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Comparing the risk of bloodstream infections by type of parenteral nutrition preparation method: A large retrospective, observational study

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SUMMARY

Background and aims: Complications such as blood stream infections (BSI) have been observed with the administration of parenteral nutrition (PN). Prior published studies reported the incidence of BSI for inpatient hospitalizations by comparing patients treated with custom compounded parenteral nutrition to those treated with premixed multichamber bag (MCB) formulations. Previous publications grouped patients treated with MCBs into a single category and no distinction was made between patients receiving only a MCB and those receiving a MCB supplemented with manual additions. This Study aims to assess differences in risk of blood stream infection, cost, and clinical outcomes among patients receiving multichamber bag parenteral nutrition products only (MCB-only), MCB with additions (MCB-addition), and compounded (COM) PN products using seven years of Premier Healthcare Data from 688 hospitals in the United States of America.

Methods: Adult inpatients who were discharged between 01/01/2008 and 12/31/2014, had a hospital length of stay ≥3 days and received PN during the index hospitalization were analyzed. PN preparation method was determined by billing charge descriptions. BSI was defined as having primary or secondary ICD-9 diagnosis codes of 038.x (septicemia), 995.91 (sepsis), 995.92 (severe sepsis), and 790.7 (bacteremia). Multivariable regression models were used to assess effect of PN preparation on patient outcomes, adjusting for confounders.

Results: 84,564 patients were analyzed (MCB-only: 6.3%; MCB-addition: 14.8%; COM: 78.9%). Multivariable analysis indicated that compared to COM group, MCB-addition group had similar risk of BSI (7.0% vs. 6.8%, $P > 0.05$) and a 2.7% lower average total hospitalization cost ($28,072 vs. $28,861, $P < 0.05$) but had a higher PN treatment cost ($1135 vs. $1,031, $P < 0.05$) and a higher percentage of being discharged to rehabilitation or other acute care facilities (39.4% vs. 31.1%, $P < 0.05$). MCB-only group had lower risk of BSI and hospitalization cost.

Conclusions: In the U.S., compounded PN is the most commonly used in clinical practice followed by MCB with additions. MCB-addition group had similar BSI risk with COM. The slightly lower overall cost in MCB-addition group may be offset by higher post-hospitalization care cost to providers and payers under bundled payment methods in the U.S.

1. Introduction

Parenteral nutrition (PN) is a vital treatment for patients with medical conditions that severely impair gastrointestinal absorption or for those who are severely malnourished and cannot benefit from enteral nutritional supplements. Appropriate use of this high risk therapy is critical for maximizing its clinical benefits and limiting its

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potential risk for complications [1]. Among the many issues related to appropriate use of PN products, whether patients should be prescribed more commercially available premixed multichamber bags (MCB) or traditional customized formulations prepared using manual or automated compounding techniques (COM) remains unresolved. Although several organizations have released guidelines on PN use for patients with different medical conditions, due to lack of reliable research evidence, there is no consensus on the clinical advantages and disadvantages of different PN preparation methods [1–4]. However, both the American Society of Parenteral and Enteral Nutrition (A.S.P.E.N) and the British Pharmaceutical Nutrition Group agree that clinical outcomes, safety and cost shall be considered when selecting appropriate PN delivery system for patients [1,5].

The use of premixed MCB formulations has long been promoted as a safer, more efficient and less costly alternative to customized COM formulations by its manufacturers and some researchers. These statements, however, have ignored two important limitations of MCB products: 1) most MCB products do not contain micronutrients or other necessary components required to meet individual patient's specific needs and manual additions to MCBs are an extremely frequent occurrence in hospital pharmacies. 2) high dextrose concentrations in MCB products may increase the risk of hyperglycemia and infection [1,5]. If proper aseptic techniques are not followed, the process of adding components to the MCB formulations may increase the risk of blood stream infection (BSI) and related cost [3]. Prior studies assessing the impact of PN preparation methods on BSI risk and other patient outcomes focused on the comparison between patients receiving MCBs and COM without differentiating between MCB with or without additions.

Several studies reported lower risk of BSI [6–9], shorter length of stay (LOS) [6], and lower total hospitalization or treatment costs [8] for MCB vs. COM or other methods requiring manipulation of the PN mixture. Utilizing the Premier research database for discharges occurring in calendar years 2005–2007 inclusive, Turpin et al. reported that the BSI infection rate for patients using pharmacy prepared compounded PN was 25.9% compared to 19.6% for patients using MCB [10]. Leveraging more recent Premier data (January 1, 2010 – June 30, 2011), Magee et al. reported no statistically significant differences in infection rates, LOS, death, 30-day readmissions for COM vs. MCB, but overall hospital costs were lower for patients receiving MCB [11]. Using chart review data of 1995 patients from a German hospital, Turpin et al. also found that both the COM and MCB with ward addition groups were associated with increased risk of BSI and cost compared to MCB without ward addition group [9]. In this German study, the MCB without ward addition group included not only patients who received MCB only but also patients who received MCB with nutrients added in hospital pharmacies. In addition, the PN products used and the PN administration process differ significantly in Germany and in the United States (U.S.). More evidence is needed to assess the cost and clinical outcomes associated with different PN preparation methods in the U.S.

When comparing the effectiveness of COM and MCB in achieving nutritional goals, Blanchette et al.'s study showed that MCB was as effective as COM PN in achieving estimated caloric requirement but it was less effective in achieving estimated protein requirements and was associated with a higher frequency of hyponatremia [12]. The PN needs of patients vary significantly based on their type and stage of illness conditions, physical conditions, medications used, and comorbidities. These patients usually present with multiple medical problems that are associated with significant metabolic and nutritional alterations, which may require customized PN formulas providing higher protein in a reduced volume. During the Study period, higher protein reduced volume MCBs were not commercially available in the U.S. No known United States study has used population-based data to comprehensively assess the difference in risk of BSI and related cost between MCB with and without added components. This study aimed to comprehensively assess the differences in key patient outcomes including risk of BSI and cost between patients receiving MCB only (MCB-only), MCB with additions (MCB-addition), and COM PN products using multiple years (2008–2014) of Premier healthcare data. We hypothesized that patients who used different PN formulations had different risk of BSI and different LOS, total hospitalization cost, and other clinical outcomes.

2. Materials and methods

2.1. Data source

Data for the study were derived from the statistically de-identified PHD Premier Healthcare Database (PHD), the largest hospital discharge database in the United States. It currently contains data from more than 619 million patient encounters, or one in every five hospital discharges in the United States. The PHD is a complete census of inpatient and hospital-based outpatient encounters from over 600 geographically diverse hospitals in the nation. Patient-related information including demographics, disease status, and charges on medications, laboratory, diagnostics and therapeutic services in patient's service records is collected from all therapeutic areas. In addition, information on hospital characteristics, including geographic location, bed size and teaching status, is also available.

2.2. Ethical statement

Institutional review board (IRB) approval for this study was not required, based on US Title 45 Code of Federal Regulations, Part 46, because the study used existing de-identified hospital discharge data, and recorded information could not be identified directly or through identifiers linked to individuals.

2.3. Study design

We used a retrospective cross-sectional design to address the study objectives. First we identified all eligible patients meeting the selection criteria from the PHD. We then assessed the PN preparation method and outcomes of interest (e.g., BSI, length of stay, total hospitalization cost, discharge status, 30- and 90- day all-cause readmissions, and PN-related cost) using the PHD data. A power analysis showed that the study has sufficient sample size to detect any difference between different PN preparation methods in key outcome variables if there was a difference with a statistical power of 80% and the probability for rejecting the null hypothesis as 0.05.

2.4. Study population

Inclusion criteria included: 1) inpatient discharge during 2008–2014; 2) patient age $\geq$18 years at the time of index admission; 3) hospitalized for at least three days; 4) had charge master description of PN administration during index hospitalization. Exclusion criteria included: 1) Patients who had blood stream infection, acute cholecystitis, phlebitis, thrombophlebitis, hepatic dysfunction, renal failure, cirrhosis and bacterial meningitis or encephalitis at time of index admission; 2) Patients who had antibiotic charges except charges for topical antibiotic use (e.g., ointment, eye drop, cream) before any PN formulation was first administered; 3) Patients who were exposed to multiple types of PN preparation within the index admission (e.g. both MCB and compounded PN).

2.5. Variable definitions

PN preparation method was classified into three categories using information from billing charges: 1) MCB-only: If a patient had a premixed PN product but did not have any other individual PN components (e.g., trace elements, IV/INJ multivitamins, lipids) charged on the same day of the premixed PN product or other compounded PN product charges during the index admission, the patient was considered having premixed MCB with no component added in hospital; 2) MCB-addition: If a patient had a premixed PN product AND had at least one other individual PN component (e.g., trace elements, IV/INJ multivitamins) charged on the same day of the premixed PN product charge, the patient was considered having premixed MCB with component added in hospital; 3) COM (manual or automated): All patients who did not meet the premixed MCB category definitions but had one of the compounded PN product-related charges were considered having compounded PN.

The primary outcome variables included: BSI (having primary or secondary ICD-9 diagnosis codes of 038.x [septicemia], 995.91 [sepsis], 995.92 [severe sepsis], and 790.7 [bacteremia] during the index admission), total hospital LOS, total hospitalization cost, discharge status (home/home health/rehabilitation or other acute care facility), 30-day and 90-day all cause readmission. Secondary outcome measure included PN-related cost. All cost estimates were adjusted to 2015 U.S. dollars using the Consumer Price Index for All Urban Consumers Inpatient Hospital Services [13].

Patient, hospital and clinical characteristic variables that were assessed included sex, age, race/ethnicity, insurance type, hospital size, teaching status, population served, region of hospital, admission point of origin, admission type, discharge status, Charlson comorbidity index score, total number of days on PN, all patient refined diagnosis related groups (APR-DRGs) severity level, and underlying diseases that may be related to PN use and outcome variables (i.e., nutritional deficiency, intestinal malabsorption, peritonitis and retroperitoneal infections, Crohn's disease, malignant neoplasm of digestive organs and peritoneum, diabetes mellitus and tuberculosis).

2.6. Statistical analysis

Descriptive statistics for patient-, hospital-, and clinical covariates were calculated separately for each PN preparation method. Categorical variables were summarized using frequencies and percentages and continuous variables were summarized using mean and standard deviation for each subgroup. Chi-square tests were used to examine the statistical differences in categorical variables. Two sample T-test or Wilcoxon Signed Rank Sum test was used to assess the statistical differences in continuous variables.

Multivariable logistic regression modeling was used to estimate the risk of BSI, 30-day and 90-day all cause readmission, and being discharged to acute care or rehabilitation facilities for different comparison groups adjusting for all potential confounders including patient, hospital, and clinical characteristics as defined in methods section. The Hosmer and Lemeshow goodness-of-fit test was used to assess the fit of each model. Adjusted means and 95% confidence intervals (CI) were reported.

Multivariable generalized linear regression modeling (GLM) with a gamma distribution and log link was used to assess the differences in cost-related variables between different PN preparation methods adjusting for the aforementioned confounders. Multivariable negative binomial modeling was used to assess the differences in LOS-related variables between different PN preparation methods adjusting for known confounders.

All analyses were performed using SAS/STAT software, Version 9.4 of the SAS system. (Copyright (2016) SAS Institute Inc., Cary, NC, USA.). Statistical significance level was set at alpha = 0.05.

3. Results

3.1. Characteristics of the study population

A total of 84,564 patients were included in the study. Among which, 5359 (6.3%) patients only received MCB products, 12,533 (14.8%) patients received MCB products with components added, and 66,672 (78.9%) used COM PN products.

Compared to the COM group, a higher percentage of patients in the MCB-only and MCB-addition groups were in the older age groups, were identified as non-Hispanic White, reported having public insurance, and were admitted to hospitals of smaller size, non-teaching, or rural status as well as hospitals in the South (see Table 1).

A higher percentage of MCB-only and MCB-addition patients were admitted through the emergency department than the COM patients. Similarly, a higher percentage of MCB-only and MCB-addition patients were discharged to post-acute care rehabilitation settings such as nursing homes, rehabilitation hospitals or hospice facilities or other acute care hospitals compared to COM patients (see Table 2)In terms of severity of illness, a slightly higher percentage of MCB-addition patients were in the major or extreme level of APR-DRG severity of illness scale than the COM patients (71.7% vs. 63.6%). An analysis of the case-mix index shows a higher percentage of MCB-only and MCB-addition patients were in the <2 category than the COM patients. For length of parenteral nutrition (PN) treatment, 62.0% of MCB-only patients had PN treatment for 4 days or less, the percentage was 34.6% for MCB-addition and 56.1% for the COM patients. For PN treatment-related underlying diseases, MCB-only patients had lower prevalence of intestinal malabsorption, peritonitis and retroperitoneal infections, Crohn's disease, and malignant neoplasm of digestive organs compared to COM patients; MCB-addition patients had higher prevalence of peritonitis and retroperitoneal infections, Crohn's disease, and malignant neoplasm of digestive organs and peritoneum but lower prevalence of diabetes mellitus than the COM patients (see Table 2).

3.2. Unadjusted analysis

The unadjusted prevalence of blood stream infection was significantly lower in the MCB-only group than in COM group but there was no statistical difference found between MCB-addition and COM groups. The 30-day and 90-day all-cause readmission rates were lower in the MCB-only group but higher in the MCB-addition group compared to COM patients ($P < 0.05$). The average total hospitalization cost was lower in the MCB-only group than in the COM group ($P < 0.05$). When comparing the average total hospitalization cost between the MCB-addition and the COM groups, no statistical difference was found between. The overall PN cost was higher in the MCB-addition group than in the COM group ($ 1175. vs. $ 905, $P < 0.05$). The mean number of days of total length of stay was lower in the MCB-only group but higher in the MCB-addition group compared to the COM group ($P < 0.05$) (Table 3).

3.3. Multivariable analysis

After adjusting for patient characteristics (sex, age, race/ethnicity, insurance status), hospital characteristics (size, teaching status, population served and region), and clinical characteristics (admission point of origin, admission type, discharge status, APR-DRG severity of illness, case-mix index, length of PN treatment,

Table 1
Patient and hospital characteristics by parenteral nutrition preparation methods.

Characteristics	MCB[a]-only		MCB[a]- addition		MCB[a] Overall		COM[a]	
	N	%	N	%	N	%	N	%
# of Unique Patients	5359	6.3	12,533	14.8	17,892	21.1	66,672	78.9
Male Sex	2341	43.7	5602	44.7	7943	44.4	29,375	44.1
Age (years)								
18–44	636	11.9[b]	1740	13.9[b]	2376	13.3[b]	12,635	19.0
45–64	1488	27.8	3951	31.5	5439	30.4	22,710	34.1
65–74	1074	20.0	2912	23.2	3986	22.3	14,056	21.1
75–84	1251	23.3	2578	20.6	3829	21.4	11,858	17.8
85+	910	17.0	1352	10.8	2262	12.6	5413	8.1
Race/Ethnicity								
Hispanic	392	7.3[b]	598	4.8[b]	990	5.5[b]	2841	4.3
Non-Hispanic White	2307	43.1	5070	40.5	7377	41.2	15,868	23.5
Non-Hispanic Black	421	7.9	903	7.2	1324	7.4	2732	4.1
Non-Hispanic Other	238	4.4	657	5.2	895	5.0	2909	4.4
Unknown race/ethnicity	2001	37.3	5305	42.3	7306	40.8	42,532	63.7
Health Insurance Type								
Public insurance	3825	71.4[b]	8719	69.6[b]	12,544	70.1[b]	42,941	64.4
Private insurance	1209	22.6	3195	25.5	4404	24.6	20,220	30.3
Uninsured	288	5.4	506	4.0	794	4.4	2995	4.5
Other	37	0.7	113	0.9	150	0.8	516	0.8
Hospital size (n, %)								
1–299 beds	2116	39.5[b]	4978	39.7[b]	7094	39.6[b]	16,872	25.3
300–499 beds	2289	42.7	4985	39.8	7274	40.7	27,677	41.5
500 + beds	954	17.8	2570	20.5	3524	19.7	22,123	33.2
Non-teaching hospital (n, %)	4840	90.3[b]	9546	76.2[b]	14,386	80.4[b]	36,624	54.9
Rural hospital (n, %)	502	9.4[b]	2518	20.1[b]	3020	16.9[b]	5374	8.1
Region of hospital (n, %)								
Midwest	988	18.4[b]	2597	20.7[b]	3585	20.04[b]	15,072	22.6
Northeast	137	2.6	715	5.7	852	4.8	7763	11.6
South	4038	75.3	8177	65.3	12,215	68.3	32,520	48.8
West	196	3.7	1044	8.3	1240	6.9	11,317	17.0

[a] MCB = Multichamber bag parenteral nutrition; COM=Compounded parenteral nutrition.
[b] Indicates *P*-value<0.05 for comparisons between each MCB PN group and the COM group.

number of Charlson comorbidities, and selected underlying diseases), the adjusted mean risk of having blood stream infection (BSI) was lower in the MCB-only group (2.1%, 95% CI: 2.0%, 2.2%) but similar in the MCB-addition group (7.0%, 95% CI: 6.8%, 7.2%) compared to the COM group (6.8%, 95% CI: 6.7%, 6.9%). While the MCB-only group had lower risk of having 30-day or 90-day all cause readmission, the MCB-addition group had higher risk of 30-day or 90-day all cause readmission than the COM group (see Table 4). The adjusted average total hospitalization cost was 11.3% lower in the MCB-only group but only 2.7% lower in the MCB-addition group than in the COM group. The adjusted PN treatment cost was 10.1% higher in the MCB-addition group than in the COM group. There was no statistically significant difference between the MCB-overall group and the COM group in the adjusted mean total length of stay (Table 4).

Adjusted analysis on the difference in risk of being discharged to rehabilitation or other acute care facilities post hospitalization indicated that the COM group had a much lower risk of being discharged to rehabilitation or other acute care facilities (31.1%, 95% CI: 31.0%, 31.3%) than the MCB-only group (44.8%, 95% CI: 44.1%, 45.5%) and the MCB-addition group (39.4%, 95% CI: 38.9%, 39.8%).

4. Discussion

Using the largest population-based hospital discharge data in the U.S., we found that compounded PN accounted for nearly 80% of the PN utilization and MCB with added components accounted for 15% of the PN utilization. Only a very small percentage of patients used premixed MCB products only. In clinical practice, additions are made to premixed formulations in an attempt to meet patients' specific nutritional needs. In our study population, 7 out of every 10 patients had manual additions to their premix formulations which increased the compounding complexity for the MCB-addition population. Prior studies have grouped MCB-only and MCB-addition when comparing to COM [10,11]. It appears that patients in the MCB-only and MCB-addition groups differ significantly in many characteristics and it may not be clinically appropriate to group these treatment alternatives when comparing to patients in the COM PN group.

Our findings are consistent with industry guidelines: commercially available premade multichamber PN products can be considered alongside compounded (customized or standardized) PN formulations to best meet patients' needs [1]. The British Pharmaceutical Nutrition Group also made specific requirements for implementing premixed MCB PN products to patients including consultation with suitable professionals and screening patients' nutritional needs prior to commencement, additions must be added by pharmacy using aseptic techniques or provided via another route of administration if needed, and MCBs must not be available as ward stocks [5]. These requirements imply that administering MCB products is not as simple and safe as what is claimed by MCB manufacturers. They are intended to be used for individual patients after assessment by appropriately trained professionals.

After adjusting for known confounders, although the MCB-only group had lower BSI risk and lower hospitalization cost compared to the COM group, the MCB-addition and the COM groups were comparable in key patient outcomes of interest such as risk of BSI and 30-day and 90-day all-cause readmission. These findings are consistent with what Turpin et al. found in the German study [9] but different from what was reported by Turpin et al. using the PHD data [8,10]. The risks of BSI in our study for each PN group are lower than what was reported in Turpin et al.'s study but higher

Table 2
Clinical characteristics by parenteral nutrition preparation methods.

Variables	MCB[a]-only		MCB[a]-addition		MCB[a] Overall		COM[a]	
	N	%	N	%	N	%	N	%
# of Unique Patients	5359	6.3	12,533	14.8	17,892	21.2	66,672	78.8
Admission Point of Origin								
Emergency department	3478	67.4[b]	6391	52.3[b]	9869	56.7[b]	29,650	46.7
Transfer from another facility or same hospital	367	7.1	1158	9.5	1525	8.8	5430	8.6
Other	1317	25.5	4678	38.3	5995	34.5	28,412	44.8
Admission Type								
Emergency	3564	66.8[b]	6705	53.9[b]	10,269	57.8[b]	31,712	47.8
Urgent	856	16.0	3000	24.1	3856	21.7	16,020	24.1
Elective	910	17.1	2724	21.9	3634	20.5	18,437	27.8
Trauma or injury center	3	0.1	10	0.1	13	0.1	183	0.3
Discharge Status								
Home/Home health	2846	53.1[b]	7150	57.4[b]	9996	56.1[b]	43,877	65.9
Nursing, rehabilitation or hospice facility	2190	40.9	4258	34.2	6448	36.2	17,830	26.8
Transfer to another acute care hospital	33	0.6	124	1.0	157	0.9	473	0.7
Expired	259	4.8	881	7.1	1140	6.4	3990	6.0
Other	30	0.6	52	0.4	82	0.5	368	0.6
APR-DRG severity of illness								
Minor	419	7.8[b]	662	5.3[b]	1081	6.0[b]	6142	9.2
Moderate	1715	32.0	2879	23.0	4594	25.7	18,179	27.3
Major	2478	46.2	5981	47.7	8459	47.3	27,585	41.4
Extreme	747	13.9	3011	24.0	3758	21.0	14,765	22.2
Case-Mix Index								
<2	4471	83.4[b]	7568	60.4[b]	12,039	67.3[b]	37,769	56.8
2–3	455	8.5	2168	17.3	2623	14.7	10,832	16.3
>3	433	8.1	2787	22.3	3220	18.0	17,947	27.0
Length of PN treatment (days)								
1–2	1456	27.2[b]	1603	12.8[b]	3059	17.1[b]	24,920	37.4
3–4	1865	34.8	2730	21.8	4595	25.7	12,491	18.7
5–9	1674	31.2	5065	40.4	6739	37.7	17,681	26.5
10+	364	6.8	3135	25.0	3499	19.6	11,580	17.4
Number of comorbidities								
<2	2830	52.8[b]	6636	52.9[b]	9466	52.9[b]	38,769	58.2
≥2	2529	47.2	5897	47.1	8426	47.1	27,903	41.8
Underlying diseases								
Nutritional deficiency	5359	100.0	12,533	100.0	17,892	100.0	66,672	100.0
Intestinal malabsorption	37	0.7[b]	235	1.9	272	1.5[b]	1163	1.7
Peritonitis and retroperitoneal infections	49	0.9[b]	454	3.6[b]	503	2.8[b]	2079	3.1
Crohn's disease	93	1.7[b]	376	3.0[b]	469	2.6	1752	2.6
Malignant neoplasm of digestive organs and peritoneum	479	8.9[b]	2117	16.9[b]	2596	14.5[b]	8162	12.2
Diabetes mellitus	1322	24.7	2743	21.9[b]	4065	22.7[b]	15,825	23.7
Tuberculosis	1	0.0	8	0.1	9	0.1	24	0.0

[a] MCB = Multichamber bag parenteral nutrition; COM=Compounded parenteral nutrition.
[b] Indicates *P*-value<0.05 for comparisons between each MCB PN group and the COM group.

than what was reported in Glenn et al.'s study [10,11]. This is possibly due to the differences in study population selection and BSI definition in these studies. We excluded patients with any possible infections prior to PN administration while the other two studies did not. Glenn et al.'s study added antibiotic or antifungal use to the BSI definition in addition to ICD-9 codes while our study and Turpin et al.'s study only used ICD-9 codes.

Although the adjusted average total hospitalization cost was $789 less in the MCB-addition group than in the COM group, MCB-addition group were more likely to be discharged to post acute care rehabilitation centers than the COM group. In a bundled payment for care program, such as U.S. Medicare's Comprehensive Care for Joint Replacement Model, there are obvious cost implications to the provider when additional unanticipated care is required beyond the acute care episode; conversely, from a payer perspective, the additional post acute care payments in a fee for service model would result in higher costs to the payer. In addition, the adjusted average PN-related cost was $104 higher in the MCB-addition group than in the COM group, which corroborated prior findings on the cost advantage of COM treatment over MCB [14].

Table 3
Unadjusted analysis results for clinical and economic outcomes by parenteral nutrition preparation methods.

Variables	MCB[a]-only	MCB[a]-addition	MCB[a] Overall	COM[a]
# of Unique Patients	5359	12,533	17,892	66,672
Blood stream infection (n, %)	117 (2.2)[b]	884 (7.0)	1001 (5.6)[b]	4515 (6.8)
30-day all cause readmission (n, %)	946 (18.6)[b]	2589 (22.2)[b]	3535 (21.1)[b]	12,785 (20.4)
90-day all cause readmission (n, %)	1372 (26.9)[b]	3709 (31.8)[b]	5081 (30.3)[b]	18,374 (29.3)
Total hospitalization cost (in 2015 U.S. dollars), Mean (Std.)	14,589. (14,370.)[b]	26,141. (30,536.)	22,673. (27,249)[b]	27,531. (36,287.)
Total length of stay (days), Mean (Std.)	8.4 (9.2)[b]	13.0 (10.4)[b]	11.6 (10.2)[b]	11.7 (12.4)
Overall PN cost (in 2015 U.S. dollars), Mean (Std.)	315 (922)[b]	1175. (3250.)[b]	916 (2791.)[b]	905 (2151.)

[a] MCB = Multichamber bag parenteral nutrition; COM=Compounded parenteral nutrition.
[b] Indicates *P*-value<0.05 for comparisons between each MCB PN group and the COM group; Std: Standard Deviation.

Table 4
Multivariable adjusted analysis results for clinical and economic outcomes by parenteral nutrition preparation methods.

Variable Name	Value	MCB-Only[a]	MCB-Addition[a]	MCB Overall[a]	COM[a]
BSI risk (%)	Mean	2.1[b]	7.0	5.5[b]	6.8
	95% Confidence Interval	2.0, 2.2	6.8, 7.2	5.4, 5.7	6.7, 6.9
Discharged to rehabilitation or other acute care facility risk (%)	Mean	44.8[b]	39.4[b]	41.0[b]	31.1
	95% Confidence Interval	44.1, 45.5	38.9, 39.8	40.6, 41.4	31.0, 31.3
30-day all cause readmission risk (%)	Mean	18.5[b]	22.2[b]	21[b]	20.5
	95% Confidence Interval	18.3, 18.6	22.0, 22.3	20.9, 21.1	20.4, 20.6
90-day all cause readmission risk (%)	Mean	26.8[b]	31.7[b]	30.2[b]	29.4
	95% Confidence Interval	26.6, 27.0	31.5, 31.8	30.1, 30.3	29.4, 29.5
Total hospitalization cost (2015 U.S. dollars)	Mean	25,594. [b]	28,072 [b]	27,479[b]	28,861
	95% Confidence Interval	24,540., 26,692.	26,975., 29,213.	26,412., 28,590.	27,759., 30,007.
PN-related cost (2015 U.S. dollars)	Mean	549.[b]	1135. [b]	997. [b]	1031.
	95% Confidence Interval	501., 603.	1040., 1240.	912., 1088	945., 1124.
Total length of stay (days)	Mean	11.7[b]	12.6[b]	12.4	12.3
	95% Confidence Interval	11.2, 12.1	12.2, 13.1	12.0, 12.9	11.9, 12.7

[a] MCB = Multichamber bag parenteral nutrition; COM=Compounded parenteral nutrition.
[b] Indicates *P*-value<0.05 for comparisons between each MCB PN group and the COM group.

Compared to previous studies, this study has at least three strengths. First, different from a traditional cross-sectional study, we know the timing of the exposure (PN administration) and outcome (e.g., BSI). There is no temporal ambiguity between the exposure and outcome as seen in regular cross-sectional studies. Second, because there was detail medication charge information in the database, we were able to differentiate MCB only and MCB with addition groups. Third, the large study population from geographically diverse hospitals is more representative of the general patient population in need of PN than studies from single healthcare facilities.

The findings of this study should be interpreted within the scope of three limitations. First, the classification of PN preparation methods was based on hospital claims data. The descriptions of PN medications may vary from hospital to hospital. Although we tried all possible combinations to identify the PN products, misclassification may still exist. Second, hospital characteristics other than size, population served, teaching status, and region may impact patients' outcomes as pointed out by a recently published study [15]. Such factors may include skills of physicians and nurses and how they chose to treat given illnesses, which were not measured in the PHD and therefore not adjusted in our analysis. If such factors are disproportionately distributed between each PN group, they may affect the comparisons between groups but the direction could be either way. And finally, as previously stated, the two MCB groups differ significantly and it may not be clinically appropriate to group these treatment alternatives when comparing to patients in the COM PN group.

In conclusion, this Study of patients treated in U.S. hospitals reveals that compounded PN is the most commonly used PN product in clinical practice followed by MCB with added components. Only a small percentage of patients solely received premixed MCB products without adding any additional elements. After adjusting for known confounders, the MCB-addition group and the COM group are comparable in key patient outcomes of interest. A higher percentage of MCB patients were discharged to rehabilitation or other acute care facilities, which may imply additional costs after hospitalization. More studies are needed to evaluate the cost and benefit of different PN preparation methods using more thorough clinical and cost data covering the full spectrum of a patient's treatment process including rehabilitation services and quality of life.

Statement of authorship

All persons who meet authorship criteria are listed as authors and all authors certify that they have participated sufficiently in the work to take public responsibility for the content. Each author certifies that this material or similar material has not been submitted and will not be submitted to or published in any other publication before it appears in *Clinical Nutrition.*

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2019.01.011.

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