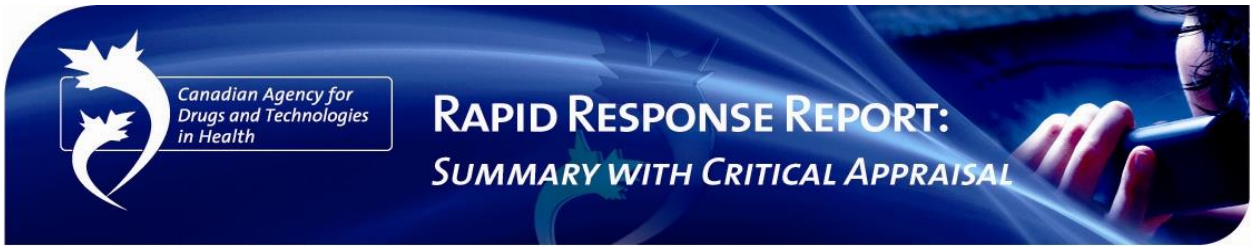

TITLE: Changing Total Parenteral Nutrition Tubes in Pediatric in-Hospital Patients: A Review of Clinical Effectiveness and Guidelines

DATE: 4 August 2015

CONTEXT AND POLICY ISSUES

Total parenteral nutrition (TPN), the delivery of all required nutrients directly into the bloodstream through a central or peripheral line, is used in children or newborns whose digestive systems are non-functional as a result of prematurity, congenital abnormality, surgery, severe gastrointestinal disease, or severe side-effects of chemotherapy.[1] TPN is associated with metabolic abnormalities, cholestasis, liver abnormalities, and increased risk of blood-stream infections.[1]

Catheter associated bloodstream infections (BSIs) increase the risk of death. In a Canadian cohort study, rates of death were higher in all patients (adult and child) with central line infections compared with those without (23.8% versus 14.6%),[2] and in a US multicentre study, the corresponding rates were 15% and 7%.[3] As well as increasing the risk of death, central line infections were associated with prolongation of hospital and ICU stay, with a mean increase in hospital stay of 19 days.[3] There are no reports of costs associated with central line infections in the Canadian context, but based on European and US data, the average cost of a pediatric central line infection has been estimated as $US 55,646.[3]

Interventions designed to reduce hospital acquired infections[4,5] and a more stringent case definition[3] has reduced reported rates. Nevertheless, prevention remains a significant concern, given the increasing prevalence of multiply resistant antibiotic strains. This Rapid Response report concerns the optimal time between changes of the administration set for TPN (tubing outside the patient, as distinct from the implanted catheter). Too frequent changes increase the risk of introducing pathogens, while too infrequent changes enable pathogens introduced to grow, particularly in the nutrient-rich TPN medium.

RESEARCH QUESTIONS

1. What is the clinical effectiveness associated with different total parenteral nutrition tube changing times (≥24 hours) in pediatric in-hospital patients?

2. What are the evidence-based guidelines associated with the timelines surrounding changing total parenteral nutrition tubes in pediatric in-hospital patients?

KEY FINDINGS

Two systematic reviews and two national clinical practice guidelines addressed the frequency of administration set changes in children and neonates. One systematic review of neonates alone concluded there was insufficient evidence to conclude that increasing the intervals between set changes increased the risk of sepsis. The other, which included all ages, concluded that there was some evidence to support changes at intervals of up to 96 hours for sets not containing lipids, but that some evidence suggested increased risk of mortality in neonates. Current guidelines recommend that administration sets that are in continuous use and do not contain lipids (i.e., amino acids and dextrose) can be changed at 96 hour intervals without increasing the risk of catheter-related infection, although there was a suggestion that the risk of death in neonates might be increased at longer intervals. Administration sets containing lipids were recommended to be changed at 24 hour intervals. However, the data for neonates are limited to two trials, and neither the systematic reviews nor the guidelines identified studies examining administration set changes for TPN in children other than neonates.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2005 and July 6, 2015.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Pediatric (≤ 18 years of age) patients requiring total parenteral nutrition (TPN) within the hospital setting
Intervention	Total parenteral nutrition (TPN, also can refer to TPN plus fat emulsion [lipids])
Comparator	No comparator Different tube changing times
Outcomes	Clinical effectiveness (e.g. tube changing times [how long in between]), safety (e.g. introduction of bloodstream infections) Guidelines
Study Designs	HTAs/systematic reviews/meta-analyses, randomized controlled trials, non-randomized studies, guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, including a separate consideration of children/neonates and TPN, they were duplicate publications, or were published prior to 2005.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using AMSTAR[6] and guidelines were assessed with the AGREE II instrument.[7] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 721 citations were identified in the literature search. Following screening of titles and abstracts, 705 citations were excluded and 16 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 14 publications were excluded for various reasons, while four publications met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Study characteristics are tabulated in Appendix 2.

Study Design

The evidence retrieved comprises two systematic reviews, one by the Cochrane Anaesthesia Group[8] and one by the EPIQ (Evidence-Based Practice for Improving Quality) Review Group[9] and two clinical practice guidelines published in 2011[10] and 2014.[11]

The Cochrane systematic review was an 2013 update of a review originally published in 2005, with a search current to June 2012.[8] The EPIQ review was published in 2012, with a search current to January 2012.[9]

Country of Origin

The authors for the systematic reviews were based in Australia[8] and Canada[9]. The clinical practice guidelines originated from the US[10] and from the UK.[11]

Patient Population

The inclusion criteria in the Cochrane systematic review included hospitalized patients of any age, with age stratification in a planned subgroup analysis.[8] The EPIQ review specified neonates.[9] The clinical practice guidelines included adults and children.[10,11]

The pediatric studies identified in both the guidelines and systematic reviews focused exclusively on neonates.

Interventions and Comparators

The Cochrane review selected and pooled randomized controlled trials (RCTs) and controlled clinical trials (CCTs) that compared different frequency of changes of administration sets.[8] Administration sets in the intervention group were replaced every 48 to ≥96 hours, and those in the comparator group were replaced every 24 to ≥72 hours.[8] The EPIQ review compared replacement at >24 hour intervals with replacement at 24 hour intervals.[9]

Outcomes

Outcomes of interest to the systematic reviews were rate of catheter-related[8] and infusate-related BSI,[8] catheter-related[8] and infusate-related BSI[8] per 100 patient-days, infusate[8,9] and catheter[8] colonization, all-cause BSI,[8] sepsis[9], mortality,[8] and costs (not specified).[8] Data for neonates were available for catheter-related and infusate-related BSI and mortality.

Both clinical practice guidelines evaluated outcomes of infection, intravascular catheter-related infection[10] and healthcare-associated infection.[11]

Summary of Critical Appraisal

Critical appraisal is tabulated in Appendix 3.

The two systematic reviews were generally well-conducted, with an *a priori* research design, a comprehensive literature search with duplicate study and data selection, a list and tabulation of characteristics of included studies, and assessment of the scientific quality. Chirinian 2012[9] did not provide a list of excluded studies or report on potential conflicts of interest. Neither systematic review included an appraisal of publication bias, because of the small number of studies overall.

Ullman 2013[8] included meta-analyses of studies and subsets of studies, including age-related and TPN-related subsets. Evidence for the subsets was sparse, with six studies contributing to the age-related (one neonatal) and five studies contributing to the TPN-related analysis (two TPN). Increased variance due to small numbers could obscure an existing difference. For the overall analysis, although there was low statistical heterogeneity according to the applied tests, these tests tend to be insensitive if the number of studies is small. Clinically, there was heterogeneity between trials, with a mixture of populations and pooling of interventions into two groups.

The two guidelines were multi-institution, national guidelines, with clear overall objectives, health questions, populations, target users, criteria for selecting evidence, descriptions of strengths and limitations of trials, standardized assessments of strength of evidence, and explicit links between strengths of evidence and recommendations. In both cases the question of frequency of changes of administration sets was reviewed as part of a larger suite of interventions for reducing hospital-related infection. Loveday 2014[11] described a comprehensive search that encompassed multiple review questions around the management of intravascular access devices, with broad search terms and appropriate inclusion criteria. Certain aspects of O'Grady 2011[10], including details of the search, could not be reviewed in detail, as the only available methodological description was for an updated process,[12] and the published guideline emphasized clinical background, evidence and, recommendations. A broad group of stakeholders was listed as consulted for each guideline, with no obvious omissions. Neither

guideline included contextualization, as the authors intended the guidelines to be adapted for application at local and institutional levels. Neither guideline described monitoring or auditing criteria, as there are established regional and national standards for tracking nosocomial infection.

Summary of Findings

Study findings are tabulated in Appendix 4.

What is the clinical effectiveness associated with different total parenteral nutrition tube changing times (≥24 hours) in pediatric in-hospital patients?

The two systematic reviews retrieved the same two RCTs of TPN in neonates, and reached substantively the same conclusion.

Ullman 2013[8] updated a 2005 Cochrane review of optimal timing for administration set replacement in all patients with a central or peripheral venous or arterial catheter. They selected studies that contrasted less frequent with more frequent replacement, and prospectively defined subgroup analyses including TPN/lipids versus non-TPN/lipids and adults versus neonates.

They retrieved 16 studies involving a total of 5001 patients, including two RCTs which involved neonates (Fox 1999, Matlow 1999). Meta-analysis showed no overall difference in catheter-related BSI for less frequent versus more frequent replacement for all patients and all fluids, relative risk (RR) 1.06 (95% confidence interval [CI] 0.67 to 1.69, 8 studies) and no evidence for an interaction in the TPN/lipids versus non-TPN/lipids subgroup analysis. There were no data for this subgroup analysis for other endpoints. There was no difference in infusate-related BSI, RR 0.67 (95%CI 0.27 to 1.70, 10 studies), and no evidence for an age-related effect (5 adult studies, 1 study in neonates). There were no data for this subgroup analysis for other endpoints.

The two studies reporting mortality were of neonates receiving TPN. The RR for mortality with the intervention was 1.84 (95%CI 1.00 to 3.36) and the authors interpreted that as suggesting an increase in mortality in neonates with less frequent replacement.

On quality appraisal, they considered the majority of their studies to be at moderate to high risk of bias (where there was the information to allow appraisal). They considered mortality an endpoint at low risk of bias, however, the larger of the two studies of interest for this endpoint, which was weighted at 96% in the meta-analysis, had a clinically significant difference in mean birthweight (a predictor of mortality) at baseline between the two groups. With the exception of catheter colonization, the overall quality of evidence for all individual endpoints was appraised as low by the GRADE framework; catheter colonization was appraised as moderate.

The authors concluded that some evidence showed that changing intravascular sets that did not contain blood, blood products, or lipids at up to 96 hour intervals did not affect the risk of catheter- or infusate-related bacteraemia, but that some of the evidence suggested that mortality in neonates increased with infrequent administration set replacement.

Chirinian 2012[9] retrieved RCTs that assessed the effect of frequency of administration set replacement of ≥24 hours versus 24 hours in neonates receiving TPN on sepsis within 7 days of discontinuation of infusion and infusate contamination. They found two studies, one testing

replacement every 48 hours and the other testing replacement every 72 hours. In each, the intervention was compared with replacement every 24 hours.

Narrative rather than statistical synthesis was conducted. Neither study reported on the primary review outcome of sepsis. Neither found a statistically significant difference in positive blood cultures. One reported deaths before sampling (three, all in the 48 h group) but did not assess mortality (Fox 1999), and the other found no statistical difference in mortality. (Ullman 2013[8] included the three deaths from Fox 1999 in their analysis of mortality). Neither study found a statistically significant difference in microbial contamination of infusate, with the following exceptions: one (Fox 1999) found a statistically significant difference in the fungal contamination of infusions between 48 hours and 24 hours (3.1% versus 0.5%), although they attributed that to a single patient who had multiple fungi, and the significance disappeared when that patient was removed from the analysis. Matlow 1999 found that there was a statistically significant difference in the contamination rate for lipid infusates between 72 hours and 24 hours (3.5% versus 1.4%).

On quality appraisal, they considered Fox 1999 at to be of good quality, although the statistical analysis did not allow for repeat sampling of neonates and there was no information on the number of TPN administration set manipulations. Mallow 1999 was of fair quality, since infants would be re-randomized if they had had more than a 7 day interruption of TPN, samples were missed in ~50% of the randomizations, the blinding status of people drawing samples was unclear, and the analysis did not allow for repeat sampling of neonates.

They concluded that there was insufficient evidence to determine whether decreasing the frequency of administration set changes increased the incidence of sepsis, and therefore there was insufficient evidence to support or refute routinely changing administration sets every 48 hours.

What are the evidence-based guidelines associated with the timelines surrounding changing total parenteral nutrition tubes in pediatric in-hospital patients?

The two major guidelines were a 2011 multi-disciplinary US guideline[10] for prevention of intravascular catheter related infection prepared under the auspices of the Healthcare Infection Control Practices Advisory Committee (HICPAC) of the Centres for Disease Control and Prevention, and a 2014 UK guideline[11] for reducing in-hospital infection prepared by request of the UK Department of Health under the auspices of the National Institute for Health and Care Excellence (NICE). The 2014 UK guideline incorporated the 2011 US guideline, as well as the Cochrane review (Ullman 2013)[8] described above.

Overall recommendations of the two guidelines were consistent:[10,11]

- Administration sets that were in continuous use but that were not being used to deliver blood, blood-products or lipids did not have to be changed more frequently than every 96 hours.[10,11] One of the guidelines recommended changing them at least every 7 days.[10] Both guidelines considered this the highest grade of recommendation.[10,11]
- Administration sets that carried lipids should be changed within 24 hours of starting infusion[10] or every 24 hours.[11] One guideline considered this a weak recommendation (Class D)[11] and the other considered it moderately strong or reflective of accepted practice (Class 1B).[10]

Neither guideline provided recommendations on the intervals for changing intermittently used administration sets, due to lack of evidence.[10,11]

One guideline specified that the guideline applied to children older than 1 year, and could not be applied to neonates,[11] while the other did not separate the age groups for this intervention, although it did for others.[10]

Limitations

Although the systematic reviews and guideline development were of high quality methodologically, the underlying data on the specific intervention in children or neonates was sparse. One systematic review restricted inclusion to neonates,[9] while the other included children and adults,[8] and meta-analyzed subsets where the data were available (mortality and infusate contamination for neonates). One set of guidelines was intended to be used for children aged one year or older and adults, but was not considered to apply to neonates.[11] The other made distinct recommendations for adults and children for some interventions, but not for change of administration sets. [10]

Both studies on a pediatric population were on neonates and were published in 1999, with the patient accrual prior to that (1991-1993, in one case). Hospital infection control practices, design of design of administration sets, and underlying epidemiology of nosocomial infection are all liable to have changed in the intervening years. The studies themselves were of fair to good quality, although the intervention could not be blinded in either, which carries a significant risk of bias. Furthermore, there were no RCT data on children other than neonates, so practice must be extrapolated from adult studies.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Two systematic reviews and two national clinical practice guidelines addressed the frequency of administration set changes in children and neonates. One systematic review of neonates alone concluded there was insufficient evidence to conclude that increasing the intervals between set changes increased the risk of sepsis. The other, which included all ages, concluded that there was some evidence to support changes at intervals of up to 96 hours for sets not containing lipids, but that some evidence suggested increased risk of mortality in neonates. Current guidelines recommend that administration sets that are in continuous use and do not contain lipids (i.e., amino acids and dextrose) can be changed at 96 hour intervals without increasing the risk of catheter-related infection, although there was a suggestion that the risk of death in neonates might be increased at longer intervals. Administration sets containing lipids should be changed at 24 hour intervals. However, the data for neonates are limited to two trials, and neither the systematic reviews nor the guidelines identified studies examining administration set changes for TPN in children other than neonates.

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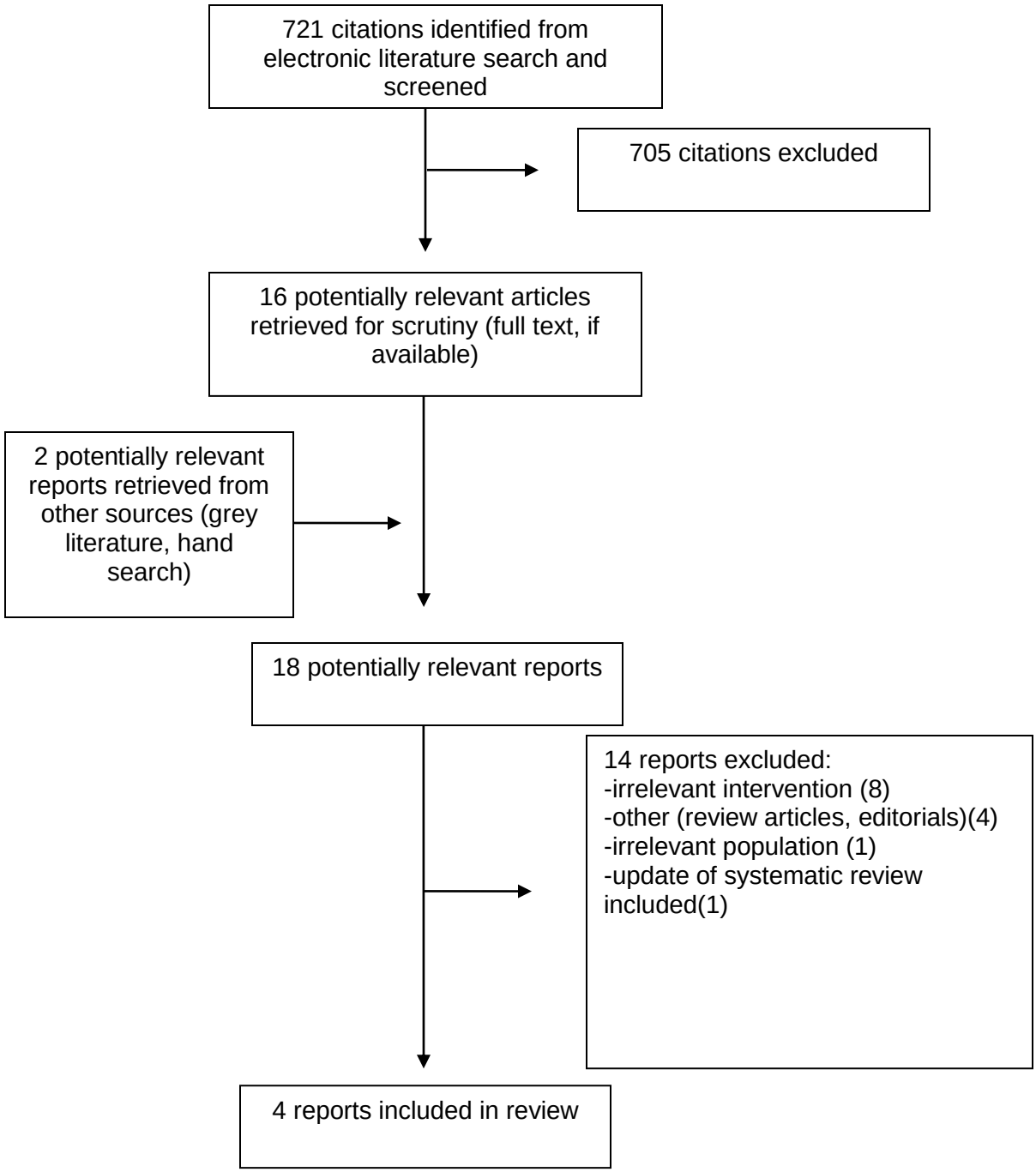
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A2-1: Characteristics of Included Systematic Reviews and Meta-Analyses

Author Year Country	Primary studies included Research question	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Subgroup analyses
Ullman, 2013[8] Australia	16 studies (all patients; 2 involving neonates); RCTs and CCTs. "[t]o identify any relationship between the frequency with which administration sets were replaced and rates of microbial colonization, infection and death."(p 1)[8] Search updated to: June 2012.	Hospitalized patients of any age with central or peripheral venous or arterial catheter.	Administration set replaced every 48 to ≥96 hours Studies had to compare a less frequent with a more frequent interval for replacement.	Administration set replaced every 24 to ≥72 hours Studies had to compare a less frequent with a more frequent interval for replacement.	Primary endpoints: • Rate of catheter-related BSI (defined criteria) • Rate of infusate-related BSI (positive culture infusate plus positive peripheral culture, no other source found) Secondary endpoints: • Catheter-related BSI per 1000 patient-days • Infusate-related BSI per 100 patient-days • Infusate colonization • Catheter colonization • All-cause BSI • Mortality • Cost Planned subgroup analyses: • Central versus peripheral catheters • TPN/lipids versus non-TPN/lipids • Adults versus neonates • Arterial versus venous catheters.
Chirinian, 2012[9] Canada	Two studies. RCTs. "To determine whether decreasing the frequency of changing IV administration sets (>24h versus every 24h) in neonates increases the incidence of sepsis within seven days of discontinuation of TPN and microbial contamination of the infusate."(p 501)[9]	Neonates admitted to ICU and prescribed TPN	Administration set replaced at intervals >24 hours.	Administration set replaced every 24 hours	• Sepsis within 7 days of discontinuation of TPN • Microbial contamination of infusate

BSI = bloodstream infection; CADTH = Canadian Agency for Drugs and Technologies in Health; CCT = controlled clinical trial; RCT = randomized controlled trial; TPN = total parenteral nutrition.

Table A2-2: Characteristics of Included Guidelines						
Objectives			**Methodology**			
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendations development and Evaluation**	**Guideline Validation**
O'Grady, 2011[10] Lead: Society of Critical Care Medicine (SCCM), Collaborators: Infectious Diseases Society of America (IDSA), Society for Healthcare Epidemiology of America (SHEA), Surgical Infection Society (SIS), American College of Chest Physicians (ACCP), American Thoracic Society (ATS), American Society of Critical Care Anesthesiologists (ASCCA), Association for Professionals in Infection Control and Epidemiology (APIC), Infusion Nurses Society (INS), Oncology Nursing Society (ONS), American Society for Parenteral and Enteral Nutrition (ASPEN), Society of Interventional Radiology (SIR), American Academy of Pediatrics (AAP), Pediatric Infectious Diseases Society (PIDS), and the Healthcare Infection Control Practices Advisory Committee (HICPAC) of the Centers for Disease Control and Prevention (CDC)						
"[H]ealthcare personnel who insert intravascular cathethers […] persons responsible for surveillance and control of infection in hospital […] settings"(p e162)[10]	Replacement of administration sets	Intravascular catheter-related infections.	Systematic review.	Quality appraisal according to CDC and HIPAC criteria.	Guidelines developed by working group headed by the SCCM.	Guidelines underwent extensive external review.
Loveday, 2014[11] University of West London, NICE accredited (2013), commissioned by UK Department of Health						
"… aimed at hospital managers, members of hospital infection prevention and control teams, and individual healthcare practitioners."(p	Change intravenous administration sets (part of National Evidence-Based Guidelines for Preventing Healthcare-Associated Infections in	Healthcare associated infections	Systematic review; duplicate study selection, quality appraisal and data extraction. Recommendation based on O'Grady 2011;[10] 2005	Quality appraisal and classification of strength of evidence according to Scottish Intercollegiate Guideline Network.	Guidelines drafted by Guideline Development Advisory Group: considered nature of evidence, applicability to practice, patient preference, costs, knowledge of healthcare system.	Guidelines underwent extensive external review.

Table A2-2: Characteristics of Included Guidelines						
Objectives			Methodology			
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendations development and Evaluation**	**Guideline Validation**
S11)[11] "..apply to caring for all adults and children over the age of 1 year in NHS acute care settings with a CVC or PVC …"(p S38)[11]	NHS Hospitals in England)		Cochrane review updated as Ullman 2013[8]			

CADTH = Canadian Agency for Drugs and Technologies in Health

APPENDIX 3: Critical Appraisal of Included Publications

Table A3-1: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[6]

Strengths	Limitations
Ullman, 2013[8]	
• An 'a priori' design was provided. • There was duplicate study selection and data extraction. • A comprehensive literature search was performed. • A list of studies (included and excluded) was provided. • The characteristics of the included studies were provided. • The scientific quality of the included studies was used appropriately in formulating conclusions. • Conflict of interest for the reviewers and individual studies (where reported) was considered.	• Most endpoints required the combining of small numbers of trials. In particular, the subgroup analysis pertinent to this review, examining age, included only a single neonatal trial. • Publication bias could not be assessed, due to the small number of studies.
Chirinian, 2012[9]	
• Although the paper itself did not include detailed methodology, the process was detailed elsewhere.[13] • There was duplicate study selection and data extraction. • A comprehensive literature search was performed. • A list of included studies was provided. • The characteristics of the included studies were provided. • The scientific quality of the included studies was assessed and documented. • The scientific quality of the included studies was used appropriately in formulating conditions. • As only 2 studies were retrieved, statistical combination was not indicated.	• Restricted to published literature; grey literature was not searched for. • A list of excluded studies was not provided. • Conflict of interest for the included studies was not reported. • As only 2 studies were retrieved, the likelihood of publication bias was not assessed.

Table A3-2: Strengths and Limitations of Guidelines using AGREE II[7]	
Strengths	**Limitations**
O'Grady, 2011[10]	

• The overall objectives of the guideline are specifically described.
• The health questions covered by the guideline are specifically described.
• The populations to whom the guideline is meant to apply are specifically described.
• The guideline development group includes individuals from all relevant professional groups.
• The target users of the guideline are clearly defined.
• Systematic methods were used to search for evidence.
• The criteria for selecting the evidence are clearly described.
• The strengths and limitations of the body of evidence are clearly described.
• The methods for formulating the recommendations are clearly described.
• The health benefits, side effects, and risks have been considered in formulating the recommendations.
• There is an explicit link between the recommendations and the supporting evidence.
• The guideline has been externally reviewed by experts prior to its publication.
• A procedure for updating the guideline is provided.
• Key recommendations are clearly identifiable.
• The views of the funding body have not influenced the content of the guideline.
• Competing interests of guideline development group members have been recorded and addressed.
	• No major limitations.
	  ○ Unclear whether to what extent patient preferences were sought. (Processes have subsequently been updated).[12]
	  ○ This is a national guideline intended to be contextualized according to local circumstances, thus details of implementation, facilitators and barriers, and resource implications are deferred.
	  ○ Guideline does not present monitoring and/or auditing criteria, but institutional and national surveillance programs are in effect.

Loveday, 2014[11]	

• The overall objectives of the guideline are specifically described.
• The clinical situations covered by the guideline are specifically described.
• The populations to whom the guideline is meant to apply are specifically described.
• The Guideline Development Team and Guideline Advisory Group included members from all relevant disciplines.
• Patient input was sought and patient groups were involved in review.
• The target users of the guideline (all healthcare workers) are clearly defined.
• Systematic methods were used to search for evidence.
• The criteria for selecting the evidence are clearly described.
• Quality appraisal was described for both the individual studies and the overall body of evidence underlying each recommendation.
• The methods for formulating the recommendations are clearly described.
• The health benefits, side effects, and risks have been considered in formulating the recommendations.
	• No major limitations.
	  ○ This is a national guideline intended to be contextualized according to local circumstances, thus details of implementation, facilitators and barriers, and resource implications are deferred.
	  ○ Guideline does not present monitoring and/or auditing criteria, but refer readers to institutional and national surveillance programs.

Table A3-2: Strengths and Limitations of Guidelines using AGREE II[7]	
Strengths	**Limitations**
• There is an explicit link between the recommendations and the supporting evidence. • The guideline has been externally reviewed by experts prior to its publication. • A procedure for updating the guideline is provided. • The recommendations are specific and unambiguous. • Key recommendations are clearly identifiable. • The views of the funding body have not influenced the content of the guideline. • Competing interests of guideline development group members have been recorded and addressed.	

APPENDIX 4: Main Study Findings and Summary of Guideline Conclusions

Table A4-1: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
Ullman, 2013[8]	
16 RCTs/CCTs, 5001 patients total; 2 RCTs, 1355 neonates (Fox 1999, Matlow 1999). No studies able to blind personnel to intervention. Most at moderate-high risk of bias for primary endpoints, or did not adequately report methods to decrease bias. • Catheter-related BSI (all patients, 8 studies) RR 1.06 (95%CI 0.67 to 1.69). TPN/lipids versus non-TPN/lipids subgroup: No evidence for an interaction, RR 0.8 (95%CI 0.21 to 3.01). • Infusate-related BSI (all patients, 10 studies). Adults versus neonates subgroup analysis (5 adult studies, 1 neonate). No evidence for an interaction, RR 0.65 (95%CI 0.29 to 1.46). • Mortality in neonates given TPN (2 studies) RR 1.84 (95%CI 1.00 to 3.36). Risk of bias for this endpoint considered not high, but clinically significant difference in confounder mean weight between groups in one study.	• "Overall, some evidence shows that changing intravascular administration sets that do not contain lipids, blood or blood products at an interval of up to 96 hours does not affect the risk of infusate-related or catheter related bacteraemia in participants with central or peripheral, venous or arterial catheters."(p 16)[8] • "Some evidence shows that mortality increased within the neonatal population with infrequent administration set replacement."(p 16)[8] • "More data are required requiring the rates and incidence of infusate-related and catheter-related bacteraemia in participants who receive parenteral nutrition, in particular lipid emulsions."(p 16)[8]
Chirinian, 2012[9]	
Two studies retrieved (Fox 1999, Matlow 1999). Neither reported on the review primary outcome of sepsis. **Fox 1999**. Neonates receiving TPN and admitted to Level III NICU randomized to administration sets and lipids changed every 48 h (n=97) versus 24 h (n=51). Amino acids and dextrose changed daily in both. Number of infants with positive blood culture not significantly different (25.5% versus 20.6%). Bacterial contamination of infusion not significantly different for amino acids and dextrose (3.1% versus 2.9%) or lipids (6.0% versus 5.1%). Rate of fungal contamination significantly different (3.1% versus 0.5%) but influenced by one patient with multiple organisms. Authors considered study of good quality. Statistical analysis did not account for repeat sampling. **Matlow 1999**. Neonates in NICU receiving lipid emulsion randomized to administration sets changed every 72 hours (n=939) versus 24 h (n=250). Clinically significant difference in birthweight. No statistically significant difference in contamination between groups for contamination of amino acids-dextrose solution (1.1% versus 0.36%, P=0.76);	• "There is insufficient evidence to support or refute that decreasing the frequency of IV administration set changes increases the incidence of sepsis."(p 504)[9] • "There is evidence from one good quality RCT supporting the safety of changing TPN and lipid IV administration sets every 48 hours compared with every 24 hours."(p 504)[9] • "Based on this single study, there is insufficient evidence to support or refute routinely changing IV administration sets every 48 h."(p 504)[9]

Table A4-1: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
statistically significant difference between groups for lipids (3.54% versus 1.35%, P=0.001), and on regression analysis (OR 2.69 95%CI 1.4 to 5.13). No difference in mortality, no difference in positive blood cultures (although more samples were drawn from the 72 hour group). Reviewers considered study of fair quality: infants were randomized more than once, could not obtain infusate samples in ~50% of randomizations; repeat sampling not accounted for in analysis; uncertain blinding status.	

Table A4-2: Summary of Recommendations in Included Guidelines	
Recommendations	**Strength of evidence**
O'Grady, 2011[10]	
• "In patients not receiving blood, blood products or fat emulsions, replace administration sets that are continuously used, including secondary sets and add-on devices, no more frequently than at 96-hour intervals, but at least every 7 days. (Category 1A)" (p e180) • "Replace tubing used to administer blood, blood products, or fat emulsions (those combined with amino acids and glucose in a 3-in-1 admixture or infused separately) within 24 hours of initiating the infusion. (Category 1B)" (p e180)	• Category 1A = "Strongly recommended for implentation, strongly supported by well-designed, experimental, clinical, or epidemiologic studies." (p e163)[10] • Category 1B = "Strongly recommended for implementation, and supported by some experimental, clinical or epidemiologic studies and a strong theoretical rational; or an accepted practice (eg, aseptic technique) supported by limited evidence." (p e163)[10]
Loveday, 2014[11]	
• "[…] guidelines apply to caring for all adults and children over the age of 1 year in NHS acute care settings with a CVC or PVC […] They do not specifically address the more detailed, technical aspects of the care of infants under 1 year of age […]"(p S38)[11] • "Administration sets in continuous use do not need to be replaced more frequently than every 96 h, unless device-specific recommendations from the manufacturer indicate otherwise, they become disconnected, or the cardiovascular access device is replaced. (Class A)"(p S50)[11] • "Administration sets used for lipid-containing parenteral nutrition should be changed every 24 h. (Class D/GPP)"(p S50)[11]	• Class A = ≥1 high quality meta-analysis, systematic review, OR body of evidence of well-conducted studies with consistent findings, directly applicable to target population. • Class D = non-analytic studies, expert opinion, legislation, or extrapolated from observational studies with low risk of bias. • GPP (Good Practice Points) = recommended best practice by the Guideline Development Advisory Group and patient preference and experience