Is undernutrition prognostic of infection complications in children undergoing surgery? A systematic review

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Summary

Background: Healthcare-associated infections are costly and increasingly viewed as a quality indicator of care. Although strategies to reduce infections have become widespread, few studies have formally investigated the role of undernutrition on the development of infection related complications in children after surgery.

Aim: To determine from systematic review of the literature whether undernutrition is prognostic of postoperative infection complications in children.

Methods: Electronic bibliographic and research databases were searched from 1950 to 2014. Inclusion criteria were studies in children (<18 years) evaluating preoperative nutritional status and reporting postoperative infection complications. Quality assessment was performed using the Newcastle-Ottawa Scale with appraisal and data extraction performed independently by two reviewers. Disagreements were resolved by a third reviewer.

Findings: Ten cohort and two case-control studies met the inclusion criteria and used a variety of nutritional assessments. Postoperative infection complications were either reported combined or individually. Quality of the evidence was judged low in the majority of studies, with only two of moderate quality. Direct comparison between studies was difficult due to clinical and diagnostic heterogeneity. Univariate statistical analysis was suggestive of a relationship between undernutrition and postoperative infection complications.

Conclusion: There was low quality evidence that undernutrition may be predictive of postoperative infection complications in children. However, inconsistencies in nutritional and outcome assessments made drawing conclusions difficult. Larger studies are warranted to investigate further this potential prognostic relationship.

Keywords

- Healthcare-associated infection
- Undernutrition
- Nutritional assessment
- Paediatric surgery
- Postoperative infection

Introduction

Healthcare-associated infections (HCAI) incur a cost to the NHS in excess of £700 million per year.[1] In addition, rates of HCAI are increasingly being viewed as an indicator of quality healthcare.[2] Efforts to reduce incidence have become widespread, most noticeably with the introduction of evidence-based clinical guidelines for reducing surgical site infection both in the UK and USA.[3,4] There have been few studies in children which have looked at nutritional status – in particular undernutrition - as a potential risk factor for postoperative infection related complications.

Undernutrition - as one form of malnutrition - can be defined as an imbalance between nutrient requirement and intake, resulting in cumulative deficits of energy, protein or micronutrients that may negatively affect growth, development, and other outcomes.[5] There is evidence that nutritional status deteriorates in children following hospital admission,[6,7] often when associated with chronic or critical illness.[8,9]

Poor nutritional status (measured by lower weight-for-age *z*-scores) has been associated with increased duration of mechanical ventilatory support, increased length of stay and increased 1-year mortality in neonates undergoing surgery within an intensive care setting.[10] A recent evidence-based review of the literature found weak evidence of preoperative nutritional assessment being predictive of adverse clinical outcomes in pediatric surgical patients.[11] However, this review only identified a total of six studies, five of which were undertaken in a paediatric cardiac surgical population limiting external validity of the findings to other surgical populations. Of particular relevance to our research hypothesis, only two of the included studies reported infection-related outcomes,[12,13] identifying potential omissions in their search strategy to detect pertinent literature.

Therefore, with some peirastic evidence suggesting a relationship between undernutrition and adverse clinical outcome in children, to date the exact relationship between undernutrition and postoperative infection complications has not been fully evaluated. Undertaking a systematic review of the existing research literature may determine this relationship further. This is important because nutritional status is a potentially modifiable risk factor which may be manipulated prior to undertaking surgical procedures in some children. Potentially, this could not only reduce the physical and psychosocial consequences of infection-related complications occurring after surgery in both child and family, but also reduce the financial burden associated with treatment, prolonged hospital stay/readmission, or further procedures which may be required as a consequence. These costs have yet to be evaluated within paediatric surgical populations.

Methods

Any study assessing the preoperative nutritional status of children < 18 years of age undergoing surgery and reporting infection related post-operative complications were eligible for inclusion. Studies which also included participants >18 years were excluded if outcome data were unable to be extracted by age. Studies were identified by searching Cochrane Central Register of Controlled Trials (CENTRAL); OvidSP MEDLINE (1950 to 2014); OvidSP EMBASE (1980 to 2014) and NHS Evidence CINAHL (1982 to 2014). Index terms were exploded. A search strategy sensitive to the identification of prognostic studies was adopted.[14,15] Studies were also identified by forward and backward citation searching of all identified papers and relevant review articles. OpenGrey and ETHos were searched in an attempt to identify relevant grey literature. Studies were restricted to English language. Any study design evaluating nutritional status prior to surgery and reporting infection related complications in children (<18yrs) was eligible for inclusion in the review.

Data extraction was performed using forms specific to this review and based on the Cochrane Collaboration template.[16] If further clarity on content was required, attempts were made to contact study authors. Where more than one published paper reported results from the same study participants, all papers were utilized to gain information relevant to this review.

The following data were extracted: study design and characteristics; country of origin; type and length of surgery; baseline participant data and eligibility criteria; nutritional assessment method with stratification of nutritional status; infection-related outcomes including definition, incidence and size of effect; duration of follow up; assessment of confounders; authors' conclusion.

For dichotomous infection outcomes, the appropriate relative risk or odds ratio were extracted or calculated, accompanied by 95% confidence intervals. Where more than one analysis was presented in the published article, the most adjusted analysis was extracted. Studies demonstrated significant clinical and methodological heterogeneity in terms of participants and outcome reporting, therefore meta-analysis was not appropriate and a narrative synthesis was used to explore the relationship between classification of nutritional status and incidence of infection-related complications.

Quality assessment of included studies

Methodological quality of studies which met the inclusion criteria were independently assessed. The Newcastle Ottawa Scale (NOS),[17] has a version for both cohort and case control studies and so was used to assess study quality in three domains: participant selection (representativeness); comparability (due to design or analysis), and outcomes (assessment and follow-up). A maximum score of 9 was judged as providing high quality evidence. Studies scoring 7 or 8 were considered as providing moderate quality evidence. Studies achieving 5 or 6 were considered as providing low quality evidence. Those scoring 4 or less were considered as providing very low quality evidence.

Participants needed to reflect the ‘average’ paediatric surgical population, and so were judged accordingly. Specialist, homogenous surgical populations were therefore downgraded for the purposes of this review,[18] and studies recruiting from voluntary surgical databases were judged as being at unclear risk of bias.[19]

As BMI is not a valid indicator of undernutrition in children without being adjusted for age and sex,[20] studies using this as their sole ascertainment of undernutrition were downgraded accordingly.[21] Where cut-offs for categories of nutritional status were inadequately defined to make a judgement, studies were judged as being at unclear risk of bias.[22]

Studies excluding participants on either age; co-morbidity; death and/or incomplete follow-up data were downgraded. Lack of transparency regarding the number of participants excluded from the studies was considered a potential source of bias, especially when excluded populations accounted for 20% of the surgical cohort.[21,22] Where participant numbers were low for the given study period, downgrading to unclear risk of bias occurred.[13,23,24]

Both cohort and case-control studies faced similar problems in terms of exposure/case selection, due either to unclear or non-validated infection definitions,[23] or unclear or less than accepted durations of follow-up.[13,21,24,25,26] These studies were downgraded accordingly.

Any study adjusting for age and/or case complexity met the criteria for comparability.[18,19,21,22] Where no statement, a reported 'no difference between groups', or only performing unadjusted analysis occurred this criterion was not judged to have been met.[13,22,25,26,27]

The results of quality assessment are presented in Figure 2. Overall, two studies achieved a 'moderate' rating for quality, whilst 8 achieved a 'low' quality rating. The remaining cohort studies achieved a 'very low' quality rating.

Results

Search results

The search strategy resulted in 1095 citations, with 28 duplicate titles. No further studies were identified by CENTRAL database or grey literature searching. Following independent review of titles and abstracts, 970 were discarded. A further 28 citations were identified by forward and backward citation searching of the remaining 69 database citations, with 14 discarded following abstract screening. A total of 83 full text articles were screened, with 53 progressing to eligibility screening. Two articles referring to the same study were identified.[25,26] Data from both papers were combined for data extraction purposes. Ten cohort studies and two case control studies were included for this review (Figure 1).

Twelve studies (thirteen papers) with a sum total of 92,386 participants fulfilled the inclusion criteria for this review. The effect estimate of the individual study's results regarding the relationship between nutritional status and infection outcome can be found in Table I: Summary of Findings. All participants had some form of nutritional assessment undertaken prior to their surgery, classified within this table as the prognostic indicator.

Two studies included participants aged 18 years or older.[23,28] As both presented individual patient characteristics with related outcome data, these participants were excluded from univariate statistical analysis. The remaining ten studies were carried out in children with a minimum age reported as 3 days and overall median age reported of 10.6 months.[21] Three studies excluded a neonatal population: one excluded infants less than 2 months of age,[27] whilst a further two excluded neonates either less than 31 days or 28 days.[12,19]

Four studies were undertaken in cardiac surgical populations,[13,18,21,29] and four in general surgical populations, mainly gastrointestinal/abdominal surgery.[24,25,26,27] Two studies were in spinal surgical populations,[23,29] and one comprised of cardiac, neuro and general surgical participants.[22] One study included

children undergoing any type of surgery with data entered onto the American College of Surgeons NSQIP Pediatric report form.[19]

<u>Methods of nutritional assessment</u>

A variety of methods was used to assess nutritional status with 13,902 participants classified in an undernutrition category, giving a combined incidence of 15%. This incidence was greater than 50% in four of the included studies,[12,13,21,24] whereas the lowest rate was found in the largest cohort study which reported an incidence of 14.5%.[19]

A formula using height and/or weight parameters was most commonly used to assess nutritional status. Five studies relied on weight-for-age *z*-scores,[18,19,28] or BMI *z*-score calculations.[21,29] Prospective studies were more likely to use Waterlow's criteria based on expected values of height/weight-for-age.[13,24,25,26] Two studies used one of the above measures with the addition of triceps skin fold, the latter used to estimate subcutaneous fat.[24,29]

Two studies included some element of biochemical testing.[13,24] One study used biochemical assessment markers of serum albumin and haematocrit solely to classify nutritional status.[23] Two studies compared a nutrition history questionnaire – the Subjective Global Assessment (SGA) - against anthropometric assessments to assess the efficacy of the tool in identifying children at risk of post-operative complications.[12,27] The focus of these studies was to identify and compare undernourished children with their well-nourished counterparts; outcome data were extracted for both groups. Both studies provided unadjusted results from bivariate analyses, and made little or no adjustment for potential confounding variables.

Relationship between undernutrition and infection

Six studies reported outcomes for surgical site infection (Table 1).[19,22,23,25,28,29] Definitions used for the identification of this outcome were consistent across three studies[18,22,29] using Center for Disease Control criteria.[4] Two studies used either an ASEPSIS score >21 or the National Nosocomial Infections Surveillance (NNIS) criteria, both recognized criteria.[30,31] The remaining study within a spinal surgical population used an individualized definition stated as wound breakdown with purulence, exposed instrumentation or positive wound culture.[23]

Two studies performed adjusted analyses controlling for important clinical factors (age, case mix and comorbidity) with results not demonstrating an association between undernutrition and surgical site infection (SSI), although in univariate analysis this association was suggested.[19,22] The studies were well-powered, but both had significant participant exclusions. The remainder studies, on reported or unadjusted results, all presented relative risks equal or greater than 1,[23,25,28,29] with only one study demonstrating confidence intervals suggestive of statistical significance.[23]

Five studies reported an outcome for combined infection related complications. Two studies both presented relative risks suggestive of an association between undernutrition and infection, with confidence intervals achieving statistical significance.[12,18] In the one study undertaking adjusted analysis, this association persisted.[18] Two further studies had no episodes of infection in their normally nourished groups,[13,27] with only one demonstrating a significant p value.[13] The remainder study did not find an association; however, the reported outcome for this study combined three infection diagnoses – pneumonia, mediastinitis and septicaemia, with a duration of follow-up assessed as inadequate to be certain all cases were identified.[21]

Outcome data for pneumonia were presented by four studies, and all reported unadjusted risk estimates. However, direction of effect was not consistent across studies, and only one study achieved statistical significance.[19] Two studies did not provide meaningful data sufficient to enable interpretation.[21,26]

One study presented unadjusted results of statistical significance demonstrating an association between undernutrition and postoperative urinary tract infection; however, this was not included in the adjusted analysis.[19] One further study presented data for septicaemia which also demonstrated an association with undernutrition in univariate analysis. However, confidence intervals were extremely wide, suggesting an extent of imprecision from which it would be unwise to draw conclusions.

Discussion

This systematic review shows that there is insufficient evidence to make a judgment regarding an association between undernutrition and incidence of surgical site infection. There is tentative evidence to suggest a relationship between undernutrition and infection related complications. There is also insufficient evidence to make a judgment regarding the association between undernutrition and the individual infectious complications of pneumonia and septicaemia, although there is weak evidence to suggest there may be an association between undernutrition and postoperative urinary tract infection.

No studies were judged as providing high quality evidence, and only two were judged as moderate quality.[19,18] Downgrading the level of evidence for the remaining studies was mostly due to study design – cohort studies had significant participant exclusions prior to study entry; inadequate definitions of exposure or outcome – or because of the lack of reported information with which to make a clear judgment regarding methodological quality.

Both moderate quality studies demonstrated an association between undernutrition and postoperative infectious complications when grouped together. Although the direction of effect in the larger heterogeneous surgical study did not support a relationship between SSI and undernutrition following adjusted analysis, confidence intervals contained the null value.[19] However, in the small, homogeneous surgical population this relationship persisted and, on adjusted analysis confidence intervals, did not contain the null value.[18] Two further studies also demonstrated an initial association, with statistically significant confidence intervals.[12,23] The remaining studies were equally split in terms of direction of effect, but none were able to demonstrate statistical significance.

Anthropometric variables were used to assess nutritional status in all but one study,[23] though varying thresholds for defining undernutrition were utilized. Due to significant heterogeneity direct comparison across studies was complicated, and formal pooling of results for estimating effect was not suitable. Weight based assessments were the commonest variable, not unexpected as this forms part of routine pre-operative assessment. Studies prior to the year 2000 more frequently used Waterlow's criteria to classify weight, whereas those after 2000 were more likely to use *z*-scores, reflecting World Health Organization recommendations.[32] This wide variation in assessment method is likely to be reflective of the retrospective design of most studies, and the necessity of using weight-based data, in addition to the technique most favored during the study era.

For infection related outcomes, again, a variety of definitions and systems for classification were utilised. The Center for Disease Control criteria (CDC) were cited most commonly,[4] but variable or unclear durations of follow-up made it difficult to determine if studies were treating participants in a comparable way. This introduced an element of uncertainty in terms of whether all incidents were captured.

Sample sizes were less than 100 in more than half the included studies.[13,18,23,24,27,28,29] Studies were generally underpowered to detect important clinical differences, with only one study providing an *a priori* power calculation having an 80% chance of detecting an odds ratio of 2.1, or a 50% chance at 1.5.[29] Those studies which were specific to a surgical specialty were underpowered to detect differences, especially when the event rate of infection related complication was 16% across all studies, with a range between 2% and 42%.[19,23] Studies which included multiple surgical specialties within one study significantly increased clinical heterogeneity, especially when there was no attempt to control for surgical complexity. This heterogeneity increased the likelihood that any true effect of undernutrition on the incidence of infectious complications would be masked.

Although attempts were made to identify unpublished literature, none were found. A lack of unpublished articles may have introduced publication bias and increased the risk of a Type II error (failure to reject the null hypothesis of no difference). Using a search filter sensitive to the identification of studies regarding prognosis would not have excluded the identification of controlled trials of nutritional intervention in which control groups may have been eligible for inclusion, although none were identified. Despite an a priori decision to exclude foreign language papers, none were found which met review eligibility criteria.

The nature of the review question created complex search strings crossing many diagnostic fields, which may have contributed to the number of articles identified by backward and forward citation searching. Also inconsistencies in MeSH terminology within the bibliographic databases searched, and variation between databases in how articles regarding prognosis are indexed, may have compounded this further.

Decisions regarding study quality were based upon the information presented in the published paper, as it was identified following data extraction. Otherwise it would have been necessary to contact all primary authors for further information regarding some aspect of their methodology. This may have adversely affected the quality rating of those papers where English was not the authors' first language, or where word restrictions imposed from publishers led to omission of methodological process.

The Newcastle Ottawa Scale was chosen as the preferred tool for quality assessment as both case-control and cohort studies were included.[17] However, as the nature of the review question related to prognosis, we deviated from protocol to enable the method of quality assessment to be adapted. We continued to assess quality using the NOS categories of Selection, Comparability and Outcome or Exposure (dependent on cohort or case control methodology) but we also incorporated the domains included in Hayden's framework developed specifically for studies considering prognosis.[33] This adaptation was felt to enable a more rigorous assessment of the quality of each included study in addressing heterogeneity of both exposure and outcome measures. As observational studies are susceptible to uncontrolled confounding factors and bias, mainly in the selection of study participants, careful evaluation was undertaken to judge the reliability of the evidence provided. The reproducibility of this technique, however, has not been tested.

Applicability of the findings are likely to be of relevance to the surgical specialties included in the review. Due to the higher quality studies not including neonates, evidence is severely lacking with respect to children aged less than 28 days.

Future research needs to make a distinction between viewing undernutrition as a potential prognostic factor for infection, or it being explored as a potential risk factor for infection related complication. In this way, studies will be adequately powered to detect clinical and statistical significance, with nutritional status being included in multivariate analysis of potential confounders on outcome.

The review question remains unanswered. However, it remains an important question particularly to those patient populations with chronic disease where growth failure has already been recognized and who as part of their management will require surgical intervention.[8,34] Especially pertinent are those surgical specialties where patients will be critically ill postoperatively, and it is anticipated they will require a proportion of their recovery time within an intensive care environment. These patient populations are known to be most vulnerable to postoperative morbidity and also are most vulnerable to further nutritional depletion during their inpatient stay.[6,9,10]

There remains a need for large, adequately powered prospective studies incorporating a gold-standard method for nutritional assessment, with consistent definitions of undernutrition in order to determine the potential impact on infection related outcomes in children following surgery. Definitions for infectious complications will also need to be robustly defined and consistently applied.

If undernutrition is identified as a risk factor, aspects of both pre and postoperative feeding practices could be manipulated, with special considerations or precautions being explored for these children that may potentially reduce the physical, psychosocial and financial burden of healthcare acquired infection.

Author contributions

Concept and study design R.H., M.P.D., M.A.H., B.C.; Manual searches R.H.; Screening R.H., S.P.; Data extraction R.H, S.P.; Writing to authors of papers for additional information R.H.; Arbitration for screening and data extraction M.P.D.; Manuscript preparation R.H., S.P., M.P.D., M.A.H and B.C.

Acknowledgements

Heitor Pons Leite for responding to primary author queries.

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