assistance with the PN ordering
  - Time by which the order needs to be received for processing
  - Location of venous access device (central or peripheral)
  - Height, weight/dosing weight, diagnosis, PN indication
  - Hang time guidelines
  - Institutional policy for infusion rates
  - Information regarding potential incompatibilities
- Strongly recommended for inclusion on the PN order form:
  - Educational tools (eg, dosing guidelines)
  - Guidelines to assist in nutrient/volume calculations
  - Recommended PN lab tests (baseline, monitoring and special circumstances)

- Guidelines for stopping/interrupting PN
- Contents of multivitamin and trace element preparations
- Brand names of products (eg, amino acids, IVFE)
- Guidelines for use of insulin
- Guidelines for recognizing additional calorie sources
- Worthy of consideration for inclusion on PN order form
  - Identification of who will review the order in addition to pharmacy
  - Guidelines for nutrient restriction in various disease states
  - Guidelines for long term PN (eg, Selenium, Iron administration)
  - Guidelines for special amino acids (eg, Trophamine + cysteine)

The ASPEN's Practice Guidelines for ordering parenteral nutrition are as follows:<sup>3</sup>

1. Standardized order forms (or order entry screens) shall be developed and designed for adult and pediatric PN formulations to aid prescribers in meeting the estimated daily patient nutritional requirements and improve order clarity.
2. The clinician and compounding pharmacist shall assess the PN formulation to determine whether its contents are within an acceptable standard range based on the specific patient population (eg, adult or pediatric). They shall also assess whether a clinical disease state or condition warrants a dose outside the standard range.
3. The use of percent concentration in PN orders should not be used. The use of total daily dose is encouraged.
4. Potentially dangerous abbreviations and dose expressions should be avoided. Specifically:
  - Do not use trailing zeros (eg, 5 mg, and not 5.0 mg)
  - Use leading zeros for doses less than one measurement unit (eg, 0.3 mg and not .3 mg)
  - Spell out the word UNITS (eg, never U which could be easily mistaken as a zero).
  - Spell out routes of administration and all intended instructions.
5. All components of the PN order must be re-written when PN is reordered.

Common factors associated with PN prescribing errors include:<sup>3</sup>

- Inadequate knowledge regarding PN therapy
- Certain patient characteristics related to PN therapy (eg, age, impaired renal function)
- Calculation of PN dosages
- Specialized PN dosage formulation characteristics and prescribing nomenclature.

#### Verifying and reviewing the parenteral nutrition order

Prior to compounding the PN admixture based on the submitted order, the order needs to be reviewed and verified. The verification process ensures that the PN order is complete and timely, that any transcription has occurred correctly and that, for a new patient, intravenous access is confirmed. The review process includes 2 aspects:

- A clinical review that dosing of each nutrient is appropriate for the individual patient and
- A pharmaceutical review that the ordered components are compatible and that the preparation is expected to be stable.<sup>36</sup>





The ASPEN recommends that the clinician and compounding pharmacist assess the PN formulation to determine whether its contents are within an acceptable standard range according to the specific patient population (eg, adult or pediatric). They shall also assess whether a clinical disease state or condition warrants a dose outside the standard range.<sup>3</sup>

The ASPEN's Practice Guidelines for screening the PN order are:<sup>3</sup>

1. The calorie, protein, fluid, electrolyte, vitamin, trace element and medication content is reviewed for each and every PN prescription to assure that a complete and balanced nutrient formulation is provided. 'Balance' is defined as the presence of the proper proportion of calories, protein, fluid, electrolytes, vitamins and trace elements to ensure adequate use by and assimilation into the body.
2. Each of the PN components should be assessed for appropriateness of dose and for the potential of a compatibility or stability problem.
3. Any dose of a nutrient outside a normal range, which is not explained by a specific patient condition or history shall be questioned and clarified before the PN is compounded.

#### Compounding the parenteral nutrition

Serious consequences are possible when quality compounding practices are not in place. Serious harm may come to patients receiving a PN formulation that has precipitates resulting from a chemical interaction between components that are present in an excessive dose, exposed to extremes of temperature, or admixed in an improper sequence.<sup>3</sup>

Automated or manual methods of PN compounding are available.<sup>3</sup> Any manual data entry of PN orders into the pharmacy computer system and then into automated compounders needs to be verified if an electronic interface does not exist<sup>36</sup>. A benefit of automation is to build in dose-warning limits that should remain active for all PN orders. In addition to alerting prescribers at the point of order entry, these will alert pharmacists at the time of order review and compounding and may help prevent otherwise fatal errors.<sup>36</sup>

When compounded from commercially available sterile products, PN is considered to be a medium-risk sterile preparation. The pharmacist has the responsibility to strictly follow standards, guidelines and recommendations related to compounding and delivery of safe PN admixtures.<sup>36</sup>

The ASPEN's Practice Guidelines for PN compounding are as follows:<sup>3</sup>

1. The additive sequence in compounding shall be optimized and validated as a safe and efficacious method.
2. If the manual method currently in use at an institution has not been recently reviewed, or if the contract with a particular manufacturer of macronutrients is about to change, then a review of the compounding method is strongly recommended. This review shall include an evaluation of the most current literature as well as consultation with the manufacturer when necessary.
3. Manufacturers of automated methods of PN compounding shall provide an additive sequence that ensures the safety of the compounding device. This compounding sequence should be reviewed with the manufacturer of the parenteral nutrient products used by the institution.

4. Each PN formulation compounded should be visually inspected for signs of gross particulate contamination, particularly formation and/or phase separation of TNAs.

The stability of PN formulations principally focuses on the degradation of nutritional components over time. The complex formulations typical of PN pose several possible physicochemical incompatibilities.<sup>3</sup>

The ASPEN's Practice Guidelines for PN stability and compatibility are as follows:<sup>3</sup>

1. The dose, admixture preparation, packaging, delivery process, and storage and administration method should be confirmed to ensure that the PN is stable and all components are compatible.
2. The responsible pharmacist should verify that the administration of drugs with PN either admixed in the PN or co-infused through the same intravenous tubing is safe, clinically appropriate, stable and free of incompatibilities.
3. If there is no information concerning compatibility of the medication with PN, it should be administered separately from the PN.
4. Compatibility information should be evaluated according to concentration of the medication used and whether the based formulation is a 2-in-1 or a TNA.
5. Insulin use in PN should be done in a consistent manner according to a method about which healthcare personnel have adequate knowledge.
6. Decisions related to stability and compatibility are made according to the most reliable information available from the literature or manufacturer of intravenous nutrients. If no information exists, stability and compatibility of the PN shall be determined in consultation with the manufacturer before it is dispensed to the patients.
7. Given the limited amount of published stability information available, the use of a 2-in-1 formulation with separate administration of IVFE is recommended for neonatal/infants patients.

#### Labeling parenteral nutrition formulations

The labels of PN formulations should be standardized and express clearly and accurately what the patient is receiving at any time. The ASPEN's Practice Guidelines for labeling PN formulations are as follows:<sup>3</sup>

1. The amount per day is the only column required on the label of the base formula, electrolyte additives, micronutrients and medications. This supports the use of the 24 hour nutrient infusion system.
2. Using the quantity per liter option in parenthesis supports those programs that continue to admix in 1 liter volumes.
3. The dosing weight is required on the label.

The PN label should specify the route, date and time of administration, as well as the beyond-use date and time.

#### Dispensing and administering the parenteral nutrition

The admixture should be refrigerated and kept out of the light between preparation and administration.<sup>36</sup>



Safe administration of PN includes:<sup>3</sup>

- Proper venous access device selection, care and assessment
- Appropriate use of the medical equipment needed to deliver the PN solution
- The chemical properties of the PN formulation itself
- Monitoring the patient's response to the PN therapy.

Before PN administration, the patient's identity is verified and the PN label is reviewed for accuracy and expiration dates.

ASPEN's Practice Guidelines for PN administration are as follows:<sup>3</sup>

1. Central PN is administered via a central venous catheter (CVC) with the distal tip placed in the superior vena cava adjacent to the right atrium.
2. The use of femoral catheters for PN administration should be avoided.
3. Proper CVC tip placement shall be confirmed prior to initial PN administration and/or any other time signs/symptoms indicate an improper catheter position. Proper CVC tip placement shall also be confirmed/validated in the pediatric patient when there has been significant growth.
4. Care and maintain venous catheters used for PN according to published standards.
5. Equipment used to administer PN formulations shall be selected based on the safest mode of delivery for both the patient and the healthcare provider.
6. A 1.2 micron filter may be used for all PN formulations. Alternatively a 0.22 micron filter may be used for 2-in-1 formulations.
7. A filter that clogs during PN infusion may be indicative of a problem and may be replaced but shall never be removed.
8. PN final containers and administration sets shall be free of the plasticizer, DEHP if IVFE is a component of the nutrient regimen.
9. Administration sets for IVFE infusions separate from PN formulations shall be discarded after use or if the IVFE is infused continuously, at least every 24 hours.
10. Administration sets for TNA are changed every 24 hours.
11. Administration sets for 2-in-1 formulations are changed every 72 hours.
12. PN is to be administered via an infusion pump having adequate protection from 'free flow' and reliable, audible alarms.
13. Medical devices for PN administration should be used that minimize risk of needle-stick injuries and exposure to blood-borne pathogens.
14. Prior to PN administration, the patient's identify is verified and the PN label is reviewed for accuracy and expiration dates.
15. Visually inspect each PN prior to administration, do not infuse the PN formulation if visual changes or precipitates are apparent.
16. The PN infusion shall be completed within 24 hours of initiating the infusion.
17. IVFE infused separately from PN formulations shall be completed within 12 hours of entry into the original container.
18. The patient receiving PN should be monitored to determine the efficacy of the PN therapy, detect and prevent complications, evaluate changes in clinical conditions and document clinical outcomes.

19. A policy and procedure should be in place to deal with the use of PN formulations prepared by an outside facility.

Royal Cornwallis Hospital's PN clinical guideline requires the following:<sup>7</sup>

- Ensure the intravenous access has been approved for use and is documented in the medical notes before administering PN.
- Before administering any PN, check that it is due and has not been given already.
- To ensure the patient is given the correct drug in the prescribed dose using the appropriate diluent and by the correct route, before administering any PN, consult the patient's prescription chart and ascertain the following:
  - Drug
  - Dose/rate
  - Date and time of administration
  - Route and method of administration
  - Validity of prescription
  - Signature of prescriber
- Wash hands with bacterial soap and water or bactericidal alcohol handrub.
- To ensure removal of air from the set and check that tubing is patent, prime the intravenous administration set with PN mixture and hang it on the infusion stand.
- Administration sets used for PN should be changed every 24 hours or immediately upon suspected contamination or when the integrity of the product or system has been compromised. PN should never be disconnected and then reconnected unless in an emergency (if it is necessary to disconnect the PN in the middle of an infusion, then the whole bag must be discarded and a new one commenced).

#### Documentation

Each step of the PN use process needs to be documented in the patient's chart and/or in the pharmacy system as appropriate whether using an integrated electronic medical record or a paper record. Any deviations from standard of care as well as PN associated medication errors are then easier to capture and evaluate.<sup>36</sup>

#### Parenteral nutrition monitoring

Monitoring patients is necessary to determine efficacy of specialized nutrition therapy, detect and prevent complications, evaluate changes in clinical condition and document clinical outcomes.<sup>39,40</sup>

#### *Monitoring for efficacy*

The ASPEN's Practice Guidelines Monitoring for Efficacy are:<sup>25</sup>

1. Nutrition and outcome goals should be stated in the nutrition assessment prior to the initiation of specialized nutrition support (SNS).
2. Nutritional and outcome parameters should be measured serially during SNS therapy.
3. Periodic comparison of nutritional and outcome measures with SNS goals should occur to monitor efficacy of therapy.



Monitoring for compliance and effectiveness should include monitoring of documentation and completion of the parenteral nutrition care plan, including accurate completion of fluid balance charts, peripheral and central line care plans, blood monitoring as per guideline. This may include regular sampling of ten charts per clinical area for fluid balance or as they arise and annually.<sup>7</sup>

## *Monitoring for complications*

It is the responsibility of the medical staff in each clinical team to ensure that appropriate blood testing is carried out on all their patients receiving PN. Results should be monitored by the clinical team and also be reviewed by the Nutritional Support Team when prescribing further PN. It is important to start correcting any electrolyte results which fall outside normal range before the commencement of PN.<sup>7</sup>

The ASPEN's Practice Guidelines for Monitoring for Complications are as follows:<sup>23</sup>

1. Malnourished patients at risk for refeeding syndrome should have serum phosphorus, magnesium, potassium and glucose levels monitored closely at initiation of specialized nutrition support (SNS).
2. In patients with diabetes or risk factors for glucose intolerance, SNS should be initiated with a low dextrose infusion rate and blood and urine glucose monitored closely.
3. Blood glucose should be monitored frequently upon initiation of SNS, after any change in insulin dose, and until measurements are stable.
4. Serum electrolytes (sodium, potassium, chloride and bicarbonate) should be monitored frequently upon initiation of SNS until measurements are stable.
5. Patients receiving intravenous fat emulsion should have serum triglyceride levels monitored until stable and when changes are made in the amount of fat administered.
6. Liver function tests should be monitored periodically in patients receiving PN.
7. Bone densitometry should be performed upon initiation of long-term SNS and periodically thereafter.
8. Postpyloric placement of feeding tubes should be considered in patients at high risk for aspiration who are receiving EN.

## 4.6 Expertise Essential for Quality and Safety in Parenteral Nutrition

The following quote emphasizes the urgency of attention to quality and safety in the use of parenteral nutrition:

'Mode, timing and adequacy of nutritional support affect glycemic control and outcomes in critically ill patients. The delivery of correctly formulated and safely administered nutritional and metabolic support is a matter of life or death in surgical and critical care units. Yet increasingly, this essential service is supplied without appropriate staffing, oversight or financial compensation. The traditional nutrition support services model, a multidisciplinary team headed by highly skilled internists or general surgeons, has given way to care under the guidance of diverse specialists, working with pharmacists, and at times dietitians. This trend exposes patients to unacceptable levels of risk. Physician directed teams deliver the highest level of enteral and parenteral support with the lowest level of PN related complications, especially infectious morbidity'.<sup>4</sup>

The knowledge required for safely ordering, reviewing, preparing, administering and monitoring PN is often found on nutrition support services (or teams) which include clinicians certified in nutrition support. However, such services may not always be available to an organization or they are not well coordinated and working together.<sup>36</sup> Clinicians with nutrition support therapy expertise are required to achieve a safe PN system.<sup>39,40</sup>

#### 4.7 Nursing Responsibilities in Parenteral Nutrition

Toronto's Sick Kids Hospital describes nursing responsibilities in PN as follows:<sup>40</sup>

- Ensure pre-PN bloodwork is done before the infusion is started.
- Check the patient's name, patient number, unit, solution type and expiry date against the order for the PN solution.
- Remove the PN from the refrigerator a minimum of 1 hour before hookup and a maximum of 24 hours to infusion completion.
- Administer PN with an infusion pump.
- For traditional two line systems, use non-vented solutions set. NICU/CCU use syringe sets. A 1.2 micron filter is needed. The two lines are joined with a Y connector.
- Medications should be added as close as possible to the entry site.
- Change tubing every 72 hours (48 hours in the NICU) if PN is continuous. If PN is cycled or stopped for more than 4 hours, change of tubing is required.
- Lipid and PN solutions expire 24 hours after hanging.
- Check the IV, IV site, the line connections, infusion rate of the pump and the volume administered hourly. Chart according to hospital procedure.

Royal Cornwallis Hospital describes nursing care and management responsibilities in PN as follows:<sup>7</sup>

- Daily weight before PN and twice weekly to assess change in tissue mass and adequacy of energy provision.
- 6 hourly temperature, pulse, respirations and blood pressure
- Accurate fluid balance chart to maintain accurate fluid balance and prevent under or over hydration.
- Capillary blood glucose monitoring 6 hourly for 48 hours, then twice daily and once a day to detect hyperglycemia and/or hypoglycemia.
- Daily assessment of vascular line to detect exit site infection/leakage.
- Dressing changes 48 hours after insertion, thereafter weekly or more frequent if loose, soiled or wet; weekly obturator changes.
- Twice weekly urinary sodium for nitrogen balance and electrolytes.
- Documentation to comply with national and hospital policy.

#### 4.8 Shortages of Parenteral Nutrition Products

According to the ASPEN, all PN products, aside from dextrose and water, have been in short supply at some point since the spring of 2010. In 2012, a number of PN micronutrients, including multivitamins, selenium and zinc, were unavailable or in short supply. Aggressive measures have been taken to ration existing supplies. Most premature infants and many infants with congenital anomalies are dependent on



parenteral nutrition for the first weeks of life to meet nutritional needs. Because of fragile health and poor reserves, they are uniquely susceptible to this problem. Shortages and rationing have been associated with adverse outcomes.<sup>41</sup>

The drug shortage crisis has been an extreme test on the PN system. Safety issues related to drug shortages have resulted from using less desirable or familiar products, confusion with the prescribing process and safety check circumvention, to name a few. Due to inadequate commercial supply, some PN products that have no oral or parenteral alternative are restricted to those patients with greatest need and/or provided in lower than normal doses with the mindset that some is better than none. The result is suboptimal therapy with nutrition deficiencies very likely or, when therapy is withheld, 'starvation' will ensue.<sup>38</sup>

#### 4.9 Inappropriate Use of Parenteral Nutrition

The use of parenteral nutrition may be an automatic response to the perceived or actual need for a nutrition intervention. Although PN has a role in nutrient support, its' inappropriate use can lead to both economic issues and complications. In a study done at the Medical University of South Carolina, the average cost for a 1 day supply of PN solution was approximated at between \$200 and \$300 vs. the EN cost of between \$10 and \$50 per day (unpublished in house data). Personnel hours to manage PN patients were also greater than for EN patients.<sup>8</sup>

The results of a study assessing PN ordering practices found inappropriate use of PN in 32% of the prescribed cases at 4 tertiary medical centres incurring at least \$125,000 in unnecessary hospital costs based on the parenteral solution alone. In approximately 66% of these inappropriate cases, qualified dietitians or other clinicians had recommended against PN therapy. 13% of the inappropriate cases were discharged home on PN. Inappropriate cases averaged 4 more hospital days on PN compared with appropriate cases although the average length of hospital stay was similar. The medical service associated with the highest rate of inappropriate PN use compared with total PN use was GI surgery.<sup>8</sup>

A retrospective medical record review was undertaken to determine the level of agreement between physician indications for initiation of PN and the ASPEN guidelines for PN. Of 103 adult patients for whom PN was initiated over a 6 month period in an urban teaching hospital, 29.1% of patients had indications for PN that were not in agreement with the ASPEN guideline. The most common physician indication not in agreement was related to poor oral intake or failure to thrive. Both are indications for EN because the GI tract is functional. Another inappropriate indication was aspiration risk/dysphagia which is an indication for EN, not PN. Another inappropriate indication for PN was pancreatitis without an initial trial of EN. According to the ASPEN guidelines, patients with pancreatitis should receive a trial of small bowel enteral feedings and PN only be initiated if EN is not tolerated.<sup>42</sup>

Improved compliance with guidelines through use of a nutrition support team, implementation of a nutrition support protocol, and physician education has been reported in the literature<sup>42</sup>. Nutrition Support Teams (NST) and certified nutrition support clinicians can curtail preventable spending from inappropriate PN use. It may be that the only effective means of controlling inappropriate PN use is with an NST that has the absolute authority to approve or reject a PN order.<sup>8</sup>

#### 4.10 Quality Improvement

Two studies addressing quality improvement in parenteral nutrition are described below:

1. In 2007, a project was undertaken by a hospital in California, the goal of which was to improve the safety and effectiveness of PN. Process improvement strategies included revisions to the PN order form, education of clinicians including physicians, increased collaboration between pharmacists and registered dietitians, and initiation of PN rounds during which PN patients were reviewed by the rounding team twice weekly. Through comparison of baseline and follow up data, improvement in compliance to mandatory safe practice standards, percentage of patients with appropriate indication for PN, adequate glycemic management, number of patients receiving PN within 10% of calorie needs, and appropriate laboratory monitoring were demonstrated. As well, substantial cost savings were realized through decreased inappropriate PN use and timely transition to oral or enteral feeding. The average number of patients receiving PN decreased from approximately 15 to less than 5 per day. Overall, this translated into a \$5.3 million decrease in PN charges. Actual pharmacy expenses decreased by \$107,000. This quality improvement project demonstrated that implementing practice guidelines published by the American Society of Parenteral and Enteral Nutrition can result in quality improvement and cost savings. Clinicians with advanced certifications in nutrition support were pivotal to the success of the project.<sup>43</sup>
2. A study done in an academic teaching hospital followed a systematic approach to document the occurrence of parenteral nutrition errors between November 2002 and May 2004. An overall incidence of 15.6 errors per 1000 PN prescriptions compounded was demonstrated.<sup>37</sup> Of these, approximately 10% could result in or contribute to temporary patient harm. A number of changes were made in the PN process in response to the research findings as follows:
  - A new PN order form was created to reduce medication errors associated with the transcription process.
  - A copy of the original PN order form was transmitted to the PN compounding area to improve verification of the final compound preparation by the pharmacist.
  - The decentralized pharmacist and nurse also used the new order form to compare the PN formulation with the original order prior to administration.
  - A series of nursing in services related to PN verification and administration were conducted by the nutrition support team to correct these process errors.

The findings of this study led to recognition of the need to establish quality improvement programs and processes for PN ordering, compounding and administration of the formulation, and to document compliance with published safe practice guidelines for nutrition support. A non-punitive approach centered on improved patient care was seen to be the primary component for creating a safe and effective PN process.<sup>37</sup>

For quality improvement purposes, parenteral nutrition incidents need to be included in risk and safety clinical governance reports and presented to the nutrition steering committee. All serious incidents require root cause analysis and development of recommendations and actions.<sup>7</sup>

## 5.0 Discussion

Over the four decades it has been in use, parenteral nutrition has proven to be highly valued for its ability to provide nutrition to patients who would otherwise not have been able to be fed. However, over recent years, the clinical complications and safety risks that can accompany parenteral nutrition have been increasingly recognized, leading nutrition experts to advise that it be reserved for those who have been proven not able to be fed through enteral means.

Significant improvements in parenteral nutrition formulations and better management of potential nutritional deficits, complications and safety issues have contributed to improved outcomes. However, both the formulation itself as well as the system of PN administration are highly complex and therefore subject to error. The literature points out that errors continue to occur, and that these have potential to significantly affect morbidity and even mortality, as well as adding to health care costs.

The literature emphasizes the importance of careful patient selection for PN as well as protocols and practices to ensure safety at all stages of the PN process. Having knowledgeable nutrition resource personnel available with authority to influence when and how parenteral therapy is used is identified as key to efficacious and safe parenteral nutrition therapy.

## 6.0 Limitations

### Project scope

A great deal of literature is available regarding specialized nutrition therapy, including parenteral nutrition therapy. Much research has been done into the appropriate clinical use, clinical complications and safety issues of parenteral therapy.

This literature review includes both published literature as well as grey literature representative of a broad range of the aspects of parenteral nutrition therapy. The objective of the literature review was to provide a relatively high level overview that would highlight a full range of potential considerations in its use and the articles synthesized in this report were selected for that purpose. It is acknowledged that only a relatively small portion of the body of literature available on the subject has been included in this review.

### Clinical practice

The literature references variation in clinical practices, including controversy, in the use of parenteral nutrition therapy. This report includes reference to a number of practice guidelines from reputable agencies as well as from health care facilities. The brevity of this report does not allow for the inclusion of the full context of these guidelines.

It is recognized that views may differ regarding clinical practice respecting parenteral therapy. This report should not be used as a source of information regarding best practice. The reader is advised to refer back to the referenced source document in order to access the complete information within its context.



## 7.0 Conclusions

Through review of systematic literature reviews and meta analyses done over the past five years, as well as grey literature from associations, societies, clinical practice guideline developers and selected journals in the area of parenteral nutrition, this review has addressed the implications for quality and patient safety with respect to the processes of parenteral nutrition. The literature reviewed has included all age groups (neonates, children and adults), all aspects of the care process (prescribing, preparing, administering, monitoring and applicable outcomes), and leading practices related to parenteral nutrition.

The review identifies the appropriate clinical use of parenteral nutrition and highlights risks related to complications and safety issues. The immense clinical benefit of parenteral therapy is recognized and the significant associated risks are emphasized. Best practice recommendations for risk mitigation from reputable sources are presented.

## Conflicts of Interest

Janet Adams is Principal, Altus Planning Inc. Tamara Durec is President, Durec Information Systems Inc. Both authors declare no conflicts of interest.



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## Appendices

### Appendix 1: Electronic Search Strategies

#### Search Strategies – Systematic Reviews & Meta analyses

##### Ovid MEDLINE 1946 to July Week 4 2013

OvidSP version: Version: OvidSP\_UI03.09.00.155, SourceID 58794

Search date: 04.08.2013

Limits: 2008-current, English

Results: 158 De-duped: 140 (remove letters, etc = 139)

1. exp Parenteral Nutrition, Total/
2. total parenteral nutrition.mp.
3. TPN.tw.
4. or/1-3
5. meta analysis.pt.
6. meta analysis.tw.
7. Meta-Analysis/
8. review.pt.
9. search\$.tw.
10. or/5-9 [HIRU review filter – best balance of sensitivity and specificity]
11. and/4,10
12. limit 11 to (english language and yr="2008 -Current")
13. remove duplicates from 12
14. (letter\$ or editorial\$ or comment\$ or lecture\$ or news).pt.
15. 13 not 14

##### EMBASE 1996 to 2013 Week 30

OvidSP version: Version: OvidSP\_UI03.09.00.155, SourceID 58794

Search date: 04.08.2013

Limits: 2008-current, English

Results: 40 De-duped: 40

1. total parenteral nutrition/
2. total parenteral nutrition.mp.
3. TPN.tw.
4. or/1-3
5. meta-analys\$.mp.
6. search\$.tw.
7. review.pt.
8. or/5-7 [HIRU review filter – best balance of sensitivity and specificity]
9. and/4,8
10. limit 9 to (english language and yr="2008")
11. limit 10 to medline
12. 10 not 11
13. Remove duplicates from 12



## Parenteral Nutrition Literature Review

### EBM Reviews - EBM Reviews - Cochrane Database of Systematic Reviews 2005 to July 2013

OvidSP version: Version: OvidSP\_UI03.09.00.155, SourceID 58794

Search date: 04.08.2013

Limits: 2008-current, English

Results: 36 De-duped: 36

1. total parenteral nutrition.mp.
2. TPN.tw.
3. or/1-2
4. limit 3 to last 5 years
5. limit 4 to withdrawn records
6. limit 4 to protocols
7. or/5-6
8. 4 not 7

### Search Strategies – Guidelines

#### Ovid MEDLINE 1946 to August Week 3 2013

OvidSP version: Version: OvidSP\_UI03.09.00.155, SourceID 58794

Search date: 28.08.2013

Limits: 2008-current, English, humans

Results: 21 De-duped: 16

1. guidelines/ or practice guidelines/
2. guideline.pt.
3. practice guideline.pt.
4. guidelin\$.mp.
5. clinical protocol\$.mp.
6. ((clinical or medical) adj guidelin\$).mp.
7. ((clinical or medical) adj (standard or standards)).mp.
8. ((clinical or medical) adj protocol\$).mp.
9. ((clinical or medical) adj recommend\$).mp.
10. ((clinical or medical) adj statement\$).mp.
11. ((practi?e or care) adj guidelin\$).mp.
12. ((practi?e or care) adj standard\$).mp.
13. ((practi?e or care) adj protocol\$).mp.
14. ((practi?e or care) adj recommend:).mp.
15. ((practi?e or care) adj option:).mp.
16. (treatment adj (guideline or standard or protocol)).mp.
17. (appropriate adj (evaluat: or care)).mp.
18. (practi?e review and criteri:).mp.
19. ((medical or clinical) adj review:).mp.
20. practi?e review:.mp.
21. practice guideline:.mp.
22. exp Parenteral Nutrition, Total/
23. total parenteral nutrition.mp.
24. TPN.tw.
25. or/22-24
26. or/1-21
27. and/25-26



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## Parenteral Nutrition Literature Review

28. limit 27 to (english language and humans and yr="2008 -Current")
29. or/1-3
30. 28 and 29
31. remove duplicates from 30

### CINAHL Plus with Full Text

Interface: EBSCOhost, advanced search

Search mode: Boolean/Phrase

Search date: 28.08.2013

Limits: 2008-current, English, Line S9 also excludes MEDLINE records

Results: 34 De-duped: 34

#	Query	Limiters/Expanders	Results
S9	S3 AND S4	Limiters - Published Date: 20080101-20141231; English Language; Exclude MEDLINE records Search modes - Boolean/Phrase	34
S8	S3 AND S4	Limiters - Published Date: 20080101-20131231; English Language Search modes - Boolean/Phrase	135
S7	S3 AND S6		1,096
S6	S4 OR S5		278,582
S5	best practice* OR standard* OR statement OR guideline* OR CPG		278,582
S4	(MH "Practice Guidelines")		40,900
S3	S1 OR S2		6,385
S2	TPN		435
S1	(MH "Total Parenteral Nutrition") OR (MH "Parenteral Nutrition Solutions") OR (MH "Parenteral Nutrition") OR (MH "Nutritional Support")		6,293

Website	URL
<b>GUIDELINE DEVELOPERS</b>	
A.S.P.E.N. American Society for Parenteral and Enteral Nutrition	<a href="http://www.nutritioncare.org">www.nutritioncare.org</a>
American Academy of Pediatrics	<a href="http://www.aap.org">www.aap.org</a>
Academy of Nutrition and Dietetics (formerly American Dietetic Association)	<a href="http://www.eatright.org">www.eatright.org</a>
Australasian Society of Parenteral and Enteral Nutrition	<a href="http://www.auspen.org.au">www.auspen.org.au</a>



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October, 2013

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## Parenteral Nutrition Literature Review

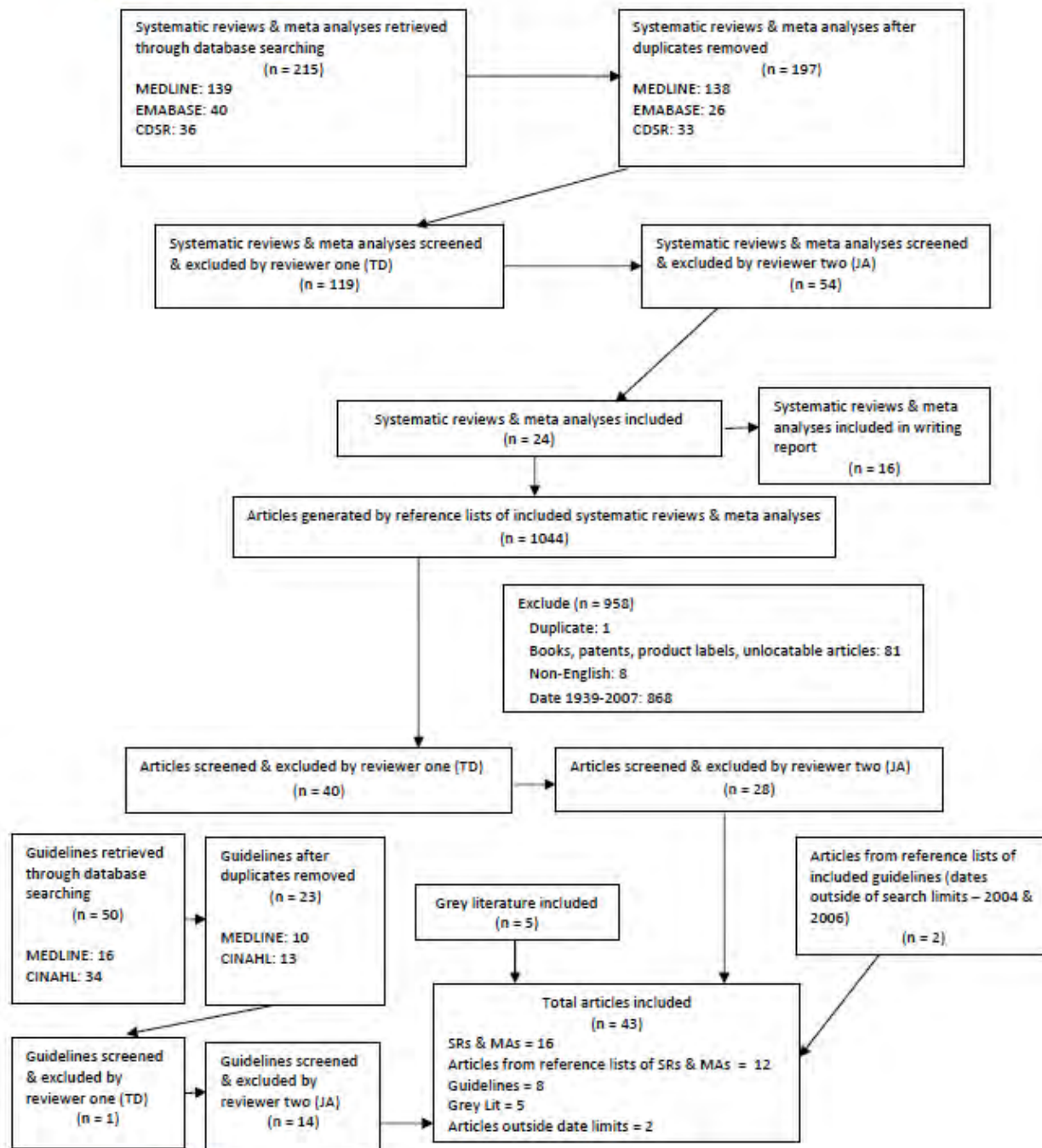
(AuSPEN)	
Canadian Agency for Drugs and Technologies in Health (CADTH)	<a href="http://www.cadth.ca">www.cadth.ca</a>
Canadian Association of Gastroenterology	<a href="http://www.cag-acg.org">www.cag-acg.org</a>
Canadian Critical Care Society	<a href="http://www.canadiancriticalcare.org">www.canadiancriticalcare.org</a>
Canadian Paediatric Society	<a href="http://www.cps.ca">www.cps.ca</a>
Canadian Pharmacists Association	<a href="http://www.pharmacists.ca">www.pharmacists.ca</a>
Critical Care Nutrition	<a href="http://www.criticalcarenutrition.com">www.criticalcarenutrition.com</a>
Dietitians of Canada	<a href="http://www.dietitians.ca">www.dietitians.ca</a>
Enhanced Recovery After Surgery (ERAS)	<a href="http://www.erassociety.org">www.erassociety.org</a>
Guidelines International Network (GIN)	<a href="http://www.g-i-n.net">www.g-i-n.net</a>
International Association for Surgical Metabolism and Nutrition (IASMEN)	<a href="http://www.iasmen.org">www.iasmen.org</a>
National Clearinghouse	<a href="http://www.guideline.gov">www.guideline.gov</a>
National Institute for Health and Care Excellence (NICE)	<a href="http://www.nice.org.uk">www.nice.org.uk</a>
New Zealand Guideline Group (became inactive 2012)	<a href="http://www.health.govt.nz">www.health.govt.nz</a>
Registered Nurses Association of Ontario (RNAO)	<a href="http://rnao.ca">rnao.ca</a>
Scottish Intercollegiate Guidelines Network (SIGN)	<a href="http://www.sign.ac.uk">www.sign.ac.uk</a>
Society, European Society for Clinical Nutrition and Metabolism (ESPEN)	<a href="http://www.espen.org">www.espen.org</a>
The Association of Women's Health, Obstetric and Neonatal Nurses Canada	<a href="http://www.awhonn.org">www.awhonn.org</a>
<b>NON-GUIDELINE GROUPS: Associations, Societies, Safety Organizations</b>	
Agency for Healthcare Research and Quality (AHRQ)	<a href="http://www.ahrq.gov">www.ahrq.gov</a>
FDA (US)	<a href="http://www.fda.gov">www.fda.gov</a>
Health Canada	<a href="http://www.hc-sc.gc.ca">www.hc-sc.gc.ca</a>
Institute for Safe Medication Practices (ISMP)	<a href="http://www.ismp.org">www.ismp.org</a>
Institute of Medicine	<a href="http://www.iom.edu">www.iom.edu</a>
National Coordinating Council for Medication Error Reporting and Prevention	<a href="http://www.nccmerp.org">www.nccmerp.org</a>
Society of Critical Care Medicine	<a href="http://www.sccm.org">www.sccm.org</a>
<b>JOURNALS</b>	
American Journal of Clinical Nutrition	<a href="http://ajcn.nutrition.org">ajcn.nutrition.org</a>
American Journal of Health-System Pharmacy	<a href="http://www.ajhp.org">www.ajhp.org</a>
Clinical Nursing Research	<a href="http://cnr.sagepub.com">cnr.sagepub.com</a>
Clinical Pharmacology & Therapeutics	<a href="http://www.nature.com/clpt">www.nature.com/clpt</a>
Critical Care Medicine	<a href="http://journals.lww.com/ccmjournal">journals.lww.com/ccmjournal</a>
JAMA Internal Medicine (formerly Archives of Internal Medicine)	<a href="http://archinte.jamanetwork.com">archinte.jamanetwork.com</a>
JAMA: The Journal of the American Medical Association	<a href="http://jama.jamanetwork.com/journal.aspx">jama.jamanetwork.com/journal.aspx</a>
Joint Commission Journal on Quality and Patient Safety	<a href="http://www.ingentaconnect.com/content/jc-aho/jcqs">www.ingentaconnect.com/content/jc-aho/jcqs</a>
Journal of Clinical Nursing	<a href="http://onlinelibrary.wiley.com/journal/10.1111/%28ISSN%291365-2702/issues">onlinelibrary.wiley.com/journal/10.1111/%28ISSN%291365-2702/issues</a>
Journal of Critical Care	<a href="http://www.jccjournal.org">www.jccjournal.org</a>
Journal of Nutrition	<a href="http://jn.nutrition.org">jn.nutrition.org</a>



## Parenteral Nutrition Literature Review

Journal of Pediatric Gastroenterology and Nutrition	<a href="http://journals.lww.com/jpgn">journals.lww.com/jpgn</a>
Journal of The American Dietetic Association	<a href="http://www.elsevier.com/journals/journal-of-the-american-dietetic-association/0002-8223">www.elsevier.com/journals/journal-of-the-american-dietetic-association/0002-8223</a>
JPEN: Journal of Parenteral and Enteral Nutrition	<a href="http://pen.sagepub.com">pen.sagepub.com</a>
Nutrition	<a href="http://www.journals.elsevier.com/nutrition/">www.journals.elsevier.com/nutrition/</a>
Nutrition in Clinical Practice	<a href="http://ncp.sagepub.com">ncp.sagepub.com</a>
Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy	<a href="http://onlinelibrary.wiley.com/journal/10.1002/%28ISSN%291875-9114">onlinelibrary.wiley.com/journal/10.1002/%28ISSN%291875-9114</a>

## Appendix 2: Article Flow Chart



## Appendix V: Memo to Alberta Health Services



# Memo

To: Verna Yiu, VP Quality and Chief Medical Officer, AHS

From: Patricia Pelton, Acting CEO, HQCA

Date: March 13, 2014

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**Re: Review of Processes Related to Parenteral Nutrition in Alberta Health Services (AHS) Edmonton Zone**

In March 2014, the HQCA review team conducted site visits at the pharmacies in the Edmonton Zone at the Royal Alexandra (RAH) and University of Alberta (UAH) Hospitals, as well as the central production pharmacy in the Calgary zone. The central production pharmacy was used as a comparator. During these site visits, the team conducted a brief review of randomly selected parenteral nutrition (PN) orders to see how the PN prescription was conveyed to pharmacy. Concerns have been raised by the PN experts on the HQCA review team about a number of dosing irregularities observed on some PN orders received by the Edmonton zone pharmacies referenced above.

The HQCA review team believes these dosing irregularities are significant and need to be communicated as an incidental finding in advance of the HQCA's final report. A summary of the observations, best practice recommendations from the literature, and some photographs (see Appendix 1) documenting the observed irregularities are provided below. It is important to note that the review team has insufficient information to quantify the magnitude of the issue or to comment on the clinical appropriateness of the dosing for specific patients.

As the identified dosing irregularities are incidental findings, the HQCA review team suggests that AHS conduct a more in-depth review to validate the HQCA review team's interpretation of the irregularities. It is suggested that the AHS review include:

- Clarification of the clinical indication for high dose folic acid in the patients for whom this is prescribed.
- Review of the ordering process to identify how clinical decisions are made and communicated regarding addition of folic acid, thiamine and heparin to PN.
- Clarification of how the dosing interval for vitamin K is communicated, particularly for repeat orders of an existing PN prescription. This should include determining what the common understanding is of all those involved in the PN ordering and review process (physician, dietician, pharmacist) regarding the ordering interval for this drug.

The HQCA review team requests that AHS provide a summary of the actions and outcomes related to these concerns regarding dosing irregularities so this issue can be appropriately addressed in our report.

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## Summary of observations regarding selected dosing irregularities noted on PN order forms

1. *Folic Acid:* Of most concern to the PN experts on the review team were the excessively high doses of folic acid prescribed for some adult patients (5 to 10 mg per day). This was noted on a number of orders and was verified by reviewing photographs taken as part of the site visits. Of the nine adult PN orders photographed (two from UAH, one from RAH, one from the Cross Cancer Institute (CCI), two from the Grey Nuns Hospital (GN), and three from the Misericordia Hospital (MCH)), three prescribed folic acid. Of those three, one prescribed 10 mg per day (MCH) and two prescribed 5 mg per day (UAH & CCI). Examples of order forms illustrating the irregularities are shown in Appendix 1. Furthermore, all three orders which prescribed folic acid also prescribed 10 mL per day of multiple vitamin solution. All multivitamin products routinely added to PN contain the daily folic acid dose recommended for parenteral nutrition patients. Consequently, the patients receiving PN with both the added folic acid and multiple vitamin solution received a substantially higher than recommended daily dose of folic acid. The recommended dose for folic acid in PN is 0.6 mg per day for adults (Vanek 2012). Observed prescribed doses were up to 10.6 mg per day which at the highest is over ten times the recommended dose. The HQCA review team could not find any literature that supports the use of parenteral folic acid in these doses.
2. *Thiamine:* At one site there appeared to be a failure to order thiamine for neonates who were not receiving a multivitamin preparation because of a back order in the parenteral pediatric multivitamin product. Safety recommendations in the event of a shortage of the multivitamin product include the addition of thiamine to PN for all patients. This enables PN to meet the daily nutritional requirement for thiamine.
3. *Heparin:* Heparin was ordered for some adult PN patients. An example is shown in Appendix 1. This practice is not currently recommended by the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.).
4. *Vitamin K:* For some of the orders, it was unclear, based on the order form, if the amount of vitamin K ordered was to be given daily or weekly. A weekly dose is clinically appropriate, but the same amount ordered every day would be a high dose. It was unclear to the review team how the dose of vitamin K on the order would be treated if the pharmacy was directed to use the same order to prepare PN for subsequent days of therapy, which was a common practice at all sites.

## Best Practice from Literature

1. *Folic Acid:* A.S.P.E.N recommends adding 600 mcg per day (0.6 mg per day) to PN for adult patients (Vanek 2012). The treatment of megaloblastic anemia due to folic acid deficiency is an example of when a higher dose of folic acid is indicated; in this condition the typical dose is 1 mg per day.
2. *Thiamine:* When there is a product shortage of a multivitamin preparation, A.S.P.E.N recommends adding thiamine, folic acid, pyridoxine and ascorbic acid to parenteral nutrition daily (Ayers 2013). Thiamine is noted to be critical and should never be omitted from parenteral nutrition (Ayers 2013, Vanek 2012). The suggested daily dose of intravenous thiamine in PN is 6 mg for adults, 1.2 mg for children, and 0.35 to 0.5 mg per kg for infants (Vanek 2012).
3. *Heparin:* The A.S.P.E.N Clinical Guidelines for Parenteral Nutrition Ordering, Ordering Review, Compounding, Labeling and Dispensing suggest that heparin not be included in PN admixtures for reducing the risk of central vein thrombosis (Boullata 2014). The issues with the heparin in adult PN are two-fold.
  - There is rarely an indication for including heparin (a high-alert medication) other than perhaps when administering PN through a peripheral vein, although data for this indication are weak.
  - There is a compatibility and stability concern when a PN admixture containing heparin, and especially if it also contains calcium, comes into contact with the intravenous fat emulsion (IVFE) administered by Y-site into the PN line. The stability of the IVFE is compromised and the resulting change to the IVFE is rarely visible to the naked eye. For this reason, heparin cannot be used in a 3-in-1 preparation (total nutrient admixture) where the macronutrients (amino acid, dextrose and IVFE) and micronutrients are mixed together in one bag.
4. *Vitamin K for adults:* The recommended adult PN dose of vitamin K for men and women is 150 mcg per day (Vanek 2012). If a multivitamin additive containing vitamin K is not used, options to meet the adult vitamin K requirements include once a week high dose (5 or 10 mg), daily low dose (1 mg or less), or no additional vitamin K for patients receiving 50 g or more of IVFE per day (IVFE contains 3 mcg of vitamin K per g). The review team is not aware of a consensus on the best approach to prescribing vitamin K in PN. The review team could not find any adult parenteral multivitamin products sold in Canada that contain vitamin K. Therefore the option for adults would be to prescribe a separate daily or weekly dose of vitamin K administered alone or added to the PN.



## APPENDIX I: PHOTOGRAPHS ILLUSTRATING PRESCRIBED FOLIC ACID DOSING IRREGULARITIES

### PN order from Misericordia Community Hospital

Additives	Recommended Requirements	Total 24 hour Intake	Pharmacy Use Only
Sodium <sup>1</sup>	1 - 2 mmol / kg / day	150 mmol / day	
Potassium <sup>1</sup>	1 - 2 mmol / kg / day	— mmol / day	
Calcium	10 - 15 mmol / day	— mmol / day	
Magnesium	8 - 20 mmol / day	2 mmol / day	
Phosphate	20 - 40 mmol / day	— mmol / day	
Acetate (mmol)	as required	50 mmol / day	
Multiple Vitamin Solution	10 mL / day	10 mL / day	
Vitamin K <sup>2</sup>	10 mg / week <sup>3</sup>	10 mg / week	
Trace Element Solution	1 mL / day	1 mL / day	
Heparin	1 unit / mL	— units / day	
Zinc	as required	— mg / day	
Folic Acid	as required	10 mg / day	
Famotidine	as required	— mg / day	
Insulin (units) <sup>4</sup>	as required <sup>5</sup>	— units / day	
Hydrocortisone sodium succinate	5 mg / L	— / day	
Other (specify)		— / day	

### PN order from University of Alberta Hospital

Additives	Recommended Requirements	Total 24 hour Intake	Pharmacy Use Only
Sodium <sup>1</sup>	1 - 2 mmol / kg / day	100 mmol / day	
Potassium <sup>1</sup>	1 - 2 mmol / kg / day	20 mmol / day	
Calcium	10 - 15 mmol / day	5 mmol / day	
Magnesium	8 - 20 mmol / day	5 mmol / day	
Phosphate	20 - 40 mmol / day	— mmol / day	
Acetate (mmol)	as required	— mmol / day	
Multiple Vitamin Solution	10 mL / day	10 mL / day	
Vitamin K <sup>2</sup>	10 mg / week <sup>3</sup>	10 mg / week	
Trace Element Solution	1 mL / day	1 mL / day	
Heparin	1 unit / mL	— units / day	
Zinc	as required	5 mg / day	
Folic Acid	as required	5 mg / day	
Famotidine	as required	— mg / day	
Insulin (units) <sup>4</sup>	as required <sup>5</sup>	— units / day	
Hydrocortisone sodium succinate	5 mg / L	— / day	
Other (specify)	Selenium	100 mcg / day	



## PN order from Cross Cancer Institute

Additives	Recommended Requirements	Total 24 hour intake	Pharmacy Use Only
Sodium	1 - 2 mmol / kg / day	70 mmol / day	
Potassium	1 - 2 mmol / kg / day	50 mmol / day	
Calcium	10 - 15 mmol / day	3 mmol / day	
Magnesium	8 - 20 mmol / day	5 mmol / day	
Phosphate	20 - 40 mmol / day	20 mmol / day	
Acetate (mmol)	as required	— mmol / day	
Multiple Vitamin Solution	10 mL / day	10 mL / day	
Vitamin K <sup>2</sup>	10 mg / week	— mg / week	
Trace Element Solution	1 mL / day	1 mL / day	
Heparin	1 unit / mL	2500 units / day	
Zinc	as required	— mg / day	
Folic Acid	as required	5 mg / day	
Famotidine	as required	— mg / day	
Insulin (units)	as required	— units / day	
Hydrocortisone sodium succinate	5 mg / L	12 / day	
Other (specify)		— / day	

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Boullata J, Gilbert K, Sacks G, Labossiere RJ, Crill C, Goday P, Kumpf VJ, Mattox TW, Plogsted S, Holcombe B. A.S.P.E.N. Clinical guidelines: Parenteral nutrition ordering, order review, compounding, labeling, and dispensing. *Journal of Parenteral and Enteral Nutrition* 2014;38(3):334-375.

Vanek V, Borum P, Buchman A, Fessler TA, Howard L, Jeejeebhoy K, Kochevar M, Shenken A, Valentine CJ. A.S.P.E.N. Position paper: Recommendations for changes in commercially available parenteral multivitamin and multi-trace elements. *Nutrition in Clinical Practice* 2012;27:440-491.

## Appendix VI: AHS response to HQCA March 13, 2014 memo



### Memorandum

**Date:** April 28, 2014  
**To:** Patricia Pelton, Acting CEO, HQCA  
**From:** Dr. Verna Yiu, VP Quality & Chief Medical Officer  
**RE:** Review of Processes Related to Parenteral Nutrition in Alberta Health Services (AHS) Edmonton Zone (Response to HQCA memo)

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Thank you for your correspondence on March 14, 2014 regarding the Health Quality Council of Alberta (HQCA) Review Team site visits at pharmacies in the Edmonton and Calgary Zones. In follow up to your request, I asked for an internal review of the specified dosing irregularities that were observed on some parenteral nutrition (PN) orders in the Edmonton Zone. A small group of AHS staff and medical experts recently completed this work and their response is enclosed (see Attachment 1 below). A number of relevant documents were identified during this process and they have also been provided (Attachments 2 to 6).

We look forward to feedback on this detailed information, as well as the broader report, from the HQCA Review Team. Please let me know if further clarification or discussion would be helpful.

Thank you again for the ongoing support and collaboration with HQCA in advancing the quality and patient safety of care delivered in AHS.



## ATTACHMENT 1

### Review of Processes Related to Parenteral Nutrition in Alberta Health Services (AHS) Edmonton Zone (as outlined in HQCA Memo dated March 13, 2014)

Dosing irregularities were identified in a brief review of randomly selected Parenteral Nutrition (PN) orders. To develop an understanding of current practice in regards to the identified irregularities and to respond to the HQCA team, information was obtained from multiple stakeholders including: Edmonton Zone Nutrition Services (NS) and Pharmacy management, Dietitian Program Leads at the UAH, Stollery and RAH sites, the Covenant Dietitian Program Leader, the Provincial Nutrition Service Medical Advisor, the Edmonton Zone Nutrition Medical Lead, the NS Child Health Strategy Director, and the NS Adult/ Senior Strategy Director.

The identified irregularities from Edmonton zone highlight the need for improved standardization and adherence to evidence based guidelines. Potential solutions may include provincial PN practice guidelines, targeted education and improved PN ordering processes.

#### Folate:

There is variability in folate ordering practices. Folate is a nutrient that is regularly ordered as part of the PN prescription. For pediatric patients, the practice of adding additional folate over that provided by the multivitamin (MVI) solution is not routine. It may be added in the case of acute or chronic disease known to waste this vitamin such as dialysis. The dose ordered is determined in consultation with the medical team and biochemical values would be monitored. For adult patients, orders for additional folate in PN are typically driven by the attending physician. Orders for folate that exceed the tolerable upper limit (1000 mcg) and as high as 5000 to 10,000 mcg, may be requested by the attending physician for various clinical indications (e.g. thrombocytopenia, megaloblastic/ macrocytic anemia, alcohol abuse, and CRRT).

The addition of folate at levels that exceed the tolerable upper limit are largely based on historical practices. A study in Edmonton during the 1980s found some benefit for critical care patients with low platelets; this study led to increased use of additional folate. In general, there is perceived benefit (possibly related to DNA synthesis) and low risk for the addition of folate to PN. For example, there are no solubility considerations regarding folate and risk of toxicity is low. With regular addition of folate to PN, folate deficiency is rare.

#### Thiamine:

Multivitamin solution (MVI) does contain thiamine. For PN shortages, Provincial Nutrition Services and Pharmacy worked collaboratively to develop communications (Medication Postings), which are distributed by pharmacy. (Refer to attached Medication Postings). The Medication Postings provide guidance on management of the shortage. For the MVI shortage, the aim was to provide multivitamin solution to patients with the greatest need (e.g. neonates). During shortages, general practice has been to not add multiple individual vitamins to PN solutions because of the impact on pharmacy and possible risk with more additions to the prescription. For neonates, thiamine may have been given orally or via enteral feed, and therefore would not be apparent in the PN order. At one site (RAH), the medical team decided to hold the MVI solution for the first 3 days of PN and then give at half dose if the neonate was beginning to start enteral feeds.





### Heparin:

The addition of heparin to PN is based on historical practice to prevent the risk of thrombophlebitis in peripheral PN. Heparin is not added to central PN. The reference cited in the Best Practice from Literature review: ASPEN Clinical Guidelines for Parenteral Nutrition Ordering, Ordering Review, Compounding, Labeling and Dispensing (2014) recommend that heparin not be included in PN admixtures for reducing the risk of central vein thrombosis in adults. Use of heparin is supported by limited evidence and in premixed standardized solutions, heparin is no longer an additive. Because this practice is not based on evidence, plans have been underway to discontinue its use for adult patients.

Recommendations for heparin use are included in the AHS Pediatric Nutrition Support Manual (released Sept 2013), as per the ASPEN Pediatric Core curriculum (2010). The ASPEN Pediatric Core curriculum (2010) states: *Heparin is routinely added to neonatal and pediatric PN solutions to maintain patency of the central venous catheter. Lower flow volumes, smaller catheters, and frequent interruptions of PN solutions may play a role in increased incidence of catheter clotting than in adults. Preliminary data suggest that a heparin concentration of 0.5 units/mL in neonatal PN solutions may be as effective for maintaining catheter patency as 1 unit/mL.* When heparin is used, the interaction between heparin and calcium is reviewed by pharmacy to ensure that calcium added to solutions will result in a safe product when administered.

### Vitamin K:

The practice of adding Vitamin K to PN is variable. In the last 2 years, the pediatric PN multivitamin solution was changed to include vitamin K. For pediatric patients, Vitamin K may be added in addition to that supplied by the MVI solution; this would be done in conjunction with specialist medical teams (e.g. thrombosis team).

When Vitamin K is added, it is generally given as a weekly or biweekly dose. Vitamin K is usually ordered due to perceived clinical/ therapeutic needs and convenience of adding to the PN solution. The order reviewed may be considered typical for a critical care patient with liver failure or coagulopathy.

When vitamin K is not part of the multivitamin solution, vitamin K orders need to clearly specify weekly or daily dose. Dietitians have been encouraged to specify the date for the vitamin K addition on the TPN order form; however this was not done on the example provided. Dietitians should be dosing Vitamin K in alignment with nutritional requirements, and doses meant for a therapeutic intent should only be administered in collaboration with the medical team.

Review of the evidence around the indications for addition of vitamin K is needed. In addition, guidance on the safest, most effective way to order vitamin K is needed.



#### Overall:

A common theme based on these irregularities is the need for PN guidelines/ standards to promote consistent, evidence informed practice.

Development/ review of current recommendations for safe PN in adult, pediatric and neonatal populations should include:

- Ordering practices (e.g. improving clarity of hand-written orders and a simplified form)
- Parenteral micronutrient recommendations
- Processes for optimizing PN stewardship, including assessment and decisions for non-nutrition orders or orders below or above normal requirements or therapeutic limits
- Handling of PN micronutrient shortages
- Non-nutritive additions to PN (e.g. medications)

Additional recommendations to improve the quality of care and safe delivery of PN include:

- 1) Complete an environmental scan to improve understanding of practices at site and zone levels, including orders, delivery of PN and monitoring patients.
- 2) A provincial committee should be formed to discuss evidence, recommendations, identify practice gaps, and identify strategies to bring practice closer to standards. Membership should include physicians/ medical leadership, dietitians, pharmacists, nurses, Nutrition Services management, AHS quality, AHS provincial policy, AHS Home Nutrition Support Program (HNSP) and Contracting, Procurement and Supply Management (CPSM).
- 3) Clarity is needed on who should be responsible for PN standards/ guidelines and quality monitoring provincially and within zones. In addition, clearer understanding of accountability and guidance around practice when there are shortages is needed. This includes more clear guidance regarding use of single nutrient additives during shortages.
- 4) Each disciplines' unique role in PN provision should be supported by AHS education and training. Translation of evidence into practice and continual development of skills/ knowledge of clinicians (physicians, dietitians, pharmacists and nurses) is needed. Practices such as addition of heparin; high dose folate, and vitamin K dosing should be reviewed to ensure that they are appropriate for the clinical scenario.
- 5) Ongoing audit processes are required to ensure compliance with practice recommendations and identify opportunities for improvement. Clearly identified accountabilities for who is responsible to lead improvement are also needed.
- 6) A shift to use of standardized PN solutions (Olimel) is recommended where appropriate to reduce variability in practice and improve safety. This is planned to occur in adult populations in Edmonton zone within the next few months.



## Appendix VII: HQCA response to AHS April 28, 2014 memo



# Memo

To: Verna Yiu, VP Quality and Chief Medical Officer, AHS

From: Patricia Pelton, Acting CEO, HQCA

Date: April 30, 2014

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**Re: Review of Processes Related to Parenteral Nutrition in Alberta Health Services (AHS) Edmonton Zone**

Thank you for sharing detailed information pertaining to the AHS internal review of the dosing irregularities noted during the HQCA Total Parenteral Nutrition Review. A number of the findings and recommendations identified in your response dated April 28, 2014 were aligned with findings and recommendations of the HQCA review, such as those pertaining to communicating parenteral nutrition (PN) orders, education requirements, and PN oversight. Additional strategies to further improve quality and patient safety related to PN are outlined in the HQCA review.

It is noteworthy that your review also highlighted the need to review the evidence related to prescribing selected micronutrients (i.e., vitamin K) and non-nutrient medications (i.e., heparin) in PN. The evidence for prescribing folate and thiamine in PN patients should also be reviewed. This will be helpful in developing evidence based provincial PN practice guidelines.

Per the original terms of reference, the HQCA would be pleased to continuing to support AHS by conducting a second phase of the review. This would include a review of PN practices throughout the province related to patient assessment, prescribing, and patient monitoring, as well as benchmarking them to leading practices. Findings could be used by AHS to inform the development of evidence based provincial PN practice guidelines.

## Appendix VIII: Glossary

**Admixture:** The result of combining two or more fluids.<sup>1</sup>

**American Society for Parenteral and Enteral Nutrition (ASPEN)** is a community of dietitians, nurses, pharmacists, physicians, scientists, students and other health professionals in nutrition support clinical practice, research and education. This organization strives to advance the science and practice of clinical nutrition and metabolism thorough such avenues as guidelines, standards, publications and continuing education programs.<sup>2</sup>

**Automated compounding device:** A device that is used to prepare multi-component sterile products. To compound PN preparations it transfers large-volume (dextrose, amino acids, fat emulsion, and sterile water) and small-volume parenterals (electrolytes, minerals, and vitamins) to a PN container.<sup>1,3</sup>

**Compatibility:** When two or more products are combined, the physicochemical integrity and stability of each product are not altered.<sup>1</sup>

**Compound:** Mixing two or more ingredients together where at least one is a medication but does not include reconstituting a medication or medication with water.<sup>4</sup>

**Computerized prescriber order entry (CPOE):** An electronic clinical information system in which the prescriber enters orders directly into a computer.<sup>1</sup>

**Enteral nutrition:** Feeding of a liquid food mixture containing protein, carbohydrates, fats, vitamins and minerals that may be given through different types of feeding tubes into the stomach or small bowel. Examples of these tubes are nasogastric or nasoenteral feeding tubes or a gastrostomy or jejunostomy tube which is placed through the skin into the stomach or bowel.<sup>1,5</sup>

**High-alert medications:** Medications that have a heightened risk of causing significant harm to a patient if they are used in error.<sup>6</sup>

**Independent double checks:** A process where a second practitioner verifies each component of the work process in such a way that the practitioner whose work is being checked does not influence the second practitioner so as not to create a bias or decrease the visibility of an error.<sup>7,8</sup>

**Infant:** One to 12 months of age.<sup>1,9</sup>

**Laminar airflow hood:** Is a workstation for compounding sterile preparations that provides an ISO Class 5 environment.<sup>3</sup>

**Lipid:** The macronutrient component of PN that provides the fat requirements for a patient. A lipid product (e.g. intravenous fat emulsion) is an intravenous oil-in-water emulsion of oils(s), egg phosphatides, and glycerin.<sup>1</sup>

**Neonate:** An infant during the first 28 days of life.<sup>1,9</sup>

**Nutrient:** Protein, carbohydrate, lipid, vitamins, minerals, or water.<sup>1</sup>

**Nutrition:** The result of the way a person takes in and uses nutrients.<sup>1</sup>

**Parenteral nutrition:** Mixture of nutrients (protein, carbohydrates, lipids, vitamins and minerals) given into the blood through an intravenous catheter into a large-diameter vein (e.g., superior vena cava) which is usually referred to as a central line, or through a vein in the hand or forearm which is usually referred to as a peripheral line. Examples of these catheters include Hickman, Broviac, PICC, double lumen.<sup>1,10</sup>

**3-in-1 PN formulation:** An intravenous PN formulation containing all the macronutrient components of PN (lipid, amino acids, dextrose), as well as the micronutrient components of PN (i.e., vitamins, trace elements and minerals) in a single container.<sup>1</sup> This is sometimes referred to as a **total nutrient admixture**.<sup>11</sup>

**2-in-1 PN formulation:** A formulation that combines the dextrose and amino acid in a single container.<sup>11</sup> The lipid is provided in a separate bag or syringe.

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## Appendix IX: Acronyms

ACD	Automated compounding device
AHS	Alberta Health Services
ASPEN	American Society for Parenteral and Enteral Nutrition
BPS	Board of Pharmacy Specialties
CPOE	Computerized prescriber order entry
CPP	Central Production Pharmacy
EM 2400	ExactaMix 2400
GN	Grey Nuns
HQCA	Health Quality Council of Alberta
ISMP	Institute for Safe Medication Practices
MAUDE	Manufacturer and User Facility Device Experience
MCH	Misericordia Community Hospital
PN	Parenteral Nutrition
QAC	Quality Assurance Committee
QAR	Quality Assurance Review
RAH	Royal Alexandra Hospital
RLS	Reporting and Learning System
UAH	University of Alberta Hospital
USP	United States Pharmacopeia

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