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**Systematic Review: Medical and Nutritional Interventions
for the Management of Intestinal Failure and its Resultant
Complications in Children**

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3 **Systematic Review: Medical and Nutritional Interventions for the Management**
4 **of Intestinal Failure and its Resultant Complications in Children**
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7 **Systematic review: Management of Paediatric IF**
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36 Abbreviations: CSBLT- combined small bowel liver transplant, EL- evidence level,
37 EN- enteral nutrition, IF-intestinal failure, IFALD- intestinal failure associated liver
38 disease, PN- parenteral nutrition, SBS- short bowel syndrome, UDCA-
39 ursodeoxycholic acid
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ABSTRACT

Background and Aims: Intestinal failure (IF) affects a growing number of children due to increasing numbers of preterm infants surviving intestinal resection for necrotising enterocolitis (NEC) and improving surgical techniques for congenital gut anomalies. Parenteral nutrition (PN) is the mainstay of therapy; enteral nutrition (EN) may have trophic effects on the gut. We aimed to systematically review evidence for the effectiveness of medical and nutritional interventions in the treatment of IF in children.

Methods: Retrieval of data from studies of patients aged <18yrs and receiving >28 days PN. Outcome measures: improvement in intestinal function; intestinal adaptation; growth; prevention and treatment of IF-associated liver disease; mortality. Cochrane Database (November 2009), Medline (1950-November 2009) and CINAHL (1982-November 2009) electronic database searches were made using keyword and subject headings (MeSH); IF; Short Bowel Syndrome (SBS); PN and Child. The level of the evidence (EL) was assessed using Scottish Intercollegiate Guidelines Network (SIGN) methodology (www.sign.ac.uk).

Results: From 1607620 hits, 720 abstracts were reviewed. 33 original papers were included. No studies were of high methodological quality.

Conclusions: The evidence base for medical and nutritional interventions in paediatric IF is limited and of poor quality. In the absence of RCTs, this evidence base can improve through case control and cohort research, and with better multi-agency communication the study of inter-centre differences is possible. Achievable short-term goals would include the study of; optimal ursodeoxycholic usage; novel intralipid formulations; cycled enteral antibiotics; enteral probiotics and new enteral feeding strategies.

Keywords: short bowel syndrome; parenteral nutrition; parenteral lipid; probiotics

BACKGROUND AND OBJECTIVES

Intestinal failure (IF) is defined as a reduction of functional gut mass below that needed for digestion and absorption of fluid and nutrients for weight maintenance in adults and growth in children¹⁻³. In developed countries IF, **in children**, is most commonly the result of congenital or early-life intestinal diseases, which can be separated into three main groups by pathogenesis^{4,5}: 1. Short bowel syndrome (SBS) caused by congenital intestinal atresias or secondary to resection following necrotising enterocolitis (NEC)⁶; 2. Neuromuscular disorders of the gastrointestinal tract, including long segment aganglionosis (Hirschsprung's Disease) and congenital intestinal pseudo-obstruction syndromes (CIPOS)⁷; 3. Congenital enterocyte disorders, such as microvillus inclusion disorder and intestinal epithelial dysplasia^{8,9}.

The prevalence of IF is increasing mainly due to the survival of greater numbers of infants following intestinal resection in the newborn period¹⁰. Deficit in functional gut mass can improve over time through the process of bowel adaptation. Adaptation occurs by a combination of mucosal hypertrophy and hyperplasia of small bowel tissue¹¹. The adaptation process can take several days to many years depending on the length of bowel resected, the length and condition of the remaining unresected small bowel, the presence of the ileocaecal valve and the nutritional status of the affected patient¹².

The introduction of parenteral nutrition (PN) to support infants with IF while bowel adaptation occurs has dramatically improved the historically dismal prognosis^{1,5,13}. However significant complications of management, such as central venous line sepsis, IF associated liver disease (IFALD) and growth failure, have contributed to long-term morbidity and mortality in IF^{1,5,14}. The failure of medical and nutritional treatments for IF invariably leads to a substantial minority of patients progressing to assessment for, and, sometimes, combined small-bowel liver transplantation (CBSLT)^{1,10}. Children may die before referral to CBSLT centres¹⁵.

A first group of therapeutic interventions have been postulated to accelerate bowel adaptation such as the use of enteral trophic factors, manipulation of dietary protein, fat and carbohydrate and manipulation of the gut microbiota^{1,16,17}. **A second group of**

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3 interventions are aimed at the prevention or amelioration of complications of PN such
4 as antiseptic procedures for CVCs, or treatment of IFALD with bile analogues,
5 choleretic agents and changes in the constituents of PN¹⁸.
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10 Numbers of patients with IF are low, even in large tertiary medical centres, limiting
11 the scope for controlled trials of interventions to improve outcomes in IF. The aim of
12 this review is to critically appraise the existing data on medical and nutritional
13 interventions for the treatment of IF, and effect of strategies to ameliorate or prevent
14 the complications of long term PN in children (namely sepsis and IFALD). In addition
15 we wish to suggest how future studies may be developed to expand this evidence
16 base.
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METHODS

We devised a publication search strategy to answer our key question which was to determine which medical and nutritional interventions are of value in the treatment of paediatric patients (<18 years) with IF (defined as requirement for PN \geq 28 days, while post-term age equivalent). Outcome measures sought were: improvement in intestinal function; intestinal adaptation; growth; prevention of IFALD; treatment of IFALD and mortality. We did not attempt to evaluate surgical interventions (transplant or non-transplant procedures).

Electronic searches of the Medline (January 1950-November 2009) and CINAHL (January 1982- November 2009) databases were performed using combinations of the keyword and subject heading (MeSH) 'child' with: IF; short bowel syndrome (SBS); and PN. To identify further potential studies, the reference lists on all identified potential published studies and major reviews by identified experts in this field were reviewed. In addition, citation searches of potential studies were made on the Web of Science database. A search of the 'grey literature' was performed by hand, which included the published proceedings for the past ten years of the European Society of Paediatric Gastroenterology Hepatology and Nutrition, the North American Society of Pediatric Gastroenterology Hepatology and Nutrition. This search aimed to identify studies published in abstract, but were only included in this review if they were subsequently published in full in a peer review journal. The authors' personal collections of publications were also searched.

Two authors (ARB, DCW) constructed the search strategy and identified potential studies for inclusion. Evidence based guidelines were assessed for applicability using the AGREE tool ¹⁹. For individual studies two authors (ARB, LMB) who were masked to study outcomes independently graded the level of evidence (EL) presented using the SIGN methodology ²⁰. A third author (DCW) reviewed all studies and also acted as an arbiter in cases of disagreement between the first two. All authors were involved in the writing of the manuscript. The grading assignment of EL is summarised in table 1 (also www.sign.ac.uk). Because our aim was to review original data, rather than to include expert opinion (EL 4), only publications of an EL of 1, 2 or 3 were permitted inclusion in our review.

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Evidence level (EL)	Study type
1	Systematic reviews, meta-analysis of RCTs, RCTs
2	Case control/ cohort studies, non- randomised interventions
3	Non-experimental studies, surveys
4	Expert opinion

Additional Grading (EL 1 and 2)	
++	High quality well constructed methods, very low risk of confounding bias
+	Well constructed methods, low risk of confounding bias
-	High risk of confounding bias or non-causal relationship

Table 1: The revised SIGN grading system²⁰

RESULTS

The aforementioned keywords and subject headings yielded 1607620 hits. The application of combinations of 'child' with the other search terms limited the search to 720 abstracts which were reviewed online. Although the search term 'PN' generated additional hits it demonstrated redundancy in terms of potential studies. A total of 61 potential studies were reviewed in full. Twenty seven of these were discarded because they did not concern children, it was impossible to separate paediatric data from adult data, or were available in abstract form only. The 34 remaining studies included one consensus-based guideline for the use of long term PN in children which was judged to be relevant, but not limited to, our key question ²¹.

Therefore, 33 original papers were included in our review ²²⁻⁵⁴. There were no EL 1++, EL1+, EL 2++ or EL 2+ studies. There were two EL 1-, six EL 2- and 25 EL 3 studies. The higher-level evidence studies (EL 1 and EL 2) are summarised in Table 2 and are grouped from the point of view of therapeutic modality. Limitations of each study are discussed within the text.

Author	Population	Intervention(s)	Cases	Control Data	Controls	Study Rating	Outcomes reported
Ksiazzyk 2002 ³⁷	Infants with SBS	Hydrolysed vs. non-hydrolysed formula	10	Cross-over patients	10	1-	No significant difference in enteral intake or energy expenditure.
Goulet 1999 ³⁰	Infants on long-term PN	Olive oil lipid vs. Soy bean Lipid	9	Randomised eligible infants	9	1-	No significant difference in bilirubin, ALT, AST. Significant treatment effect on total cholesterol and LDL.
Heubi 2002 ³⁴	Post-surgical Infants	TUDCA (30mg/kg/day)	22	Non-consenting infants	30	2-	No significant difference in bilirubin or ALT, AST, Alk Phos.
Chen 2004 ²⁴	Preterm infants	UDCA (10-30mg/kg/day)	12	Historical non-treated infants	18	2-	Shorter duration of cholestasis in treatment group (62.8 vs. 92.4 days p=0.006).
Gura 2008 ³³	Infants with SBS	Fish Oil lipid in established IFALD	18	Historical Cohort	21	2-	Significantly shorter duration cholestasis in treatment group. Non-significant trend towards lower mortality.
Kubota 1990 ³⁸	Post-surgical Neonates	Metronidazole (25-50mg/kg/day)	21	Historical Cohort	21	2-	Significantly lower GGT in high dose treatment group during PN.
Puder 2009 ⁴⁸	Infants with IF	Fish oil lipid in established IFALD	42	Historical Cohort	49	2-	Significantly reduced mortality, reversal of IFALD and improved cholesterol profile.
Lee 2009 ⁴⁰	Infants with IF	Fish oil lipid in established IFALD	18	Historical Cohort	59	2-	Reduction in serum triglyceride and bilirubin levels, and improvement in albumin.

Table 2: Studies of higher evidence level as appraised by the SIGN method²⁰

SBS- short bowel syndrome; PN- parenteral nutrition; ALT- alanine aminotransferase; AST- aspartate aminotransferase; LDL- low density lipoprotein; TUDCA- tauroursodeoxycholic acid; Alk Phos- alkaline phosphatase; UDCA- ursodeoxycholic acid; IFALD- intestinal failure associated liver disease; IF- intestinal failure.

PN Manipulations

Ten studies were identified that described manipulation of PN, with four studies of higher EL^{30,33,40,48}. Goulet et al³⁰ (EL 1-) investigated the use of an olive oil-based lipid formulation (ClinOleic 20%; Baxter Clintec, Mississauga, Canada) in comparison to a standard treatment of soy bean lipid (Intralipid 20%; Upjohn-Pharmacia, Bridgewater, New Jersey, USA) in 18 infants receiving long term PN. Patients were prospectively randomised into the treatment (n = 9) and control (n = 9) groups. The authors found no significant difference in serum bilirubin, ALT, and AST between the two but noted a significant treatment effect in terms of reduction of total cholesterol and low-density lipoprotein cholesterol. The authors did not state their methods of randomisation or concealment or describe the use of power calculations that lead to the numbers recruited and did not describe concurrent administration of confounding treatments. As a result this study was allocated an EL 1-.

Gura et al³³ (EL 2-) retrospectively investigated the use of a fish oil-based lipid preparation (Omeqaven, Fresenius Kabi AG, Bad Homburg, Germany) in ameliorating established IFALD in 18 infants with SBS. The data cohort was compared with those from a historical cohort of 21 infants treated with the standard soybean lipid (Intralipid, Fresenius Kabi AG, Bad Homburg, Germany). The authors reported a trend toward lower total mortality (2 vs. 7) and liver-related mortality (0 vs. 6) in the treatment group. They also reported a significantly shorter time to resolution of cholestasis in the treatment group (9.4 vs. 44.1 wk p=0.02). The use of an historical cohort, with inadequate attention to confounding patient variables and concurrent administration of confounding treatments lead this study to be assigned an EL 2-.

Puder et al⁴⁸ also retrospectively reported a larger cohort of SBS infants with established IFALD treated with Omeqaven (42 patients). The cohort was compared again with a historical cohort of 59 patients with SBS who also had established IFALD. The authors reported a significantly reduced risk of death or transplantation in the fish oil group (9.5% vs. 34.7% p=0.005). Reversal of cholestasis was also significantly greater in the fish oil group (45% vs. 4.1% p<0.0001). The use of a historical cohort, with inadequate attention to confounding patient variables and concurrent administration of confounding treatments lead this study to be assigned an EL 2-. Lee et al⁴⁰ from the same group reported on changes in triglyceride profiles in

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3 18 infants from the same fish oil cohort in comparison to the 59 infants in the
4 historical cohort. They reported a significant reduction in triglyceride levels in the fish
5 oil group at the end of treatment (40mg/dL vs. 140mg/dL $p<0.001$). The previous
6 limitations as described ⁴⁸ apply and as such this paper was also rated EL 2-.

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12 Lower level evidence studies included three case series describing fish oil lipid to
13 reverse IFALD ^{28,31,32}, two case series describing cycling of PN administration to
14 reverse IFALD in 57 eligible infants ^{26,43} and a single case report of supplementation
15 of PN with glutamine to encourage intestinal adaptation in an infant with SBS ²².

20 21 **Growth Factors**

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23 Only lower level evidence studies (EL 3) exist for the use of growth factors in
24 paediatric IF. This includes case series of five patients receiving epidermal growth
25 factor (EGF) ⁴⁹, combinations of growth hormone (GH) (0.2-0.3mg/kg/wk) and
26 insulin-like growth factors (two patients) ⁴⁶, GH (0.3mg/kg/day) and glutamine
27 supplementation (two patients), ³⁹ and a somastatin analogue (one infant) ⁴⁷.

30 31 32 33 **Bile Acid Analogues and Anticholeretics**

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35 Two studies of higher EL were identified describing the use of bile acid analogues
36 ^{24,34}. Heubi et al ³⁴ (EL 2-) aimed to prospectively investigate the potential of
37 tauroursodeoxycholic acid (30mg/kg/day) to prevent or ameliorate IFALD in post-
38 surgical preterm infants. 22 infants and 30 controls were recruited, but some patients
39 did not fulfil the criteria of post-term corrected age and PN>28 days. There were no
40 significant differences in serum bilirubin, AST, ALT and alkaline phosphatase
41 between groups. However, because of poor recruitment the authors used non-
42 consenting controls, and the resultant patient heterogeneity, enrolment bias and lack
43 of controlling for confounding factors meant that this study was allocated an EL 2-.
44 Chen et al ²⁴ (EL 2-) retrospectively analysed the effects of the duration of cholestasis
45 of commencing infants with established IFALD on ursodeoxycholic acid (UDCA)
46 (10-30mg/kg/day). Twelve patients who received UDCA were compared with 18
47 controls (who had not consented to this intervention). They reported a significantly
48 shorter time to achieve normal serum bilirubin levels in the treatment group (62.8 vs.
49 92.4 days $p=0.006$), but it should be noted that there was a non-significant trend
50 towards longer duration of PN in the control group (36.1 vs. 48.8 days) that may
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3 contribute to this difference. Given this confounding feature, as well as the study's
4 retrospective nature, heterogeneous inclusion criteria, and treatment exposure we
5 assigned this an EL 2-. Lower level evidence studies included three case series
6 reporting UDCA (15-30mg/kg/day) administration for 23 eligible children and infants
7 with established IFALD ^{27,41,50}. Tietlebaum et al ⁵¹ also described administering
8 intramuscular cholecystokinin (0.04-0.06µg/kg/day) to 11 post-surgical infants with
9 established IFALD, although only five of these infants fulfilled our entry criteria.
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17 **Dietary Manipulations**

18 Six studies were identified that described dietary manipulations, although only one
19 was of higher EL. Ksiazek et al ³⁷ (EL 1-) prospectively investigated the role of
20 hydrolysed formula in promoting growth and development in SBS. Ten infants were
21 randomly assigned to receive either a hydrolysed enteral formula (Pepti Junior,
22 Nutricia, Zoetermeer, Holland), or a non-hydrolysed mirror formula over a 60-day
23 period (cross-over day 31). They found no significant difference between the two
24 treatments in terms of weight gain, enteral feed tolerance and energy expenditure. Due
25 to minimal description of blinding, patient assignment, prior treatment exposure and
26 concurrent use of confounding treatments, this study was allocated an EL 1-. Lower
27 level evidence included reporting the use of elemental formulae, oral pectin and a
28 World Health Organisation solution ^{23,25,52 29,42}.
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41 **Bacterial Manipulations**

42 Seven studies that describe therapeutic strategies to manipulate the gut bacteria
43 (microbiota) were identified but only one was of higher EL. Kubota et al ³⁸ (EL 2-)
44 retrospectively analysed the effects of prophylactic oral metronidazole (25-
45 50mg/kg/day) on the development of IFALD in 21 infants receiving prolonged PN.
46 The control data were taken from a historical group before this treatment was
47 commenced. The authors reported no significant difference in serum bilirubin levels
48 between groups, but a high-dose subgroup (50mg/kg/day) had significantly lower
49 serum glutamic oxalocetic transferase and gamma glutamyl transpeptidase (p<0.05).
50 With its retrospective nature, use of historical controls and heterogeneous inclusion
51 and exclusion criteria this study was assigned an EL 2-.
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3 Lower level evidence includes three case series describing the combination use of
4 *Bifidobacter breve*, *Lactobacillus casei* and galacto-oligosaccharides in 12 patients
5 with SBS to reduce bacterial sepsis and encourage intestinal adaptation^{35,36,53}.

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8 Vanderhoof et al⁵⁴, in a single case series described the use of bisacodyl suppositories
9 and hypertonic polyethyglycol solution (GoLYTELY, Braintree Laboratories,
10 Braintree, U.S.A.) for D-lactate and small bowel bacterial overgrowth, and also the
11 use of *Lactobacillus planetarium* and *Lactobacillus GG* (CAG Nutrition, Omaha, NE,
12 U.S.A.) for arthritis associated with small bowel bacterial overgrowth. Newall et al⁴⁵
13 also reported that the prophylactic administration of oral warfarin (INR 2.0-3.0) to
14 eight children with SBS resulted in a significant reduction in the number of central
15 venous access device thromboses, possibly through reduction of bacterial adherence.
16 Mouw et al also reported reduced episodes of CVC sepsis by the administration of a
17 70% ethanol lock in 5 infants and children⁴⁴.

28 DISCUSSION

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30 In spite of the publication of an enormous body of literature describing methods for
31 the treatment of paediatric IF, we have shown that the evidence base for the use of
32 medical and nutritional therapies in childhood IF is clearly inadequate. Although not
33 formally studied, we believe that the evidence base for the various potential treatment
34 modalities for IF in adults is similarly limited.

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There are few paediatric data on the clinical effects of manipulations of PN and its
effect on IF and IFALD. Although a short-term adult and paediatric study suggests
that the MCT:LCT ratio of intravenous intralipid may affect hepatotoxicity⁵⁵, the
evidence in patients with established IF is lacking. Recent studies of use in infancy of
fish oil-based fats are encouraging²⁸, and newer lipid preparations with multiple fat
sources have been used effectively in adults in North America⁵⁶. Paediatric RCTs are
currently underway. However new lipids, for which there is much enthusiasm, have
been a source of immense speculation amongst paediatric gastroenterologists and
there are concerns that we are already beyond the phase of therapeutic equipoise for
these therapies, **with many units already using a variety of novel lipids in their
practice.**⁵⁷

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3 The effective use of growth factors to stimulate adaptation has been described in both
4 animal and adult studies^{58,59}. Initial data reported success in improving long term
5 intestinal function⁶⁰. However, later studies failed to reproduce these findings^{61,62}. A
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7 systematic review in 2004 of adult data on the use of GH and glutamine⁶³ identified
8 eleven published studies. The authors concluded that the data were too limited and
9 contradictory (six positive studies and four negative) to draw any conclusions on the
10 efficacies of these treatments. A recent Cochrane review again focussed on adult data
11 only⁶⁴. We have demonstrated that the data from childhood studies are even more
12 limited; the use of GH is not currently standard practice in most paediatric IF centres
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23 UDCA is the established treatment of primary biliary cirrhosis in adults⁶⁶, and short
24 term data support UDCA use in established CF liver disease⁶⁷. A systematic review
25 of the use of UDCA for patients with IFALD was published in 2007⁶⁸. The authors
26 identified six studies (five paediatric and one adult) in which UDCA was administered
27 in doses of 10-30mg/kg/day in children and 10-15mg/kg/day in adults. The authors
28 concluded that UDCA appeared to improve the signs and symptoms of IFALD but
29 that optimisation of timing, dosage and duration of UDCA administration had still to
30 be achieved. The paediatric data are limited but appear to support short term
31 improvement in biochemical markers of IFALD. Higher quality studies that examine
32 long-term efficacy are required.
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42 Convincing theoretical data and animal models exist for the use of dietary
43 manipulations, suggesting that diets high in complex carbohydrate and fat are more
44 palatable and may stimulate enteral adaptation more quickly than diets with lower
45 energy contents⁶⁹⁻⁷¹. The use of hypo-osmolar formulae and continuous feeding are
46 well described¹, but there is a lack of data from children to support the use of specific
47 enteral formulations or to advise on their relative constituents including carbohydrate,
48 fat, protein, micronutrients and potential trophic factors.
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56 Probiotics, defined as live bacteria that confer a health benefit to the host, have
57 purported protective properties⁷². Positive results exist for probiotic use in the
58 management of post-surgical inflammatory bowel disease^{73,74}, antibiotic-associated
59 diarrhoea⁷⁵ and NEC⁷⁶. Despite being used commonly to treat children with IF to
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3 reduce bacterial translocation from the gut, few studies demonstrate effectiveness of
4 probiotics^{35,36,45,53}. **Antibacterial locks such as Gentamicin or Taurolidine have been**
5 **used to prevent CVC colonisation and sepsis and a systematic review of the efficacy**
6 **of the later exists⁷⁷. However we found no studies for such practice that fulfilled**
7 **inclusion criteria to our study.** We could also find no paediatric data to support the
8 use of cycled enteral antibiotics.
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15 We identified several studies which outlined multidisciplinary management for
16 paediatric patients with IF and/or the use of a formalised 'intestinal rehabilitation
17 programme' as a treatment for IF⁷⁸⁻⁸². Although these centres describe specific
18 tailored therapeutic interventions, novel PN strategies and surgical interventions, with
19 historical controls, both the variety and potential number of combination of measures
20 described plus the resultant chance of missing specific publications despite a robust
21 search strategy precludes these studies being used in our review. We however
22 acknowledge that referral centres of excellence play an integral role in the
23 improvement in outcomes for this population, and that early referral to such centres is
24 essential for patients with potentially irreversible intestinal failure. We also recognise
25 the evolving role of non-transplant surgical bowel reconstruction⁸³ and potential for
26 isolated liver transplantation to avoid the necessity for CBSLT for IFALD⁸⁴, however
27 this subject explicitly fell out-with the scope of our systematic review.
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40 CONCLUSIONS

41 The evidence base for medical and nutritional interventions in paediatric IF is limited
42 and of poor quality (Table 3). Low patient numbers, high drop-out rates from studies
43 and ethical considerations that limit patient enrolment, have undoubtedly hindered the
44 commencement and successful completion of RCTs. Current guidelines for patient
45 management are extrapolated primarily from adult evidence and expert opinion^{85,86}.
46 RCTs in children are currently ongoing for the more expensive treatment modalities,
47 most notably PN and PN lipids⁸⁷. However, in the absence of RCTs, enhanced
48 multiagency communication between centres, an improved evidence base through
49 case control and cohort research and the study of inter-centre variations is possible.
50 The British Intestinal Failure Survey (BIFS) in the UK
51 (http://bspghan.org.uk/working_groups/nutrition.shtml) may facilitate such projects in
52 the near future.
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5 The optimisation of timing and dosage of administration of UDCA, the use of novel
6 intralipid formulations, cycling of enteral antibiotics in bacterial overgrowth,
7 prophylactic enteral probiotics and enteral feeding strategies are five achievable short-
8 term goals, which might improve the evidence base for medical and nutritional
9 therapies for IF in children. Clinical trials of these treatment modalities will likely
10 require being undertaken as prospective, carefully planned multi-centre studies in
11 order to be sufficiently powered to generate significant and unambiguous data.
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For Peer Review

Treatment strategy	Evidence	EL (number of studies)	Future Research
Growth Factors	GH and glutamine tolerated by paediatric patients, no controlled evidence of benefits to growth and intestinal function	3 (4)	Further adult study of individual growth factors
Bile analogues	UDCA decreases markers of hepatic inflammation and bilirubin in short-term. No controlled data on long term outcomes.	2- (2), 3 (4)	Clinical observation to optimise administration and dosage of UDCA
Dietary manipulation	No controlled benefits of hydrolysed formulae, Uncontrolled support of hypo-osmolar elemental feeds	1- (1), 3 (5)	RCTs of newer formulae, in particular MCT/LCT fats
PN manipulations	Some controlled evidence of benefits of olive oil and FISH oil based lipids, uncontrolled evidence to support cycling of PN.	1- (1), 2- (3) 3 (6)	Multi-centre RCT of intralipids underway in North America
Bacterial Manipulations	Data does not support routine use of metronidazole for the prevention of IFALD, some uncontrolled data describing probiotic use to prevent bacterial overgrowth	2- (1), 3 (6)	Clinical studies of the efficacy of cyclical enteral antibiotics and prophylactic oral probiotics.

Table 3: Current evidence for the use of medical and nutritional therapies in paediatric IF and potential future studies

GH- growth hormone; UDCA-ursodeoxycholic acid; RCT- randomised controlled trial; MCT- medium chain triglycerides; LCT- long chain triglycerides; PN-parenteral nutrition; IFALD- intestinal failure associated liver disease.

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Figure Legend

Figure 1: Flow chart for electronic search strategy used

For Peer Review

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Dr Andrew Barclay is the guarantor of this article

Declaration of funding interests

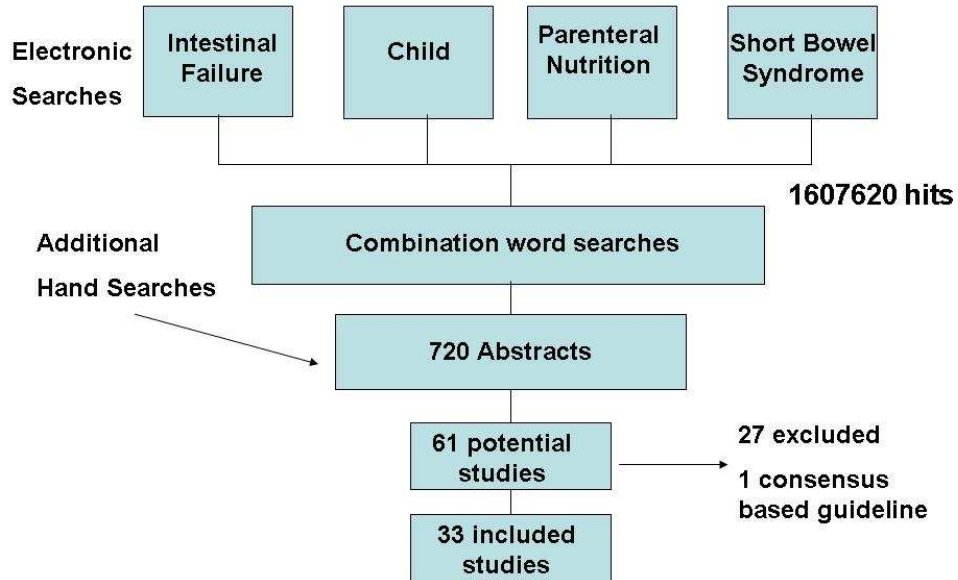
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Search Strategy (1950-Nov 2009)



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Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	none



PRISMA 2009 Checklist

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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	none
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	inaprop
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	inaprop
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	none
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8-12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

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19th October 2010

Jonathon M Rhodes MD
Assistant Editor
Alimentary Pharmacology & Therapeutics
49 Carvers Croft, Woolmer Green
Herts SG3 6LX
UK.

Dear Professor Rhodes

Thank you for your prompt and favourable response to our submission 'Systematic Review: Medical and Nutritional interventions for the Management of Intestinal Failure and its Resultant Complications in Children'. We are pleased to return a revised manuscript to you. We thank you and the reviewers for their comments and will address each in turn. We have left the editorial comments in Trebuchet text and responded in italics and Times Roman font. When quoting from the revised manuscript we have cited the page and line number.

Editors Comments for the author

Please address the reviewers' comments and in addition:
please add some more specific information in the abstract eg (i) explain briefly why intestinal failure is increasing and (ii) consider adding in something along the lines of your discussion eg perhaps based on a shorter version of:
"The optimisation of timing and dosage of administration of UDCA, the use of novel intralipid formulations, cycling of enteral antibiotics in bacterial overgrowth, prophylactic enteral probiotics and enteral feeding strategies are five achievable short-term goals ... for clinical trials ... which might improve the evidence base for medical and nutritional therapies for IF in children".

Thank-you we have amended the abstract accordingly (page 2 line 2)

Intestinal failure (IF) affects a growing number of children due to increasing numbers of preterm infants surviving intestinal resection for necrotising enterocolitis (NEC) and improving surgical techniques for congenital gut anomalies.

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4 (page 2 line 21)

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6 *The evidence base for medical and nutritional interventions in paediatric IF is limited*
7 *and of poor quality. In the absence of RCTs, this evidence base can improve through*
8 *case control and cohort research, and with better multi-agency communication the*
9 *study of inter-centre differences is possible. Achievable **short-term goals would***
10 *include the study of; optimal ursodeoxycholic usage; novel intralipid formulations;*
11 *cycled enteral antibiotics; enteral probiotics and new enteral feeding strategies.*
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19 Reviewer: 1

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21 Comments for Transmission to the Authors

22 I enjoyed reading this paper. I have 2 major comments:

23
24 1. In the background and objectives I think it would enhance the later
25 discussion if the authors describe the therapeutic interventions as falling
26 into 2 main categories namely a) enhancing bowel adaptation and b)
27 prevention of complications. They allude to the second category of
28 intervention when describing prevention of IFALD and make a brief
29 reference to anti-sepsis procedures, which is not followed up in the main
30 body of the paper.
31

32
33 *Thank you for this comment we have amended the background and objectives*
34 *accordingly (page 3 line 31).*
35

36
37 *A first group of therapeutic interventions have been postulated to accelerate bowel*
38 *adaptation such as the use of enteral trophic factors, manipulation of dietary protein,*
39 *fat and carbohydrate and manipulation of the gut microbiota¹⁻³. A second group of*
40 *interventions are aimed at the prevention or amelioration of complications of PN such*
41 *as antisepsis procedures for CVCs, or treatment of IFALD with bile analogues,*
42 *choleretic agents and changes in the constituents of PN⁴.*
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49 2. The omission of a discussion of feeding catheter line locks such as
50 gentamicin is puzzling especially as reference is made to the use of Warfarin
51 in reducing bacterial adherence. I appreciate that the recent studies of
52 taurolock would not have been available at the time of the electronic
53 search but there are a number of publications and a systematic review
54 (Bradshaw et al JPGN 2008; 47: 179-186) which support the author's
55 contention that the evidence base for interventions in children with IF is
56 currently very poor. I am not suggesting a repeat search, but perhaps this
57 paper should be included the group of papers referred to at the end of the
58 second paragraph in results section ie "relevant but not limited to our key
59 question".
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Thank you for this comment, we were aware of the systematic review by Bradshaw and Puntis⁵, and it was identified in our search strategy. However none of the studies identified in this review fulfilled our inclusion criteria, the only 2 studies that involved CVC access for PN were in two adult patients. Similarly with Gentamicin antibacterial locks; although studies describing use were identified, none of them were in paediatric patients receiving PN. We have however referenced the systematic review and mentioned bacterial locks in our discussion (page 14 line 2).

Antibacterial locks such as Gentamicin or Taurolidine have been used to prevent CVC colonisation and sepsis and a systematic review of the efficacy of the latter exists⁵. However we found no studies for such practice that fulfilled inclusion criteria to our study.

3. on page 3 line 9, I would suggest that the phrase 'in children?'
> is inserted after 'in developed countries?', because the previous
> sentence refers to both adults and children and I feel that the
> authors should signal more explicitly that from this point on the
> paper is now focusing on children.

Thank you, we have amended accordingly.

. on page 7 line 14 there is typo 'I think the word 'have' in
> line 14 occurring in the sentence beginning 'Twenty seven of
> these..?', is redundant.

Thank you; we have removed this.

Reviewer: 2

The author should define all abbreviations used in the tables in
> the table legend.

Thank you we have amended the figure legends in tables 2 and 3 accordingly (pages 8 and 16).

.On page 12, lines 52-57, it is written that 'there are concerns
> that we are already beyond the phase of therapeutic equipoise for

1
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3 > these therapies.? The author should clarify what is meant by this
4
5 > statement.

6
7 *Thank you. We have amended accordingly in the text (page 12 line 29).*

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10 *However new lipids, for which there is much enthusiasm, have been a source of*
11 *immense speculation amongst paediatric gastroenterologists and there are concerns*
12 *that we are already beyond the phase of therapeutic equipoise for these therapies,*
13 *with many units already using a variety of novel lipids in their practice.*⁶
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21 We thank you and the reviewers again for their useful comments and hope that this
22 improved manuscript will now be considered for publication.
23

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26 Yours Sincerely

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29 Andrew Barclay
30 On behalf of the Co-authors
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Preprint Peer Review