Key Advances in Pharmacological Approaches to Clinical Nutrition Therapy: 2016 Evidence Update

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Abstract

In 2016, pharmacy experts began collaborating more with those in nutrition to ensure better results for patients in healthcare settings. During that period, leading studies examined the pharmacology of parenteral and enteral nutrition, how nutrients and drugs affect each other and the role of pharmacists in nutritional care. At this time, there were major advances in using research-based care approaches, mainly in critical care, oncology and after surgery. New studies revealed that when nutrients are given according to each person's needs by clinical pharmacists, it helps avoid refeeding syndrome, plan vitamin and mineral usage and keep IV mixtures safe for use. Furthermore, the American Society for Parenteral and Enteral Nutrition (ASPEN) helped polish existing guidelines which also supports pharmacists working alongside other members of nutrition teams. Literature in this field emphasized why ongoing learning, making new protocols and increasing the involvement of pharmacists are necessary to boost the standards in nutrition support care.

Keywords: ***Pharmacy nutrition support practice, parenteral and enteral nutrition, drug–nutrient interactions, intravenous admixture safety, clinical pharmacist interventions, ASPEN and ESPEN guidelines, refeeding syndrome management.***

1.Introduction

Because of modern developments in healthcare, clinical pharmacists who practice nutritional therapy have to keep up with new and detailed information in the field. In most places today, clinical pharmacists offer not only pharmacotherapy but also manage all nutrition support responsibilities. As a result of this approach, practitioners are expected to know about new nutritional science, support strategies and emerging therapies in addition to working in various therapeutic areas.

To support nutrition now, it's important to go well beyond calorie and protein amounts, including detailed metabolic, drug and nutrient interactions, making targeted feed formulas, handling various injection medications, placing importance on micronutrients and having specific plans for monitoring patients on treatments. To help patients, clinical pharmacists must handle many varieties of evidence in gastroenterology, critical care medicine, oncology, pediatrics, geriatrics and surgical specialties given the many nutrition and treatment issues they involve. Since research in these associated areas is increasing exponentially, it becomes almost impossible for one person to review all the important literature at once(1).

In addition, by providing nutrition support, pharmacists need to pay close attention to the ways different nutritional interventions, along with medicines, influence each other. Precision medicine, personal nutrition and new drugs have increased the difficulties already faced by physicians. Having to follow recent rules, adhere to quality improvements and apply professional standards add to the knowledge management problems faced by contemporary nutrition support pharmacists.

The review covers these problems by examining the best science published on pharmaceutical nutrition support since 2016. We worked with eight clinical pharmacists to review and rank papers based on how important they were in clinical situations and the difference they might make for patients. The compilation was developed by community agreement to summarize knowledge, advance evidence-based practice and give practical advice for dealing with complex nutrition situations in clinical settings.

2.New Research in Pediatric Critical Care Nutrition Leads to Changes in Early Intervention Approaches

The PEPaNIC trial performed by Fivez and other researchers overturns widely held ideas about when and how to give nutrition aid to severely ill kids. In this important global study, researchers looked at 1,440 critically ill kids in specialized care, testing if starting nutritional support early (after 24 hours) was better than waiting until the 8th day of care. Only those classified as anticipated ICU admissions over 24 hours and STRONGkids scores of 2 or higher were included, as most patients had to be term newborns to much older adolescents.

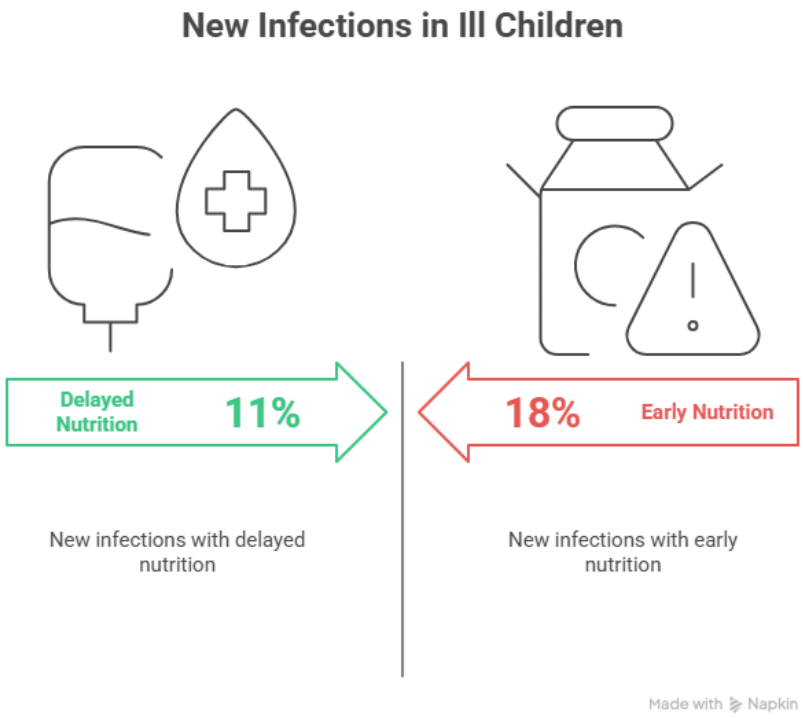

FIGURE 1 New Infections in Ill Children

It was proven that waiting to give malnourished patients parenteral nutrition was clinically much better, as it led to a 37% decrease in new infections (from 18% to 11%), reduced intensive care unit stay by 3 days (from 9 to 6) and lowered the hospital stay by as much as 4 days (from 21 to 17). Even more surprising, the benefits from starting parenteral nutrition after four weeks worked for everyone, whether they were very young neonates or babies beyond four weeks. Extra benefits were a quicker start on weaning from mechanical ventilation (2 days faster), fewer patients requiring renal replacement therapy (odds ratio 0.49) and a decrease in all healthcare costs(2).

Despite the traditional view that kid patients must eat soon to remain healthy because babies have lower metabolism and need more energy, the new research suggests otherwise. Because the research team carefully matched all participants, used consistent glucose management protocols and provided a wide range of micronutrients, there is reliable evidence that these surprising results are true. Yet, there are other issues to consider, like changes in metabolism, the body's coping methods under stress and side effects from well-meant nutrition advice.

A close examination of these results highlights many problems that need to be remembered when using them widely. Out of 75% of late parenteral nutrition patients, only a few actually went on to receive parenteral nutrition because they were safely discharged early, while of those given early parenteral nutrition, 50% were released shortly after. The data imply that likely, the studied group included many patients who were in intensive care for only a brief time and are not typical candidates for receiving parenteral nutrition under any timing policy. Estimations of a patient's energy requirements were made with predictive equations and not by measuring metabolism directly which could influence understanding of how well the patient is being fed and how much energy their body is using.

Since we lack validation of the STRONGkids nutritional screening tool for critically ill pediatric patients, concerns arise about the accuracy of stratifying nutritional risk and selecting patients. In addition, the study found that there were more episodes of low blood sugar in the late parenteral nutrition group which could suggest that additional

neurocognitive troubles may surface over a longer period. It is possible that younger patients are less similar to older pediatric patients and therefore might react differently when their nutrition is delayed.

3.Critical Care Nutrition Guided by Protein: Recent Findings Support New Ways to Treat Patients

The findings of Nicolo and colleagues from their worldwide study indicate that protein delivery may be more important than reaching calorie targets for improving the outcome of adult patients being treated in critical care. To achieve this, investigators looked at data previously collected by the International Nutrition Survey in 2013 which included statistics on 2,828 people spending at least four days in the intensive care unit and a further subset of 1,584 spending more than twelve days(3). By looking at cases from many different areas, institutions and contexts, the study gave the connections between protein intake adequacy and clinical results greater authenticity.

Those patients consuming most of their recommended protein targets (aiming for 1.2 g/kg/day) clearly had a better survival rate, with 25% fewer deaths in the four-day group and 20% fewer in the twelve-day subset compared to people not eating enough protein. Surprisingly, eating enough calories did not explain the benefits from protein, since patients achieving target energy intake of 80% or higher did not respond any differently than those with lower energy intakes. These results indicate that, on average, only 61% to 67% of the target protein amounts are delivered to patients daily.

The results agree with rising awareness that critical illness leads to fast protein breakdown, urgently needed protein and altered how amino acids are used, so extra nutrition support is often recommended. The finding that more protein appears linked to shorter recovery times in patients with critical illness for twelve days or more suggests that supplying these patients with high levels of protein may help them recover more quickly and reduce the chance of nutrition-related complications.

The limits of this investigation which depend on observation, need to be considered when turning these findings into guidelines used in medical practice. Since it is difficult to control for confounding issues, different deviations in care and backwards causation, it’s hard to say with certainty how the reported associations work. Besides, the study did not explain the details behind the shortfall in reached protein targets which might stem from regular interruptions in feeding, an intolerance to some foods, the need for special formulas or errors in writing prescriptions.

Due to the variety of underlying problems and metabolic needs in the study group, it is difficult to use targeted protein supplementation for each subset of patients(4). Furthermore, the research did not measure how well absorption makes proteins and their impact which timing is best to take protein and if amino acid mix affects results. Since we don’t always have thorough data on medications taken at the same time, the level of illness and a patient’s nutritional history, we struggle to find the best patients for aggressive protein supplements.

How to Limit Food and Support Patients in Important Care: Managing Provision of Food and Complications **Prevention**

Petros and his team performed a randomized pilot trial that contests the traditional ways we feed patients with critical illness by raising the question of using hypocaloric feeding rather than providing normal levels of food and calories. The patients participating in this single study were selected to ensure they would have artificial nutrition for more than three days. For the first seven days in the ICU, 100 of them were randomly assigned to receive either the total energy they needed, as measured or calculated or half of their needed energy. When direct calorimetry was possible, that was used and otherwise Ireton-Jones predictions were used to determine energy requirement. Nutrition through tubes was favored and parenteral nutrition or supplements were added as required.

The study found that those who ate less were more frequently infected but also benefited from better blood sugar levels, a reduced need for insulin and fewer cases of diarrhea. In spite of the higher infection rates, no meaningful differences were seen in survival rates after ICU care, hospital care or after 28 days for those fed parenterally or enterally. These results point to the many forms that nutrition-related issues take in critical care and the relationship between what one eats, metabolic stability and the immune system.

Some significant limitations found in the research methods are likely to impact how we understand and generalize these results. Since those at most risk might gain the most from nutrition support, participants whose BMI was below 18.5 kg/m², those aged over 80 and individuals getting immunosuppressive therapy were all left out of the

study. Using this purposeful enrollment may have chosen people who were generally nourished and metabolically able, limiting how the study can improve care for seriously ill or undernourished people seen in hospitals.

One of the biggest problems is that the "normocaloric" arm did not reach their recommended calories and thus received less than the calorie goal recommended. The main problem with the method causes the study to miss its main objective and leaves a possibility that those differences could result from degrees of not eating enough rather than from following various feeding plans(5). Moreover, the study did not seem to give the recommended 1.2-2.0 g/kg/day of protein, as prescribed by current critical care guidelines which may have affected the outcome.

The greater number of hospital-acquired infections in the hypocaloric group prompts us to examine the effects of energy restriction on immunity, especially under stress when people may need more energy to respond to illness and rebuild. Yet, since the study could not manage how much protein was given, the nutrition status of the animals or the health of their illnesses at the start, it's unclear if caloric limitation directly contributes to infection. The better glycemic control seen in the group on the hypocaloric diet may be due to less glucose intake, while the better stomach tolerance might reflect a reduction in feeding, not matching energy requirements.

4.Meta-Analytic Research into the Ways Calories Are Provided via Enteral Nutrition

Al-Dorzi and colleagues performed a thorough review of many randomized trials, publishing their insights on what enteral caloric feeding intensity means for critically ill adults in November 2015. A total of 7,069 patients were included in the study, with 21 qualifying trials comparing lower caloric intake to those on a higher caloric diet. Seven of these investigations compared diets that restricted calories with regular diets and fourteen showed significant differences in the amount of calories animals from intervention and control groups consumed.

There was no statistical difference in hospital survival rates among patients receiving different caloric intakes (relative risk 0.95), even when results were tested in separate groups based on age, illness severity, percent of target caloric intake and differences in the level of caloric intake received. Lower food intake led to reduced rates of bloodstream infections (relative risk of 0.718) and lower demand for dialysis (relative risk of 0.711).

Despite having longer stays in the hospital, patients in lower calorie groups did not have significant differences in ICU mortality, infections, breathing machine use or ICU stay. Such results underline that nutritional support in critical care is challenging as it should manage several concerns at the same time, including infection, stable metabolism, helping with recovery and watching the use of healthcare resources(6).

Several key strategies used in this meta-analysis helped make the results accurate and reliable: search of studies systematically, standard way to extract data, assessing the reliability of included studies and planning subgroup analysis to investigate the root of differences. Yet, limitations in how the studies were conducted and how their data were studied should be considered before using these results in daily clinical practice. Because the studies choose not to involve parenteral nutrition as a main treatment, their findings cannot be applied to everyone receiving intravenous nutrition. Also, most of the participants are medical ICU patients with different characteristics than patients who are surgical or traumatic, so results are possibly not generalizable to these groups.

Perhaps the main issue is that almost all patients in the "higher caloric" arms did not reach their intended caloric goals which means that both sets of study patients may have all received inadequate food to some extent instead of accurate caloric restriction versus kitchen-sink care. Because of this, studying and deciding on the best amount of calories for health can be challenging. In addition, studying the meta-analysis, researchers were unable to assess adequate protein delivery as emerging studies suggest this should be prioritized over sufficient calories in critically ill patients(7).

5.Research for Compatible Drugs in Parenteral Nutrition: Pushing Forward its Safety and Efficacy

Anderson and colleagues performed a landmark compatibility study that tackles crucial drug compatibility problems in pediatric parenteral nutrition by checking how calcium chloride and sodium glycerophosphate behave together. Since electrolyte solutions like calcium gluconate and sodium phosphate are presently lacking, clinicians need to develop new approaches using ingredients that have rarely or never been used before. Various concentrations of macronutrients (15% dextrose with fluctuating amino acid and lipid content) were used in 90 formulations of parenteral nutrition along with five combinations of calcium (10-50 mEq/L) and phosphate (10-50 mmol/L).

Included in the study were visual inspection protocols and an analysis of particles in the drug using standard U.S. Pharmacopeia criteria for physical compatibility, with a requirement for crystal counts at ≤12 particles/mL for particles ≥10 μm and fewer than 2 particles/mL for particles ≥25 μm. All 90 formulations tested were found to be compatible at both standard temperature and 37°C over 24 hours, with no sign of visible precipitation, color variations or formation of haze. All samples were found to lack crystals bigger than 25 μm, suggesting that sodium glycerophosphate provides a better match with soft tissue than traditional phosphate salts.

Since sodium glycerophosphate works better and is less likely to interact with calcium, these findings mean its use is likely to help in parenteral nutrition management(8). It seems the organic phosphate structure of sodium glycerophosphate improves its solubility which in turn raises the total amounts of calcium and phosphate in parenteral nutrition products, allowing for potential greater formulation strength and improved absorption. Moreover, sodium glycerophosphate contains much less aluminum than an equal amount of sodium phosphate, suggesting that this ingredient might be safer for children and patients treated long term with parenteral nutrition.

Nevertheless, we have to accept some key restrictions when applying this data in clinical practice. The use of visual analysis, supported by microscopy, may fail to notice the formation of crystals of small size that more advanced methods such as light obscuration or light extinction can detect. Because trace elements are not examined in the compatibility test, it remains unclear how the ionic interactions among calcium, phosphate and several trace elements at changing pH levels can change the risk profile of formulations used in medical applications.

Also, because the tested alternative is soybean oil-based, the compatibility data are not directly applicable to modern alternative lipid emulsions with unique pH's, ionic features or stability. The quick compatibility check over a day does not always reflect the stability concerns that can occur when the samples are stored for longer or in different conditions typical in hospitals(9). Still, the findings suggest that sodium glycerophosphate shows promise in replacing conventional phosphate salts in parenteral nutrition and provides a good starting point to explore this option, though further work using formal analytical standards would be reassuring.

6.Saving Central Veins: Useful Approaches for Catheters in Patients on Parenteral Nutrition

Dibb and his colleagues' detailed study offers important guidance for saving central venous catheters in patients who need long-term intravenous nutrition at home for illnesses such as intestine failure. Among 588 patients receiving long-term parenteral nutrition for 18 years (1993-2011), this study observed 297 bloodstream infection events in 137 patients for an overall rate of 0.38 per 1,000 catheter days. The study used accepted rules for bloodstream infection in catheters, involving culture tests from the targeted area and from the catheter's end to help with correct testing and suitable drug treatment.

Whenever possible, the protocol suggested saving the central venous catheter, so it would only be removed for serious situations like septic shock, infections with fungi, mechanical complications or infections of the tunnel. Treatment using the standardized salvage method started with systemic vancomycin and catheter lock vancomycin, plus the addition of urokinase catheter lock to prevent fibrin sheath growth, followed by a temporary break from parenteral nutrition through the affected catheter during treatment. We added or modified antibiotics in response to microbiological findings when these results were made available and gave therapy for the full 2 weeks to address the infection.

The successful completion rate for attempted central catheter retrieval in adults is impressive; it allows survival of the catheter line without risking re-infection within 1 month after completion of treatment. The high success rate is important because central venous access sites are limited and each catheter replacement can lead to more possible blood clots. While some patients receive nutrition via catheters for months or years, protecting these central venous catheters is crucial for their long-term health and life quality which makes managing efforts to salvage them vital to good care(10).

The main findings call into question common practices in healthcare institutions in the United States. Since catheter removal is often the standard choice, patients are likely to be treated according to conservative policies within institutions or a lack of access to successful salvage therapies. For years, European guidelines have advised to save

catheters whenever possible in patients receiving long-term parenteral nutrition. The approach outlined in this research gives guidelines for enacting evidence-based salvage activities with proper safety precautions.

Even so, certain features of the protocol are not universally adopted in the US such as frequent use of antibiotic and urokinase catheter locks and ceasing parenteral nutrition infusion through the catheter for all 14 days. There is not enough evidence to confirm whether using specific protocols improves salvage rates, nor is it known at what time salvaged catheters should be reused for parenteral nutrition. Furthermore, a retrospective approach and research performed at just one facility make it harder to apply the results to regions or centers with other patient groups and infection or antibiotic resistance patterns.

7. Routine Nutrition Delivery by Route: Present-Day Proof of Enteral Versus Parenteral Methods

Elke and colleagues have conducted a new review and analysis, the results of which reflect current research on how and if choosing an enteral nutrition route benefits critically ill adults, especially considering challenges presented by recent studies to the traditional view that enteral nutrition is superior. Of the 18 studies chosen for the study, 3,347 patients were involved, including 1,681 receiving enteral nutrition and 1,666 receiving parenteral nutrition. Systematic review methods were used, for example, searching a wide range of literature and applying the same data-gathering, evaluation and result methods.

Researchers found no evidence that overall mortality is lower in enteral nutrition than in parenteral nutrition, even though earlier studies had pointed to this advantage for enteral nutrition. Despite this, enteral nutrition was linked to fewer hospital infections (relative risk 0.64) and a shorter time spent in intensive care unit than parenteral nutrition. It is therefore suggested that part of the advantage of enteral nutrition in avoiding infectious problems may result from avoiding overfeeding complications when compared to parenteral nutrition(11).

These findings agree with what experts know today about critical care nutrition, as offering too many calories via IV lines often causes hyperglycemia, weakens the immune system, leads to fatty liver and increases the likelihood of infection. The results indicate that a healthy diet and preventing overfeeding are more important than route decisions for having healthy patients. This idea is validated by more recent evidence showing that having enough protein is more important than calorie balance and may also help some patient groups who are not eating enough.

When using these findings to guide clinical practice, the meta-analysis gives special attention to certain problems. Because some studies did not provide complete outcome information, the number of trials providing information on ICU stay and ventilation duration was low and caloric intake, intervention start and infection definitions were not always the same, this may introduce variation in the associations observed. The analysis did not include important covariates such as how well nutrition was delivered, the patient's nutritional status before treatment or factors special to the patients.

Because all included patients were similar, it is not possible to isolate route-specific effects in groups such as patients with high nutrition risk or who have the same serious diagnosis or level of illness. Cost factors, availability, nursing demand and patients' comfort levels are not directly examined by the meta-analysis, even though important details to consider. In spite of these problems, the study results back recommendations from contemporary critical care nutrition experts to use enteral nutrition for patients who can tolerate food and to make sure nutrition is not overloaded regardless of the delivery route.

8.Using Optimal Essential Fatty Acids: Innovative Methods for Prolonging Parenteral Nutrition

Olthof and his team designed a study to see how well patients on long-term parenteral nutrition using different oils are spared from essential fatty acid deficiency. Thirty adult patients with short bowel syndrome or problems with gut motility who were on home parenteral nutrition and received 80% olive oil/20% soybean oil lipid emulsion, dosing at 0.97 g/kg/day five to seven times weekly for at least three months, participated in this investigation. Researchers performed a biochemical assessment, determined plasma fatty acid compositions and compared the findings with those of 30 age- and sex-matched healthy people to measure essential fatty acid status.

The study's main outcome looked at the ratio between triene/tetraene (We measured eicosatrienoic acid against arachidonic acid) which acts as the main biochemical indicator for essential fatty acid deficiency. Triene/tetraene

ratios were statistically higher in home parenteral nutrition patients (0.019) than in healthy controls (0.015), but none of the patients reached the level of 0.2 that means deficiency. Importantly, essential fatty acid deficiency was not observed in any patient in the study. Skin rashes, slow wound healing or weak immune system reactions were all absent.

Since essential fatty acids differ greatly in both lipid emulsions used here, these findings have great relevance for clinical practice. While conventional soybean oil emulsions are high in linoleic and alpha-linolenic acid, the mixture of olive oil and soybean oil has a much lower total amount of these essential acids, reducing them by a huge 65%. That ample essential fatty acids were observed in patients receiving parenteral nutrition despite a big reduction in fats from the diet implies that doctors may be over-prescribing these fats for most patients on long-term parenteral nutrition.

Because patients weighing 50 kg or more are getting at least adequate essential fatty acids with this alternative lipid emulsion method, the clinical guidance for using this emulsion is essential. This is different from the past, when it was thought that a little more than a half liter of 20% soybean emulsion each week or a few grams of emulsion each day was important as a precaution against essential fatty acid deficiency.

Yet, these findings can't be widely used in the United States because the studied mixed lipid emulsion is not yet available. At the moment, conventional 100% soybean oil emulsions are available, along with new multi-oil blends containing 15% fish oil, 25% olive oil, 30% medium chain triglycerides and 30% soybean oil. Because the results in the study are not directly applicable to these formulations, it is necessary to focus on essential fatty acid amounts when deciding on lipid emulsion products and doses for such patients.

9.Conclusion and Future work

Studying 2016's key contributions in pharmaceutical nutrition support practice has led to the use of tailored, evidence-based treatments that challenge standard beliefs about feeding well-rounded meals to seriously ill individuals. Many well-designed studies have shown that correct nutrition support is possible by focusing on each patient's metabolic needs, ensuring they get enough protein and applying interventions at the proper time rather than always using routine feeding plans. The PEPaNIC trial results challenge the usual first-line therapy in children but, at the same time, findings from adults support a need for proteins and fewer calories which aids in a better metabolism than going for a faster and more nutritious approach.

Methods for Bringing Evidence into Clinical Practice

To use these findings in clinical practice, hospitals must periodically review their own protocols, train staff and introduce quality frameworks that encourage making decisions based on the latest nutrition research. Pharmacists who take part in nutrition support need to have a high level of skill in assessing metabolic needs, targeting risks in patients and planning out interventions based on both existing and promising new knowledge about nutrition. Jointly using modern medication information, updated catheter preserving methods and route-focused care improvements are progress toward providing personalized, technologically advanced nutrition support which reduces risks, saves resources and supports better outcomes.

Future Areas of Focus and What More Needs to Be Learned

Even though we now understand nutrition-outcome relationships well, we still do not know enough about the best ways to decide who should receive nutritional care, the ideal timing, the proper amount and how to maintain the best possible outcomes for all patients. Researchers should now consider how balancing proteins, reducing calories and providing optimal micronutrients affects how a patient responds to nutritional guidance. Improving nutrition practices with precision, the use of advanced metabolic tools, genetic screening and AI decisions is being explored as the next main goal, requiring cooperation among pharmacists, physicians, dietitians and biomedical experts to build the best personalized nutritional support possible.

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Conflicts of interest

The authors have no conflicts of interest to declare

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