Original Article

Long term clinical outcomes of home parenteral nutrition in Singapore

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Background and Objectives: Home parenteral nutrition (HPN) is a life sustaining therapy for patients with chronic intestinal failure. Reported outcomes for Asian HPN patients are scarce. We aim to review the clinical outcomes of adult and paediatric HPN patients in our cohort which caters for 95% of Singaporean HPN patients. **Methods and Study Design:** This is a retrospective review of HPN patients from an adult (2002-2017) and paediatric cohort (2011-2017) from the largest tertiary PN centres in Singapore. Patient demographics and clinical outcomes were reviewed. **Results:** There were 41 adult and 8 paediatric HPN patients. Mean age was 53.0(±15.1) (adults) and 8(±1.8) years-old (paediatrics). Mean duration of HPN was 2.6(±3.5) and 3.5(±2.5) years. Leading indications for adult HPN were short bowel syndrome (SBS) (n=19,46.3%), mechanical obstruction (n=9,22.0%), and gastrointestinal dysmotility disorders (GID) (n=5,12.2%). Thirteen adult (31.7%) patients had underlying malignancy, with seven (17.3%) receiving palliative HPN. Indications for HPN amongst paediatric patients was GID (n=5,62.5%) and SBS (n=3,37.5%). Central line-associated bloodstream infection (CLABSI)/1000catheter-days was 1.0(±2.1) and 1.8(±1.3). Catheter associated venous thrombosis (CAVT)/1000catheter-days was 0.1(±0.4) and 0.7(±0.8). Biochemical Intestinal Failure Associated Liver Disease (IFALD) was found in 21.9% and 87.5%. For adults, median overall survival was 90-months (4.3,175.7,95%CI), with actuarial survival of 70.7%(1-year) and 39.0%(5-years). Median survival for adult patients with malignancy was 6-months (4.2,7.7,95%CI), actuarial survival of 85.7%(3-months) and 30.7%(1-year). One adult patient died from PN related complications. No paediatric deaths were noted. **Conclusions:** Whilst patient numbers were modest, we report comparable complication and survival rates to other international centres in both our adult and paediatric cohorts.

Key Words: home parenteral nutrition, intestinal failure, Singapore, Asia

INTRODUCTION

Intestinal failure (IF) is defined as a reduction of gut function resulting in inadequate digestion and absorption of macronutrients and/or water and electrolytes such that intravenous supplementation is required for health and/or growth.[1,2] The aetiology of IF is varied and dependent on age. Short bowel syndrome (SBS), typically associated with a short bowel length of less than 200cm,[2] usually results from extensive surgical resection following an ischaemic event and is the most common cause of chronic, irreversible IF in both adult and paediatric populations, whereas rarer, congenital disorders such as intestinal epithelial/enterocyte abnormalities and chronic intestinal pseudo-obstruction are more likely amongst paediatric patients. IF is further subdivided functionally into type 1 (acute), type 2 (prolonged) or type 3 (chronic), of which chronic IF describes a chronic condition in metabolically stable patients who require intravenous supplementation over months or years, which may or may not be reversible.[3,4] In patients with chronic IF, long term home parenteral nutrition (HPN), is a life sustaining therapy for which there is little alternative.[5] Whilst a majority of patients on HPN for benign disease are able to live normal or near normal lives,[6,7] there is a significant proportion of patients that will suffer a multitude of life threatening complications from prolonged PN administration, and have severe impairments to their quality of life.[8] A structured and integrated multidisciplinary team approach in the management of IF, comprising (but not limited to) gastroenterologists, surgeons, specialist nurses, dietitians, pharmacists, speech and language therapists and social workers, has been associated with improved immediate and long-term outcomes[9,10] and reduced complication rates.

Singapore, a country of population size 5.69 million,[11] is small in comparison with Western countries where the majority of HPN data originates.[12,13] Overall, epidemiological data of HPN from East Asia is scarce with the last

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previous publication being more than 10 years ago,[14] with only adult cohorts reported thus far. Further, to our knowledge, there has been no previous published data specifically from South East Asia.

We aim to describe the experience of our local adult and paediatric multidisciplinary intestinal rehabilitation teams from two HPN centres in Singapore, with an adult cohort that has been ongoing since 2002 and a paediatric cohort that has been initiated more recently in 2011.

METHODS

Patient cohorts

This is a retrospective review of an adult HPN cohort (Singapore General Hospital, 1st of January 2002 to 30th of October 2017) and a paediatric cohort (KK Women's and Children's Hospital, 1st of January, 2011 to 30th of October 2017) in Singapore. The Singapore General hospital and KK Women's & Children's Hospital sees the majority of adult and paediatric HPN patients respectively (95% of HPN patients), within Singapore. Prior to the establishment of these services, patients requiring long term PN were cared inpatient by their primary team which may be surgeons or gastroenterologists.

HPN management

Central venous catheters were used in all HPN patients. Due to limited resources, HPN was largely administered by patients or their relatives who were taught using a stringent catheter care protocol. Only a minority of patients had HPN administered by private nursing staff. Caregivers administering PN were taught using a standardised aseptic protocol in accordance with guidance from ESPEN.[16] Competency for safe HPN administration was assessed inpatient before discharge and at regular intervals during clinic follow up or when patients were admitted for HPN-related complications. Taurolidine-citrate lock (Taurolock®, TauroPharm GmbH) was used in all paediatric patients since 2013, and in adult patients who had a previous episode of line sepsis. Secondary prophylaxis with subcutaneous enoxaparin was used for patients who had a prior episode of Catheter associated venous thrombosis (CAVT).

PN solutions were prepared by an in-house aseptic compounding laboratory and were delivered to patients' homes via courier service. The PN solutions were customised for each patient using an all-in-one bag. While Lipofundin® MCT/LCT (B.Braun) was the lipid emulsion used in adult PN solutions, SMOFlipid® (SMOFKabiven®) was the standard lipid emulsion in paediatric PN solutions.

All patients were reviewed regularly in weekly to 4-monthly intervals in a specialist outpatient clinic by a nutrition support team consisting of trained gastroenterologists, surgeons, specialist nurses, pharmacists and dietitians. Regular assessment of biochemistry, liver enzymes, triglycerides, line care, fluid status and nutritional assessment were performed at follow up clinic visit. The number of days on PN were adjusted according to patient's oral/enteral intake. Glucagon-like peptide-2 analogues are not available in Singapore and hence were not used in any of the patients.

Data collection and statistical analysis

Patient characteristics were assessed at time of PN initiation. Demographic data, anthropomorphic measures such as body weight, body mass index (BMI) were recorded. Disease specific parameters such as indications for PN, duration of PN, bowel length and biochemical parameters including liver enzymes and triglycerides (TG) were noted. Clinical outcomes including central line–associated bloodstream infection (CLABSI)/1000 catheter day, CAVT /1000 catheter day, mortality and survival analysis were evaluated.

CLABSI was defined according to the Centres for Disease Control and Prevention (CDC), National Healthcare Safety Network Definition.[17] A laboratory confirmed bloodstream infection where an eligible blood stream infection organism is identified, and an eligible central line is present, not attributable to an infection at another body site.

All cases of suspected CAVT are referred to be assessed by an interventional radiologist, attempts at catheter salvage are performed and relevant imaging in the form of doppler ultrasonography or contrast venography are performed to confirm the diagnosis of a CAVT. In the event that catheter salvage is unsuccessful, the line is removed and a new line is inserted.

Liver enzymes at baseline and follow up were compared. Intestinal failure associated liver disease (IFALD) was defined biochemically by any deranged liver enzymes of >1.5 of the upper limit normal, > 6 months after HPN initiation.[18] Patients who received HPN for ≤ 6 months were excluded from analysis for IFALD. Gammaglutamyl Transferase (GGT) is not a routine component of our adult liver enzyme panel. There were 9 patients from the adult cohort who received HPN <6 months that were excluded for IFALD analysis: 4 had achieved enteral autonomy, 5 had malignancy and passed away from their underlying disease. All paediatric HPN patients were included. Patients with deranged liver enzymes are typically assessed by imaging in the form of ultrasound, computer tomography or magnetic resonance imaging to assess for radiological features of cirrhosis, fatty liver, and to exclude other causes of liver injury such as biliary disease. An alcohol history is taken (where appropriate) and a medication review is performed. Serologies for hepatitis B, C and autoimmune liver disease are routinely performed. In the appropriate clinical context, evaluation for Wilson's disease was done. Given the rarity of primary haemochromatosis in the South-East Asian population, routine genetic testing for haemochromatosis is not done. Further, none of the patients had evidence of systemic iron loading warranting further evaluation.

Kaplan Meier Survival analyses was performed with SPSS 26 (IBM, Chicago, IL, USA). Descriptive statistics for patients' characteristic and clinical factors were presented as mean (standard deviation) for continuous variables and frequency (percentage) for categorical variables. Student's T-Test and the Mann Witney U Test was performed, where appropriate for continuous variables. Chi-Square was performed for categorical variables. The study was approved by our Institutional Review Board (IRB: 2018/2050).

RESULTS

Overall cohort

Between January 2002 to November 2017, there were 49 patients identified. There were 41 adult patients (23 male, 56.1%) and 8 paediatric patients (one male, 12.5%) respectively. For the entire cohort, the mean duration of PN was 2.7 (±3.4) years. The most common indication of PN for the entire cohort was short bowel syndrome (SBS) (n= 22, 44.8%). Overall, enteral autonomy was achieved in 13 patients (26.5%).

With regards to complications, CLABSI/1000 catheter days was 1.2 (±1.9) %). A summary of the patient profile and organisms identified during CLASBI events are summarized in Supplementary Table 1. CAVT/1000 catheter days was 0.2 (±0.5). Biochemical evidence of IFALD was found in 34.1% (n=14) of all patients. Overall median survival was 90.0 (4.3, 175.7 95% CI) months. All deaths occurred in the adult cohort. Most deaths were non-HPN related: underlying cancer (n=9, 40.9%), non-line sepsis (n=6, 27.2%), complications from ischaemic bowel (n=1, 4.5%), CLABSI (n=1, 4.5%) and unknown causes (n=4, 19.1. Of the unknown causes, these were all out of hospital deaths with all patients having underlying ischemic bowel as the underlying aetiology requiring HPN. No deaths were reported amongst the paediatric cohort during the study period.

Adult cohort

For the adult cohort, the mean age at PN initiation was 53 (±15.1) years. Mean BMI was 18.8 (±4.1). Mean duration of HPN was 2.6 (±3.5) years. (Table 1)

Short bowel syndrome (SBS) was the most common indication for HPN followed by mechanical obstruction, dysmotility and others (Table 1). The most common underlying aetiology was malignancy (n=14, 34.1%) followed by ischaemic bowel (n=9, 22.0%), gastrointestinal dysmotility (GID) (n=5 12.2%), surgical complications (n=8, 14.6%), Crohn's disease (n=1, 2.4%) and others (n=3, 7.3%) (Table 2). The commonest cause of GID was systemic scleroderma (n=4), followed by chronic intestinal pseudo-obstruction (CIPO) (n=2) (Table 2). More than half (n=21, 51.2%) had an intact small bowel and 14.6% (n=6) had a small bowel length of ≤50cm (Table 1). Enteral autonomy was achieved in nine patients (22.0%), of which, eight were patients without an underlying malignancy (29.6% of patients without an underlying malignancy) and one patient with an underlying malignancy (7.1% of patients with an underlying malignancy)

Complications are summarized in Table 3. CLABSI/1000 catheter days was 1.0 (±2.1) overall, with a rate of 1.2 (±2.3) amongst Adult, Non-Malignant patients and 0.7 (±1.6) amongst adult patients with an underlying malignancy. CAVT/1000 catheter days was 0.1 (±0.4) over-

Table 1. Demographics

	Adult (n=41)	Adults, Non-Malignant (n=27)	Adults, Underlying Malignancy (n=14)	*p*-value†	Paediatric (n=8)
Age	53.0 (±15.1)	54.0 (±16.2)	51.1 (±13.7)	NS	0.8 (±1.8)
Male (%)	23 (56.1%)	15 (55.6%)	8 (57.1%)	NS	1 (12.5%)
BMI	18.8 (±4.1)	19.8 (±4.5)	16.8 (±2.2)	<0.05	-
Duration on PN (Years)	2.6 (±3.5)	2.9 (±3.2)	2.0 (±3.9)	NS	3.5 (±2.5)
Indication for PN					
SBS	19 (46.3%)	13 (48.1%)	6 (42.9%)	NS	3 (37.5%)
GID (Including pseudo-obstruction)	5 (12.2%)	5 (18.5%)	6 (42.9%)	NS	5 (62.5%)
GI mechanical obstruction	9 (22.0%)	3 (11.1%)	0	NS	-
ECF	3 (7.3%)	1 (3.7%)	2 (14.3%)	NS	-
Others‡	5 (12.2%)	5 (18.5%)	0	NS	-
Small Bowel Anatomy					
No small bowel resection	21 (51.2%)	15 (55.6%)	6 (42.9%)	NS	5 (62.5%)
End-Jejunostomy	12 (29.3%)	8 (29.6%)	4 (28.6%)	NS	1 (12.5%)
Jejuno-Colonic Anastomosis	3 (7.3%)	2 (7.4%)	1 (7.1%)	NS	2 (25.0%)
Jejuno-Ileal Anastomosis	-	-	-		-
Unknown	5 (12.2%)	2 (7.4%)	3 (21.4%)	NS	-
Small Bowel Length					
Intact SB	21 (51.2%)	4 (14.8%)	2 (14.3%)	NS	5 (62.5%)
SB ≤50cm	6 (14.6%)	5 (18.5%)	2 (14.3%)	NS	2 (25%)
SB 51 to 200cm	7 (17.1%)	16 (59.3%)	5 (35.7%)	NS	1 (12.5%)
Unknown	7 (17.1%)	2 (7.4%)	5 (35.7%)	0.06	-
Colon in continuity					
Hemicolon	10 (24.4%)	5 (18.5%)	5 (35.7%)	NS	1 (12.5%)
No Colon	8 (19.5%)	3 (11.1%)	5 (35.7%)	NS	1 (12.5%)
Colon intact	23 (56.1%)	19 (70.4%)	4 (28.6%)	<0.05	6 (75.0%)

BMI: Body Mass Index, ECF: Enterocutaneous Fistula, GI: Gastrointestinal, GID: Gastrointestinal Dysmotility, PN: Parenteral Nutrition, SB: Small Bowel, SBS: Short Bowel Syndrome.

†*p*-value, comparing Adults, Non-Malignant, Vs Adults with Underlying Malignancy.

‡Other indications for HPN amongst Adult, non-malignant patients include: Protein Losing Enteropathy from underlying Cronkhite Canada (n=1), Radiation Enteritis (n=1), Surgical adhesions with multiple laparotomies with no further role for surgery (n=2), complications from Whipple's procedure for chronic pancreatitis (n=1).

Table 2. Underlying aetiology

	Adult (n=41)	Paediatric (n=8)
Ischemic Bowel	9 (21.9%)	-
Necrotising Enterocolitis	-	2 (25%)
Gastrointestinal Dysmotility	6 (14.6%)	5 (62.5%)
Chronic Intestinal Pseudo-Obstruction	2 (4.9%)	5 (62.5%)
Scleroderma	4 (9.7%)	-
Underlying Malignancy	14 (34.1%)	-
Colorectal Cancer	3 (7.3%)	-
Cervical Cancer	2 (4.9%)	
FAP with Desmoid Tumours	2 (4.9%)	-
Gastric Cancer (Mets)	1 (2.4%)	-
Cholangiocarcinoma/ Gallbladder Ca (Mets)	2 (4.9%)	-
Ovarian Cancer	1 (2.4%)	
Pseudomyxoma Peritoneii (Mets)	3 (7.3%)	
HPN for underlying malignancy with a Palliative Intent	7 (17.3%)	-
Cervical Cancer (Mets)	1 (2.4%)	
Gastric Cancer (Mets)	1 (2.4%)	
Cholangiocarcinoma/ Gallbladder Ca (Mets)	2 (4.9%)	
Pseudomyxoma Peritoneii (Mets)	3 (7.3%)	
Surgical Complications	8 (19.5%)	-
Crohn's Disease	1 (2.4%)	-
Others[†]	3 (7.3%)	1 (12.5%)

CIPO: Chronic Intestinal Pseudo-Obstruction, FAP: Familial Adenomatous Polyposis, Mets: Metastatic, NEC: Necrotising Enterocolitis, Surgical Complications include: ECF

[†]Other Aetiologies: Adults: Behcet's Disease with enterocutaneous fistula (n=1), Cronkhite Canada Syndrome with Protein Losing Enteropathy, (n=1), Radiation Enteritis on a background of of previous cervical cancer (n=1)

Other Aetiologies, Paediatric cohort: malrotation with midgut volvulus with small bowel resection (n=1)

all, with a rate of 0.2 (±0.5) amongst Adult, Non-Malignant patients. There were no incidents of CAVT amongst adult patients with an underlying malignancy.

The median survival was 90 months (4.3, 175.7 95% CI) with an actuarial survival probability of 70.7 % and 39.0% at 1 and 5 years respectively (Figure 1). More than half adult patients died (n=21, 51.2%) during the study period. For patients with an underlying malignancy (n=14, 34.1%), the median survival was 6 months (4.2, 7.7 95% CI), with an actuarial survival probability of 85.7% at 3 months, 50% at 6 months, 30.7% at 1 year and 7.7% at 5 years. For patients with underlying malignancy for whom HPN was initiated with a palliative intent, the median survival was 5 months (2.4, 7.5 95% CI) with an actuarial survival probability of 71.4% at 3-months and at 14.3% at 6 months. On the other hand, for HPN patients without malignancy, the median survival was 151 months (82.2, 219.8 95% CI) with an actuarial of survival of 92.8% and 53.5% at 1 and 5 years (Figure 2). The cause of death in the majority of adult HPN patients was related to their underlying disease, as described earlier. Only one death was attributed to HPN-related complications (CLABSI).

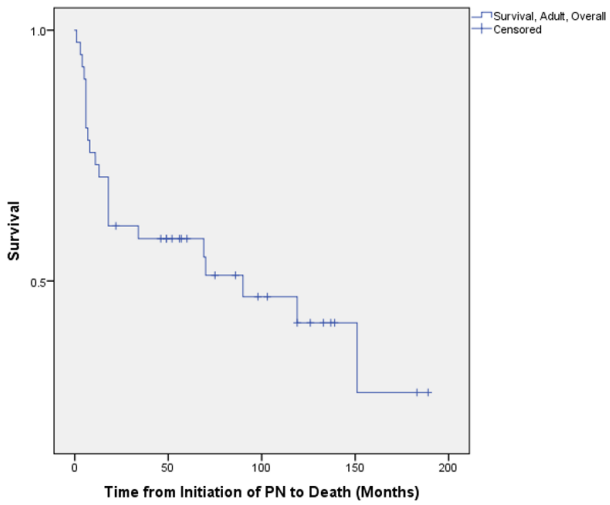


Figure 1. For all adult patients, the median survival after initiation of PN was 90 (4.3, 175.7 95%CI) months. Overall, the actuarial survival probability was 70.7 % and 39.0% at 1 and 5 years respectively.

Liver enzymes were compared (Table 4). For adult patients who had HPN for > 6 months (n=32), there were 16 (50.0%) patients overall who had biochemical evidence of IFALD. There were 10 (43.5%) adult patients without underlying malignancy and 6 (66.7%) adult patients with an underlying malignancy with an underlying malignancy (p=NS) who had biochemical evidence of IFALD.

All patients were non-cirrhotic at baseline and no patients developed decompensated cirrhosis whilst on HPN. A significant increase in serum bilirubin was noted during follow up (Table 4) in the overall cohort (29.9 (±65.7) vs 77.8 (±142.8), $p<0.05$). Whilst there were similar increases in noted in serum bilirubin amongst patients without malignancy (29.5 (±72.7) vs 77.9 (±158.1), NS) and amongst patients with malignancy (31.1 (±46.5) vs 77 (±101.3, NS), this was statistically not-significant. There were no significant changes in the other liver function test parameters.

There was a significant increase in the serum triglyceride (TG) noted during follow up (Table 4).

Paediatric cohort

In the paediatric cohort, the mean age of PN initiation was 0.8 (±1.8) years. Mean age at last follow-up was 5.1

Table 3. Clinical outcome

	Adult (n=41)	Adults, Non-Malignant (n= 27)	Adults, Underlying Malignancy (n=14)	*p-value	Paediatric (n=8)
Enteral Autonomy	9 (22%)	8 (29.6%)	1 (7.1%)	NS	4 (50.0%)
CLABSI per 1000 catheter days	1.0 (±2.1)	1.2 (±2.3)	0.7 (±1.6)	NS	1.8 (±1.3)
Gram (+) organism (n, %)	5 (15.6%)	5 (18.5%)	1 (7.1%)	NS	4 (50.0%)
Gram (-) organism (n, %)	6 (18.8%)	5 (18.5%)	2 (14.3%)	NS	5 (62.5%)
Fungal organism (n, %)	5 (15.6%)	3 (11.1%)	1 (7.1%)	NS	1 (12.5%)
CAVT per 1000 catheter days	0.1 (±0.4)	0.2 (±0.5)	-	<0.05	0.7 (±0.8)

CLABSI: Central Line–Associated Bloodstream Infection, CAVT: Catheter Associated Venous Thrombosis
†p-value comparing Adults, non-malignant vs Adults, underlying malignancy.

Table 4. Baseline and follow up liver enzymes and triglycerides for patients who received HPN > 6 months and comparison between patients with and without malignancy

	Adult, Overall (n=32)	p-value	Adult, Without Malignancy (n=22)	p-value	Adult, With Malignancy (n=9)	p-value	Paediatric (n=8)	p-value
Albumin (g/l)		NS		NS		NS		<0.05
Baseline	28.6 (±7.9)		28.7 (±7.8)		28.1 (±8.6)		24.5 (±7.4)	
Follow Up	29.3 (±9.8)		31.3 (±8.9)		24.1 (±10.7)		35.1 (±4.8)	
Improvement n (%)	16 (50%)		14 (60.9%)		2 (22.2%)		7 (87.5%)	
Worsening n (%)	16 (50%)		9 (39.1%)		7 (77.8%)		1 (12.5%)	
Bilirubin (µmol/L)		<0.05		NS		NS		NS
Baseline	29.9 (±65.7)		29.5 (±72.7)		31.1 (±46.5)		15.6 (±12.8)	
Follow Up	77.8 (±142.8)		77.9 (±158.1)		77 (±101.3)		4.9 (±3.7))	
Improvement n (%)	22 (68.8%)		7 (30.4%)		3 (33.3%)		2 (25.0%)	
Worsening n (%)	10 (31.3%)		16 (69.6%)		6 (66.7%)		6 (75.0%)	
ALP (IU/L)		NS		NS		NS		NS
Baseline	171 (±239)		114 (±111)		316(±391)		190 (±121)	
Follow Up	200 (±183)		180 (±194)		251 (±149)		224 (±108)	
Improvement n (%)	20 (62.5%)		15 (65.2%)		5 (55.6%)		5 (62.5%)	
Worsening n (%)	12 (37.5%)		18 (34.8%)		4 (44.4%)		3 (37.5%)	
ALT (IU/L)		NS		NS		NS		NS
Baseline	50.3 (±61.1)		48.9 (±64.1)		53.6 (±55.9)		20.4 (±19.6)	
Follow Up	38.1 (±27.5)		37 (±28.5)		41.1 (±26.1)		36.4 (±34.9)	
Improvement n (%)	14 (43.8%)		10 (43.5%)		4 (44.4%)		7 (87.5%)	
Worsening n (%)	18 (56.3%)		13 (56.5%)		5 (55.6%)		1 (12.5%	
AST (IU/L)		NS		NS		NS		NS
Baseline	53 (±49.4)		52.6 (±50.3)		54.0 (±50.0)		31.8 (±17.2)	
Follow Up	59.6 (±51.3)		51.6 (±39.5)		80.2 (±72.4)		35.9 (±18.3)	
Improvement n (%)	18 (56.3%)		12 (52.2%)		6 (66.7%)		4 (50.0%)	
Worsening n (%)	14 (43.8%)		11 (47.8%)		3 (33.3%)		4 (50.0%)	

ALT: Alanine Aminotransaminase, AST: Aspartate Aminotransaminase, ALP: Alkaline Phosphatase, GGT: gamma-glutamyl transferase, TG: Triglyceride

Table 4. Baseline and follow up liver enzymes and triglycerides for patients who received HPN > 6 months and comparison between patients with and without malignancy

	Adult, Overall (n=32)	*p*-value	Adult, Without Malignancy (n=22)	*p*-value	Adult, With Malignancy (n=9)	*p*-value	Paediatric (n=8)	*p*-value
GGT (IU/L)								NS
Baseline	-		-		-		64.7 (±44.9)	
Follow Up	-		-		-		117 (±164)	
Improvement n (%)	-		-		-		4 (50.0%)	
Worsening n (%)	-		-		-		4 (50.0%)	
TG (mmol/L)		<0.05		<0.05		NS		NS
Baseline	1.5 (±1.2)		1.4 (±1.0)		1.9 (±1.4)		0.9 (±0.2)	
Follow Up	2.1 (±1.4)		2.1 (±1.5)		1.8 (±1.0)		0.8 (±0.2)	
Improvement n (%)	10 (31.3%)		5 (21.7%)		4 (44.4%)		3 (37.5%)	
Worsening n (%)	22 (68.8%)		18 (78.3%)		5 (55.6%)		5 (62.5%	
Patients who Satisfy Criterion for IFALD n (%)	16 (50.0%)		10 (43.5%)		6 (66.7%)	NS	7 (87.5%)	NS

ALT: Alanine Aminotransaminase, AST: Aspartate Aminotransaminase, ALP: Alkaline Phosphatase, GGT: gamma-glutamyl transferase, TG: Triglyceride, NS: Not Significant

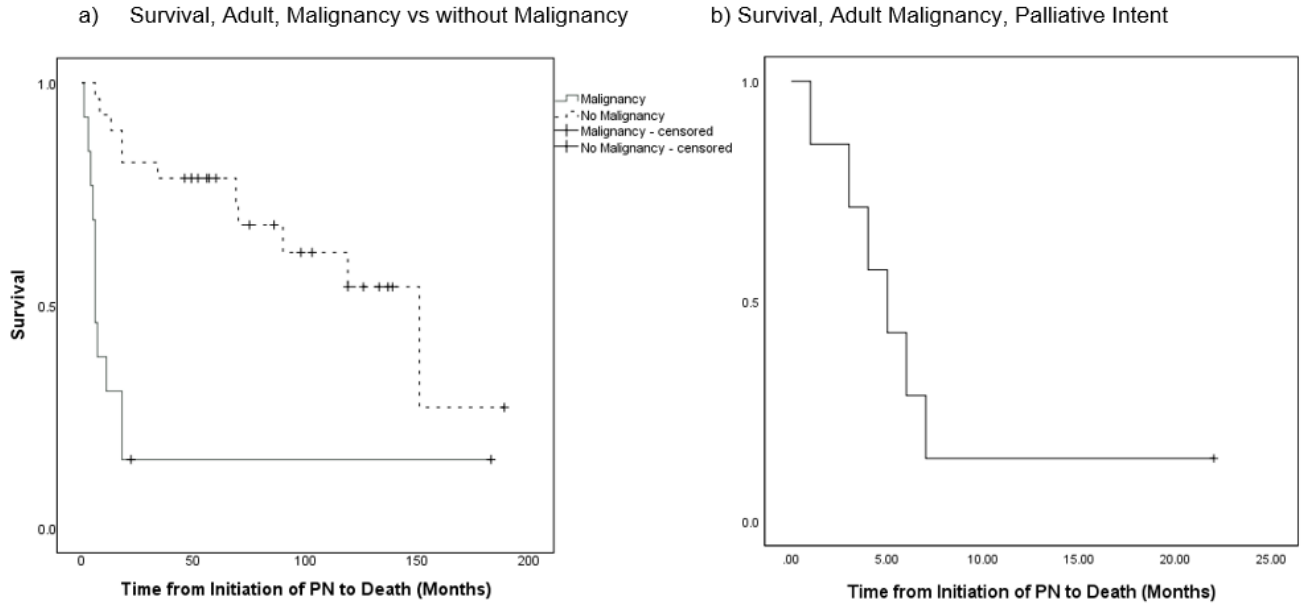


Figure 2. Survival, adult patients with malignancy. (a) For adult patients with malignancy, the median survival was 6 months (4.2, 7.7 95%CI) months, with an actuarial survival of: 85.7% at 3 months, 50% at 6 months, 30.7% at 1 year and 7.7% at 5 years. For adult patients without malignancy, the median survival was 151 months (82.2, 219.8 95% CI) with an actuarial survival of 92.8% and 53.5% at 1 and 5 years respectively. (b) For adult patients with underlying malignancy with HPN initiated for a palliative intent, the median survival was 5 months (2.4, 7.5 95% CI) with an actuarial survival probability of 71.4% at 3-months and at 14.3% at 6 months.

(±3.2) years, and mean duration of PN was 3.5 (±2.5) years (Table 1). The most common indication for PN was GID (n=5, 62.5%) followed by SBS (n=3, 37.5%). The underlying aetiology for GID was due to chronic intestinal pseudo-obstruction (CIPO). The underlying aetiologies for short bowel syndrome included necrotising enterocolitis (n=2, 66.7%) and malrotation with midgut volvulus (n=1, 33.3%) (Table 2). All five patients with CIPO had intact small bowel (n=5, 62.5%). Half of the patients achieved enteral autonomy while the other half remained dependent on PN by the end of study period. None of the patients underwent specific bowel lengthening procedure such as the STEP or the Bianchi operation.

With regards to complications, CLABSI/1000 catheter days was 1.8 (±1.3). Seven patients had CAVT with an overall incidence rate of 0.68 (±0.8) per 1000 catheter days for the paediatric cohort. Five patients had suffered recurrent CAVT in more than two central veins and remained on ongoing anticoagulation therapy.

Amongst paediatric patients, the only liver function test change that was statistically significant was an increase in serum albumin. There were no significant changes in the rest of liver function test parameters (Table 3). The entire paediatric cohort (n=8) had HPN > 6 months and 7 (87.5%) had biochemical evidence of IFALD. Only two patients had liver histology available: One patient with an ultra-short bowel secondary to NEC had bridging fibrosis at 12 months of age, while another patient with CIPO had only periportal fibrosis after 9 years of PN. None of the seven patients developed decompensated cirrhosis or portal hypertension during the period of follow up.

No deaths were reported in the paediatric cohort during the study period.

DISCUSSION

We report the long-term clinical outcomes of an adult and paediatric cohort of 41 adults and 8 children on HPN over 16 years. This represents 95% of the HPN burden in Singapore. This study also serves an update of HPN outcomes in Asia with the 2 prior adult cohorts from Japan (Takagi et al, 1995)[19] and Taiwan (Wang et al, 2007)[14] reported more than 10 years prior. This is also the first paediatric HPN cohort from Asia and further, to our knowledge, this is the first HPN cohort reported specifically from South East Asia.

The mean age of PN initiation in both our adult and paediatric cohorts are similar to cohorts from America,[20] Canadian,[21] and Taiwan.[14] Of note, our adult cohort was older than those reported in Japan where the reported mean age of PN initiation was 46 (±22) years old. This may be attributed to the fact that the majority of the adult patients in the Japanese cohort have underlying inflammatory bowel disease (IBD), which tends to have a younger onset. This is compared to our cohort, where we report a higher proportion of patients underlying malignancy, which tends to affect older patients. While it appears that underlying aetiologies necessitating HPN are similar amongst Japanese and Western adult cohorts, our cohort seems to parallel the Taiwanese cohort.[14] This suggests a heterogeneity of disease burden (in particular, IBD) in the region, and may indicate differing perspectives towards palliative HPN in patients with underlying malignancy. A multi-centre Asian HPN registry would be useful to further understand the varying demographic and sociocultural trends towards HPN across Asia.

Overall, the median survival in our adult cohort was longer than the previously reported Taiwanese cohort more than 10 years ago (90 months vs 7 months). This is likely related to stringent patient selection and improved HPN provision resulting in a reduction of PN related complications. Approximately 64.5% of the Taiwan cohort versus 34.1% of our cohort had underlying cancer (17.3% were initiated on HPN with a palliative intent). In addition, approximately 22.5% of the Taiwanese cohort died from catheter related complications and liver failure, as opposed to only one (3.4%) from our cohort who died from catheter related complications, with none dying from liver failure.[14] Other cohorts of HPN patients without malignancy have reported 1-year survival of 86% to 97%[22-31] and 5 year-survivals of 57 to 87%.[22-26,30,32-34] Whilst our 1-year survival for HPN patients without an underlying malignancy was similar at 92.8%, our cohort reported a slightly lower 5-year survival at 53.5%. For the patients who died (n=11), the majority had an underlying ischemic bowel (n=7 (63.6%)). They had deaths either related to recurrent ischemic bowel (n=1), infective endocarditis (n=1), and the rest (n=5) died out of hospital. For the other patients who died (n=4); underlying scleroderma gut (n=2), surgical complication with short bowel (n=1), radiation enteritis with protein losing enteropathy (n=1), pneumonia was the cause of death. The mean age at time of death was amongst adult HPN patients without malignancy was 64.9 years with a range 46.5 to 82.5 years, with a mean of 4.1 (±4.3) years of PN support at time of death. This suggests a more elderly disposition in this group and given the known causes of death being largely attributable to infection (non-CLASBI) or complications of their underlying disease, these deaths may not have been reasonably predicted nor prevented. The converse is probably true, without the provision of HPN, these patients would have likely succumbed to complications of gut failure, possibly much earlier in their clinical course.

For patients with an underlying malignancy, our 1-year and 5-year survival was 30.7% and 7.7% at 5 years. Reported 1 year survival for patients with malignancies range from 9.5% - 62%,29,34-42 with a median survival ranging from 1.5 to 10.5 months.[29,34,35,38-47] For patients with an underlying malignancy for whom HPN is initiated for a palliative intent (n=7), we report a median survival of 5 months with an actuarial survival probability of 71.4% at 3-months and 14.3% at 6-months with no reported incidents of catheter-related complication in this sub-group. The provision of home PN in the palliative setting is often debatable and fraught with clinical and ethical arguments for and against PN, considering patient choice, quality of life and cost.[48] In our centre, we consider palliative HPN for patients with a) proven gut failure, b) Karnofsky score ≥50, c) prognosis greater than 3 months with d) good social support. Our internal criteria are similar to recent guidance from the European Society for Clinical Nutrition and Metabolism (ESPEN).[5] Our findings, together with other observational studies support the role for HPN in a proportion of patients with underlying malignancy, who satisfy strict selection criteria.[48-50]

While our paediatric study population was comparatively small owing to the short experience of our intestinal rehabilitation program, the etiology of IF and indications for long-term PN in our cohort were similar to Western paediatric cohorts[21,51-53] with GID and SBS (most commonly from NEC) being major indications for PN. The relatively small number of HPN patients in the paediatric cohort could be contributed by a lack of support for HPN. There was a separate cohort of paediatric patients (n=8) who had SBS from NEC (n=7) and IBD (n=1) who remained inpatient > 3 months (mean 9.37 ± 5.85 months) until they achieved enteral autonomy, mainly due to socioeconomic reasons such as lack of caregiver or financial reasons, rather than for medical indications (this group was not compared formally with our larger cohort as line care was administered by healthcare professionals, and complications rates might differ). If we considered this group, NEC would be the predominant indication for prolonged PN/HPN overall amongst paediatric patients (all CIPO patients in our cohort eventually required HPN). Despite the inherent cost, HPN is more cost-effective than receiving PN in hospital long term.[54] These findings have led to more recent changes in governmental subsidies for HPN and underscores a need for more robust community HPN support.

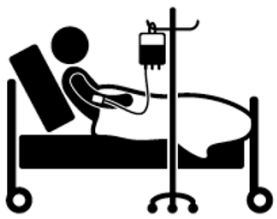
Reported rates of catheter related blood stream infections in the literature ranges from 0.38 to 4.[58,55-62] with a previous systematic review of 39 studies reporting a median of 1.31 episodes per 1000 catheter days.[63] Our CLASBI rates for adults was less than this reported median with an CLASBI per 1000 catheter days of 1.0 (±2.1) (adults, overall), 1.2 (±2.3) (adults, non-malignant) and 0.7 (±1.6) (adults, underlying malignancy), however, our paediatric cohort had a rate of 1.8 (±1.3) per 1000 catheter days. A potential recommended goal for a NSS unit to achieve was suggested as a CLASBI rate of <1 per 1000 catheter days,[64] notwithstanding, efforts should be made to bring the CLASBI rate to as close to zero as possible. In our cohorts, adult HPN without malignancy patients and paediatric patients all use a single lumen, tunnelled line. The use of a single-lumen tunnelled line has been reported to have a lower rate of infectious complications when compared to multi-lumen catheters, peripherally inserted central catheters or ports.[61,65,66] Further, we have employed Taurolock® with heparin as catheter lock solutions for all paediatric patients since 2013 and for adults who have had a previous episode of line sepsis. Taurlock® has been shown to be efficacious in reducing rates of line sepsis,[67-71] and in a network meta-analysis, it was shown to be superior other catheter lock solutions (vancomycin, ethanol, fusidic acid, amikacin).[72] Whilst there are inherent issues of cost with using Taurolock®, this is justifiable when considering the cost related to a CLASBI episode.[73]

Biochemical evidence of IFALD was found in 50.0% of adult patients and 87.5% of our paediatric patients. Of our adult patients, biochemical evidence of IFALD was seen in 10 (43.5%) patients without an underlying malignancy and 6 (66.7%) patients with malignancy. In our study, we used the criterion by Luman et al. This criterion is perhaps the most stringent by considering 1.5 x ULN of any component of a liver function test at 6 months.[18] Whilst this will likely over report IFALD, using this criterion in clinical practice is helpful to prompt further evaluation by a non-invasive measure of fibrosis such as a Fibroscan®74 or even a liver biopsy. IFALD is a multifactorial condition which may result in progressive hepatic fibrosis, and decompensated cirrhosis with antecedent patient/intestinal failure related factors and HPN related factors, which is beyond the scope of our study. In our adult cohort, neither GGT nor a direct bilirubin is not routinely performed as part of our liver biochemistry panel, and our further interpretation is hence limited. Further, patients with metastatic disease to the liver may also cause elevations in a patient's liver enzymes, hence underscoring the importance of correlating aberrations in liver enzymes clinically.

IFALD is more prevalent amongst children compared with adult HPN patients,[75-77] and whilst the overall numbers in our paediatric cohort are small, this trend is similarly reflected. This is likely due to an increased propensity for hepatotoxicity from PN in a maladapted immature liver, as all of our paediatric patients were started on PN very early during the neonatal period. As such, the use of SMOFlipids® rather than soy-based lipid has been routine in our paediatric program from the outset with the aim to minimise cumulative liver injury from PN, with intestinal transplant as last resort for end stage IFALD. Amongst pediatric patients, a baseline GGT at initiation of PN may not be as helpful an indicator that a raised ALP is likely from a hepatobiliary source. In normal full term neonates, normal GGT levels are 6-7 times the ULN of the adult reference and this only declines by the age of 5-7 months.[78] Hence the interpretation of follow up liver enzymes (at least >6 months post HPN initiation as per Luman et al's criteria18 is more pertinent.

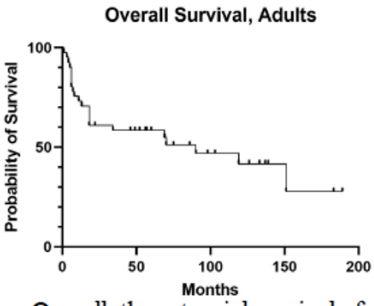
With regards to enteral autonomy, 22% (n=9) of the adult patients achieved enteral autonomy, the majority of which were patients without an underlying malignancy, this was compared with 50% (n=4) of the paediatric cohort who attained enteral autonomy and could be weaned off PN. For the adult patients, the majority of patients who attained enteral autonomy eventually, five patients had an ECF (Behcet's (n=1), Crohn's (n=1), complications from surgery (n=3)), two patients had short bowel (ischaemic bowel, 70cm in continuity with colon; ischemic bowel, 60cm in continuity with colon), one had protein losing enteropathy and one patient had malabsorption related with a Whipple's procedure. For the four paediatric patients who achieved enteral autonomy, two had PIPO (no bowel resection), one patient had NEC (63cm residual small bowel, in-continuity with the colon) and one patient had malrotation of the gut (8cm residual small bowel, in-continuity with the colon). Paediatric cohorts have reported enteral autonomy in 47% to 64.3%[51,79] of patients, and represents the remarkable ability for intestinal adaptation in paediatric patients that typically occurs in the first 5 years of life,[51,79,80] which may not be present in adults.

Our study has several limitations. Firstly, the retrospective nature of the study is exposed to inherent recall bias. Secondly, we lack important PN composition data on calories provided, macronutrients, micronutrients, frequency/week of PN provided and lipid composition. Our



- Home parenteral Nutrition (HPN) is a life-sustaining therapy for patient who has chronic intestinal failure
- HPN is resource intensive and not without complication.
- While data from the west is robust, data from asia is still scarce
- Here, we presented our HPN clinical outcome from 2002-2017 in Singapore.

- Over 15 years, the centres had supported 41 adult and 8 paediatric patients
- The commonest indication for HPN in adult was short bowel syndrome and dysmotility in paediatric patients



- Overall, the actuarial survival of adult HPN patient was70.7%(1-year) and 39.0%(5-years).
- For adult patients without malignancy, the median survival was comparable with other studies with median survival of 151 months (82.2, 219.8 95% CI)
- The actuarial survival in adult patients without malignancy was 92.8% and 53.5% at 1 and 5 years respectively.

Graphical abstract.

institutions underwent a migration to digital prescribing in 2012 and any prior paper records, in particular PN prescriptions, were culled for patients 2 years after they had passed away. This information would be crucial in correlating with the risk of IFALD and other PN related complications. Further, our paediatric HPN programme is relatively recent. With longer term follow up, we would be able to garner further outcome data to better understand the morbidity and mortality burden in our paediatric patients. Next, our cohorts have overall, small numbers, and perhaps represents only a fraction of the larger South East Asian region of which Singapore is a part of. Nevertheless, we report similar indications for HPN and comparable catheter-related complication rates when compared with western cohorts for both our adult and paediatric groups. Lastly, a deeper understanding into the impact on quality-of-life, cost and the psychosocial implications of home PN within our local context are needed and warrants further study.

In summary, we report the first descriptive demographic and outcome data of the main adult and paediatric HPN cohorts within Singapore with improved survival rates compared to other parts of Asia with low central catheter-related complications. Our findings provide insight into the understanding the burden of chronic IF in the region and highlights the need for further integrated, multicentre research.

AUTHOR DISCLOSURES

This study did not receive any funding. The authors have no conflicts of interest financial or otherwise to declare.

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Supplementary Table 1. Patient profile and organisms diagnosed during CLASBI events

	CLABSI Events	Age at PN initiation	Duration of PN Support (years)	Organism(s) Identified
Adult 1	1	44	0.5	*Candida glabrata*
Adult 2	13	28	14.6	*Staphylococcus aureus* (Methicillin Sensitive), *Klebsiella pnuemoniae*, *Acinetobacter baumannii*, *Staphylococcus hominis*
Adult 3	1	50	1.1	*Ochronbactrum antropi*
Adult 4	1	64	12.6	*Kocuria kristinae*
Adult 5	2	66	5.9	*Enterobacter gergoviae*, *Candida parapsilosis*
Adult 6	5	34	5.8	*Serratia marcescens, Enterobacter aeriogenes, Klebsiella pneumoniae, Enterobacter cloacoe, Enterobacter faecalis*
Adult 7	25	44	7.08	*Serratia sp, Candida tropicalis, Pseduomonas aeruginosa, Enterobacter sp, Klebsiella pneumonia, Enterococcus faecium (VRE), Acinetobacter baumanni, Staphylococcus aureus* (Methicillin Resistant), *Enterobacter gergoviae, Serratia marascens, Enterobacter cloacae, Coagulase negative staphylococcus, Candida glabrata*
Adult 8	1	63	1.7	*Weisella confusa, Candida glabrata, Candida parapsilosis*
Adult 9	1	58	3.3	*Candida parapsilosis*
Adult 10	1	55	2.8	*Coagulase Negative Staphylococcus*
Adult 11	2	39	1.1	*Klebsiella species, Escherichia coli, Enterobacter gergoviae*
Adult 12	1	52	0.7	*Acinetobacter baumannii*
Adult 13	1	71	0.5	*Staphylococcus aureus* (Methicillin Sensitive)
Paeds 1	2	5.6	5.6	*Staphylococcus aureus* (Methicillin Sensitive)
Paeds 2	3	0.1	7.6	*Klebsiella pneumoniae, Proteus sp, Enterococcus, Enterobacter cloacae, Serratia, Candida glabrata, Staphylococcus aureus* (Methicillin Resistant)
Paeds 3	4	0.1	7.2	*Enterococcus, Enterobacter sp, , Escherichia coli*
Paeds 4	2	1.0	4.2	*Staphylococcus aureus* (Methicillin Sensitive)
Paeds 5	1	0.1	3.5	*Serratia sp*
Paeds 6	3	0.1	2.5	*Klebsiella pneumoniae, Enterobacter sp, Pseudomonas aeruoginosa*
Paeds 7	2	0.6	1.5	*Escherichia coli, Enterobacter faecalis*