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Systematic review of reduced therapy regimens for children with low risk febrile neutropenia

Jessica Morgan[1,2], Jemma Cleminson[1], Karl Atkin[3], Lesley A Stewart[1], Robert S Phillips[1,2]

Affliations: [1] Centre for Reviews and Dissemination, University of York, Heslington, York, YO10 5DD, UK; [2] Department of Paediatric Haematology and Oncology, Leeds Teaching Hospitals NHS Trust, Great George Street, Leeds, LS1 3EX, UK; [3]Department of Health Sciences, University of York, Heslington, York, YO10 5DD, UK.

Address for correspondence: Dr Jessica Morgan, Centre for Reviews and Dissemination, University of York, Heslington, York, YO10 5DD, UK, jem539@york.ac.uk, Tel: +44 (0)1904 321082, Fax: +44 (0)1904 321041

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- Captions:
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- Online Resource 1: Database search strategies
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Abstract

Purpose

Reduced intensity therapy for children with low risk febrile neutropenia may provide benefits to both patients and the health service. We have explored the safety of these regimens and the effect of timing of discharge.

Methods

Multiple electronic databases, conference abstracts and reference lists were searched. Randomised controlled trials (RCT) and prospective observational cohorts examining the location of therapy and/or the route of administration of antibiotics in people younger than 18 years who developed low risk febrile neutropenia following treatment for cancer were included. Meta-analysis using a random effects model was conducted. I^2 assessed statistical heterogeneity not due to chance. Registration: PROSPERO(CRD42014005817).

Results

37 studies involving 3205 episodes of febrile neutropenia were included; 13 RCTs and 24 prospective observational cohorts. Four safety events (two deaths, two intensive care admissions) occurred.

In the RCTs, the odds ratio for treatment failure (persistence, worsening or recurrence of fever/infecting organisms, antibiotic modification, new infections, re-admission, admission to critical care or death) with outpatient treatment was 0.98 (95% confidence interval (95%CI) 0.44-2.19, I^2=0%) and with oral treatment was 1.05 (95%CI 0.74-1.48, I^2=0%). The estimated risk of failure using outpatient therapy from all prospective data pooled was 11.2% (95%CI 9.7-12.8%, I^2=77.2%) and using oral antibiotics was 10.5% (95%CI 8.9-12.3%, I^2=78.3%). The risk of failure was higher when reduced intensity therapies were used immediately after assessment, with lower rates when these were introduced after 48 hours.

Conclusions

Reduced intensity therapy for specified groups is safe with low rates of treatment failure. Services should consider how these can be acceptably implemented.

Background

Febrile neutropenia is the commonest life-threatening complication of treatment of children with cancer.(1) It occurs in around a third of episodes of neutropenia, at a rate of 0.75 episodes per 30 days of neutropenia and 0.15 per month of chemotherapy exposure time.(2,3) Febrile neutropenia describes a spectrum of conditions: a small number of patients suffer serious complications including organ failure and death, but most episodes have no significant sequelae. Current research into febrile neutropenia has focussed in two areas – risk stratification to define a 'low risk' population (LRFN) and reduced therapy for such groups.(4)

Reduced therapy regimens may provide benefits to both patients (including increased quality of life and reductions in hospital acquired infections) and the health service (including cost savings and reduced bed pressures).(5–8) However, they should be explored rigorously in terms of both safety and efficacy, before changes are implemented. We therefore performed a systematic review to establish the safety and efficacy of these regimes and to identify how the timing of reductions in therapy might change these features.

We anticipated, given previous reviews, that the number of randomised controlled trials (RCTs) comparing the location and route of administration of antibiotics would be small.(9,10) We also considered it important to estimate absolute numbers of patients experiencing failures, and therefore planned to use information from both prospective observational cohorts and the separate arms of RCTs to estimate failure rates.

For the purpose of this review, the three primary outcomes were treatment failure, safety and adequacy. These outcomes are likely to provide the information that patients and clinicians combine when making decisions about choice of care, thus they are the most clinically relevant outcomes for those involved in planning and delivering Paediatric Haematology and Oncology services. Multinational guidelines have recommended that the primary outcome of studies into febrile neutropenia should be a composite measure, hence our use of treatment failure (persistence, worsening or recurrence of fever/infecting organisms, antibiotic modification, new infections, re-admission, admission to critical care or death) as an outcome.(11) Meanwhile, knowledge about the safety of a strategy is essential to be able to consider its use at all, whilst information about adequacy would allow services to plan appropriately for potential re-admissions or changes in treatment associated with changing to a new low risk strategy.

Finally, we understood that there may be concern regarding reduction of therapy from patients, their parents and the healthcare professionals caring for them. Therefore we collected data on rates of declined consent, where reported, as a way of gaining insight to the potential acceptability of these approaches.

Methods

We carried out a systematic review of reduced therapy regimens for children with low risk febrile neutropenia. The protocol was prospectively registered (PROSPERO: CRD 42014005817) and published.(12) Electronic searches of MEDLINE, MEDLINE in-Process & Other non-Indexed Citations, EMBASE, CDSR, CENTRAL (via the Cochrane Library), LILACS, HTA and DARE were performed. The search strategy focused on febrile neutropenia and the interventions of antibiotics and early discharge, with a paediatric filter. No date or language filters were applied. The full database search strategy is provided in Online Resource 1. Conference proceedings of the RCPCH (Royal College of Paediatrics and Child Health), SIOP (International Society of Paediatric Oncology), ASPHO (American Society of Paediatric Haematology/Oncology), ASCO (American Society of Clinical Oncology) and ICAAC (Interscience Conference on Antimicrobial Agents and Chemotherapy) meetings were searched. Reference lists of included articles and relevant systematic reviews were also reviewed. Authors of relevant studies and prominent clinicians within the field were contacted seeking further studies.

One reviewer (JM) screened the title and abstract of all studies for inclusion. A second reviewer (JC) independently screened a sample of 1000 of the titles and abstracts. The kappa statistic for agreement showed good agreement between reviewers (k = 0.69, 95% confidence interval 0.59-0.79). Full text was obtained for all potential articles of interest. All full texts were assessed for eligibility (see Box 1) by two reviewers (JM and JC). Disagreements were resolved by consensus, or referred to a third reviewer (RP, 5 studies referred).

Box 1: Inclusion criteria

Study Design: Randomised Controlled Trials, Quasi-Randomised Controlled Trials and prospective observational cohorts

Population: Aged <18 years with low-risk fever and neutropenia secondary to treatment for cancer, or results available for this subgroup

Interventions: one or more of

- Location of treatment – inpatient, outpatient, or initial inpatient with early discharge to outpatient
- Route of antibiotic administration – intravenous, oral or intravenous with switch to oral (IVOST)

Outcomes: one or more of

- Treatment failure at 30 days- persistence, worsening or recurrence of fever/infecting organisms, modification of antibiotics, new infections, re-admission, admission to critical care services or death during treatment.
- Safety - medical complications, defined as admission to critical care services or death.
- Adequacy - resolution of the episode without change in antibiotic or location of the patient.

Data were extracted by one researcher and independently checked by a second. Risk of bias was assessed using the Cochrane risk of bias tool for controlled trials and the NICE prognostic studies tool for observational cohorts.(13,14)

For the purpose of this review, the timing of discharge was grouped into outpatient (admission of less than 8 hours), <24 hours, 24-48hrs, >48 hours and entirely inpatient treatment. Early discharge is used to refer to all categories except entirely inpatient treatment, unless otherwise specified.

For each outcome, study level data were combined with a random-effects model using the DerSimonian & Laird estimator. Heterogeneity was examined using χ^2test, the I^2 and tau^2 statistic and by visual inspection of forest plots. I^2 represents a quantitative assessment of the degree of statistical heterogeneity beyond that expected by chance. Meanwhile tau^2 provides an estimate of the between-study variance.

Subgroup and sensitivity analyses were performed as planned.(12) For the purpose of sensitivity analyses, as the studies used a variety of methods of risk stratification, the risk tools were grouped into more or less stringent tools. The more stringent tools generally required a period of observation after presentation, excluded very young patients, patients following BMT or with leukaemia (except ALL on maintenance), those with a neutrophil count $<0.1x10^9$/L and patients with respiratory symptoms. Less stringent rules all had only two or three exclusion criteria which were not restrictive. For example, a less stringent rule might exclude patients with signs of sepsis and those with social concerns such as no reliable caregiver but allow the inclusion of all other patients, regardless of age, underlying diagnosis and neutrophil count." The risk of publication bias was explored using contour-enhanced funnel plots and Harbord and Peters tests.

Results

2370 titles and abstracts were assessed and 112 full text articles retrieved (see Figure 1). The 80 full text articles excluded are detailed in Online Resource 2. Five further studies were identified from review of conference proceedings and reference searches.

Of the 37 included studies, 12 are RCTs. (15–17, 19–27) One further RCT was identified, but was not included in the RCT analyses as it compared early discharge on oral antibiotics with early discharge on an oral placebo.(18) However, the individual arms of this trial have been included in the analyses of the observational

cohorts. No quasi-randomised trials were identified by the searches. Twenty-four observational cohorts are included, describing 26 separate treatment cohorts. (7,28–50) (Online Resources 3 and 4.)

Multiple different risk stratification tools were used by the included studies; the majority of which were unnamed and unvalidated. The tools were grouped as described within the Methods. Twenty-five studies used more stringent tools and eight used less stringent tools. Four studies did not describe their risk stratification tool in enough detail to allow classification of the tool.

Risk of bias

All but one of the RCTs showed a moderate risk of bias as participants and outcome assessors were not blinded to the intervention received. Some outcomes are unlikely to be affected by this lack of blinding, including admission to critical care services or death. Other outcomes, particularly treatment failure, which are more susceptible to bias, have been specifically selected as pragmatic reflections of standard clinical practices such that the outcomes of unblinded studies are informative. Other than the issue of blinding, the RCTs were generally at low risk of bias, as were the prospective observational cohorts (see Table 1~~2~~).

Adequacy

No studies explored the concept of adequacy outwith the definition of treatment failure. The timing of the final aspect of risk stratification universally matched the timing of discharge and hence planned subgroup analyses of the timing of risk stratification were not performed.

Safety

There were two deaths within the data from the RCTs (12 studies, 1291 episodes). (15–27) One child died of an adenovirus infection on day 10 of treatment. The second died of a P~~p~~seudomonas aeruginosa infection after an acute deterioration on day 3 (notably, this child was well until day 3 and had negative blood cultures on admission). Both patients were treated entirely with intravenous inpatient therapy. A further two safety events were identified in the observational cohorts (total 2663 episodes, 42 arms). (7,15–34,36–44,46–50) These two patients were admitted to intensive care; one with pneumonia and one with diarrhoea causing hypotension. Neither patient died. Both had been treated with oral therapy as outpatients from presentation. Therefore, the proportion of low risk episodes which resulted in intensive care or death is 0.1% (95% confidence interval (95%CI) 0.03-0.3%).

Treatment failure

Three RCTs compared the risk of treatment failure between inpatient and outpatient treatment, including discharge up to 48 hours after admission.(15,20,25) The odds ratio for failure with outpatient treatment was 0.98 (95% CI 0.44-2.19, I^2=0%, tau^2=0). There were insufficient trials for subgroup analyses, providing no clear evidence of a difference in failure rates between these treatment settings.

Eight RCTs compared the risk of treatment failure between intravenous and oral therapies, including change to oral medications up to 48 hours after presentation.(15–17,19,21,23,24,26) The odds ratio for failure with oral treatment was 1.05 (95% CI 0.74-1.48 I^2=0%, tau^2=0), providing evidence of no clear difference between the two approaches.

Treatment failure rates were then further explored using data derived from the observational cohorts combined with the individual arms of the RCTs. Within these data, 42 prospective arms in which patients were treated on any outpatient or early discharge regimen were included. (7,15,17–25,27–43,46,49,50) The estimated rate of failure using these approaches was 11.2% (95%CI 9.7-12.8%, I^2 = 77.2%) and included patients treated on any outpatient or early discharge regimen.

Given the significant clinical and statistical heterogeneity in this group, this combined estimate suggests there are features of an early discharge strategy which will alter the risk of treatment failure. We therefore proceeded to analyse these as subgroups split by timing of discharge. For studies including patients treated entirely as outpatients, the treatment failure rate was 14% (95%CI 9.7% -19%, I^2 = 81.93%, Figure 2a). The rate of failure for the seven studies of patients receiving early discharge after 48 hours was 2.2% (95%CI 1.2-4.1%, I^2 = 0%, Figure 2b).

34 cohorts (from observational cohort studies and the individual arms of the RCTs) were included in the assessment of treatment failures following any oral therapy regimen. (15–27,29–33,36,37,39–43,46–49) The

estimated rate of failure using this approach was 10.5% (95%CI 8.9-12.3%, I^2 = 78.3%) Due to high heterogeneity in this composite analysis, we again proceeded to subgroup analysis based on timing of change to oral antibiotics.The rate of failure for those receiving oral antibiotics after 48 hours of intravenous administration was 3.4% (95%CI 2-5.7%, I^2 = 11.21%) and for patients treated entirely with oral antibiotics the rates of treatment failure were 17% (95%CI 12-25%, I^2 = 74.45%).

Sensitivity analyses

The rates of the outcome measures were unaffected by the use of full text articles alone, fixed effect meta-analysis or location of the study. There is a suggestion that using a more stringent risk stratification tool reduces the rates of treatment failure, as might be expected given the features used in risk tools. When considering location of treatment, studies using the most stringent risk tools report failure rates of 7% (95%CI 4.7-10.3%, I^2 = 82.31%) compared with failure rates of 19.1% (95%CI 11.7-29.6%, I^2 = 77.15%) in studies with the least stringent risk tools. Similarly, regarding the route of administration of antibiotics, studies using the most stringent risk tools reported failure rates of 7.8% (95%CI 5.2-11.6%, I^2 = 85.33%). There were only two studies exploring the route of administration of antibiotics and using less stringent tool. These found a failure rate between 8.8% and 51%.

Publication bias

As the meta-analyses which provided the estimates of rates of treatment failure included the largest numbers of studies, we assessed publication bias primarily using these studies. When examining the studies which reported patients receiving early discharge or outpatient care, Peters test did not reveal evidence of heterogeneity (p=0.21) whilst Harbord's test suggested that publication bias might be present (p<0.001). Examination of the contour enhanced funnel plot (Figure 3a) reveals that there is a wide spread of proportion of failures in studies with small standard error, but that in studies with a larger standard error, few evidenced high levels of treatment failure. This pattern does not differ between RCTs and observational cohorts. In the arms relating to oral antibiotic regimens, both Harbord and Peters tests suggest publication bias (p= 0.06 and 0.004 respectively), whilst the funnel plot (Figure 3b) presents a similar picture to that of location.

Refusal to consent

10 studies provided data on refusals to participate (Table 2~~1~~).(15,19,20,25,26,32,36,42,46,50) The data provided were very heterogeneous and thus not amenable to meta-analysis. However the data can be conceptually grouped into the issues of refusal to enrol in a study and refusal to confirm consent following enrolment (in study designs when enrolment takes place prior to episodes of febrile neutropenia and then further consent is sought at the time of presentation with an episode).

Eight studies looked at failure to consent to enrolment in the study. They found 147 of 782 patients (18.8%, range 1.3-30.1%) who were eligible for enrolment refused to participate. Two of these studies also included data on episodes that were not enrolled as the physician was uninterested or not willing for the patient to take part. These found that in 19.6-26.5% of otherwise eligible episodes the treating physician chose not to enrol the patient in the study.

Three studies provided data on confirmation of consent following enrolment. One looked at physicians' attitudes and found that in 7(14%) of 50 otherwise eligible episodes, the oncologist decided not to include the patient in the study. Meanwhile, two studies examined parental confirmation and found refusals of 8.3% and 12% of eligible episodes. Finally, one study did not separate parental and physician refusal to confirm consent, but found that 8 of 67 episodes in enrolled patients were not included due to the preference of the physician or family.

Discussion

Outpatient therapy and oral antibiotics are safe treatment options for paediatric low risk febrile neutropenia. The episodes included in this review had a very low risk of death or admission to critical care services. Furthermore, for the few adverse events observed, there was no obvious association between occurrence and route or location of treatment. Remaining as an inpatient receiving intravenous antibiotics did not prevent all deaths within this group. This should be clearly recognised: low risk febrile neutropenia is not 'no risk febrile neutropenia'. The overall rates of treatment failure are also low.

We found that studies that moved patients from a more intensive regimen to a reduced regime at 24 or 48 hours had lower rates of treatment failure than those who were treated entirely on reduced regimes. This is an indirect

comparison of observational cohorts, which may also differ by factors other than treatment protocol, making it inappropriate to draw firm conclusions. However, the finding is clinically plausible. Given this difference, a combined estimate of treatment failure rates is not meaningful and it would be seem prudent to use rates for each group separately to inform the design of future services.

For some studies, the reasons for re-admission, and therefore treatment failure, were clearly reported. In others, they were unclear or not documented. Where provided, the indications were variable (such that failure rate recorded within studies is driven by the components of the definition of treatment failure). For example, in some studies, a single repeated fever after reduction in therapy would be defined and counted as a treatment failure. This does not necessarily describe an unwell child and may not be of concern to either parents or clinicians. Additionally, where a child is on a reduced regime, there may be a tendency for physicians to increase therapy more rapidly than for children where standard, more familiar, treatment is already ongoing. Thus, the estimates of treatment failures within this review may be higher than the rates of clinically meaningful deterioration for children on reduced therapy regimens.

In the exploration of treatment failure in relation to the timing of discharge, we also note that a substantial proportion of data is from one group (Paganini et al). Most data about discharge after at least 48 hours of inpatient care are provided by this group. Along with this, the studies examining patients treated entirely as outpatients seem to be grouped within the forest plot into two distinct areas. Studies with smaller numbers of episodes have more variable failure rates compared to those with more episodes. Interestingly, the treatment failure rates in larger studies seem to be lower than for smaller studies, however, again the Paganini group provide much of these data. Therefore, it is unclear whether these differences are due to variations in treatment failure at the various time points or whether they are instead due to the impact of this group's definitions and approaches.

Within the literature, two previous systematic reviews have considered the role of both outpatient therapy and oral antibiotics and have generally found that these approaches are safe and efficacious. However, both reviews had areas for improvement. The Cochrane review focused mainly on adult patients, included only eight RCTs and examined the impact of oral antibiotics alone, without consideration of the role of location of treatment.(10) Meanwhile, Manji et al focused only on the broad concepts of outpatient and oral therapy and combined data from very different groups, resulting in the loss of some of the nuanced information from the original trials.(9) Furthermore, neither review included non-English studies despite the presence of very active research groups from South America.

Our review had more focused aims and objectives, a more extensive search strategy and considered the large volume of prospective observational cohort data that exists in this area. It provides more depth and clarity to the prior works.

When considered alongside the results of the two previous reviews by the Cochrane group and Manji et al, our work reinforces the conclusion that reduced therapy can be safely achieved in children with low risk febrile neutropenia.(9,10) However, our treatment failure rates contrast with those of Manji et al.(9) The previous review had found that treatment failure was more likely in patients treated as inpatients than those who received outpatient care. Our review has found that the rate of treatment failure was higher in the group who were treated as outpatients earlier in their course. This difference in results is likely to be due to the differences in inclusion criteria for the two reviews, resulting in the comparison of different inpatient regimens. The Cochrane review by Vidal et al found similar rates of failure for intravenous and oral regimens as our review.(10)

We found there are high rates of refusal to participate in trials of these regimens, which relate to both families and physicians. In many areas of research, a refusal to consent rate of up to 30% may not be considered problematic. However, in the context of children's cancer where high recruitment rates are generally seen, this rate of refusal is noteworthy.(51) Refusal to consent to enrolment was generally greater than refusal to confirm consent following enrolment. In studies that examined the number of refusals by physicians, these were similar to or greater than the refusals by parents. This may reflect physician refusal as a proxy for parents, or alternatively may represent uncertainty amongst physicians about the safety or efficacy of reduced therapy. No studies provided data on why families and physicians refused to participate, but two discussed potential issues. They used anecdotal evidence to describe practical issues as a potential barrier to participation for families, whilst a perceived lack of safety may be an issue for both families and physicians considering reduced therapy options.

The main strength of our work is in the examination of a large amount of data. The RCTs are few, and although they suggest that reduced therapy regimens are safe, the additional consideration of observational cohort data

provides further support for these strategies. The inclusion of a large number of episodes also allows the consideration of the issue of timing in early discharge so as to inform service development in this area.

The main weakness within this work is its inability to completely define the features of a low risk strategy that result in the lowest rates of treatment failure. This is mostly due to the considerable heterogeneity within the literature, with regards to the inclusion criteria and interventions used. In particular, we were unable to fully explore the influence of various risk stratification tools, as a large number of tools were used by the studies and thus sensitivity analysis could only be performed using broad groups.

Future work should consider further defining the features of a reduced therapy regime that influence failure rates, including the risk stratification tool, the definitions of treatment failure and the timings of assessment, discharge and change to oral antibiotics. Researchers should also intend to explore the issues surrounding the acceptance of reduced therapy, specifically looking for potential barriers and facilitators, and the differences in perspectives between families and health care professionals.

Conclusions

Reduced therapy regimens for paediatric low risk febrile neutropenia are safe and have low rates of treatment failure. The adverse events observed seem to occur regardless of the route or location of treatment. The risk of treatment failure seemed to be higher when reduced intensity therapies were used immediately after assessment, with lower rates observed when these were introduced after 48 hours. High rates of refusal to participate in trials of these regimens, by both families and physicians, require further investigation.

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First/Corresponding Author: Jessica Morgan

E-mail: jem 539@york.ac.uk

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Author 1 (printed name): Jessica Morgan

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☐ Consultant/advisory role: Entity:
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Signature: JMorgan. Date: 9/5/15

☐ Author 2 (printed name): Jemma Cleminson NONE.

☐ Remuneration Entity:
☐ Consultant/advisory role: Entity:
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☐ Funding Entity:

Signature: JCleminson. Date: 14.5.2015

☐ Author 3 (printed name): Karl Atkin NONE

☐ Remuneration Entity:
☐ Consultant/advisory role: Entity:
Stock ownership Entity:
☐ Funding Entity:

Signature: Ka At Date: 13.05.2015

☐ Author 4 (printed name): Lesley A Stewart None

☐ Remuneration Entity:
☐ Consultant/advisory role: Entity:
Stock ownership Entity:
☐ Funding Entity:

Signature: Lesley Stewart. Date: 12/5/15

☐ Author 5 (printed name): Dr Robert S Phillips: NONE

☐ Remuneration Entity:
☐ Consultant/advisory role: Entity:
Stock ownership Entity:
☐ Funding Entity:

Signature: RSPhillips Date: 7/May/2015

☐ Author 6 (printed name):

☐ Remuneration Entity:
☐ Consultant/advisory role: Entity:
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☐ Funding Entity:

Signature: Date.

Figure 1 Flow diagram for study selection

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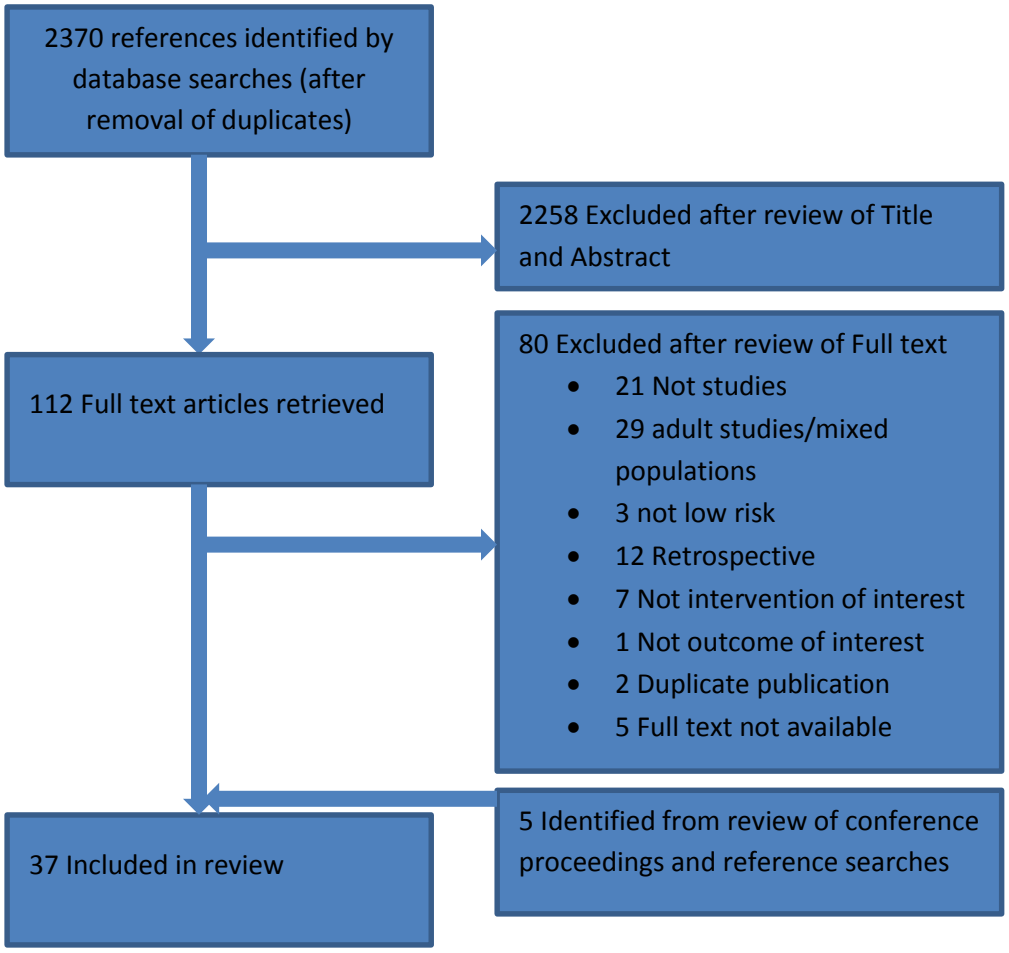

Figure 2 Forest plots of rates of treatment failure

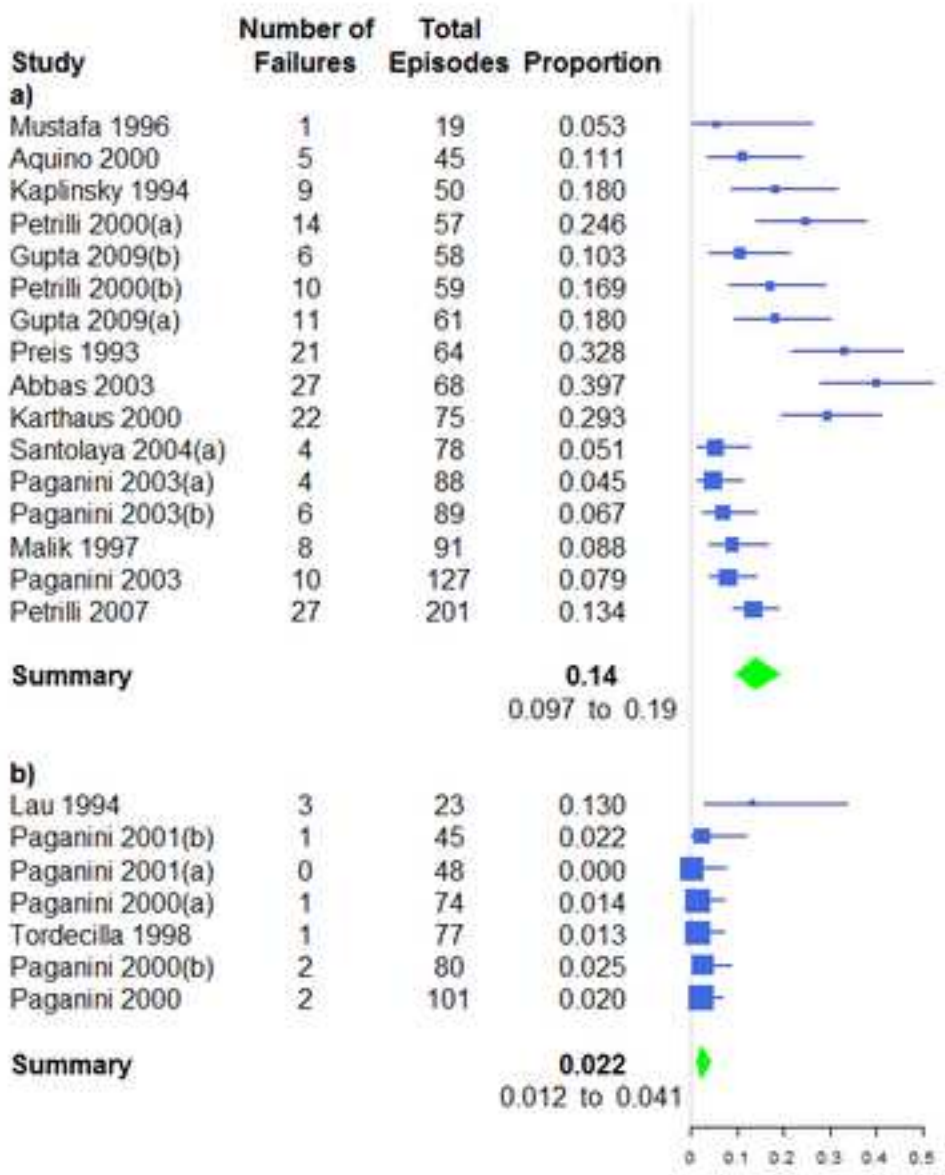

Figure 3a Contour enhanced funnel plot for treatment failure in early discharge or entirely outpatient treatment

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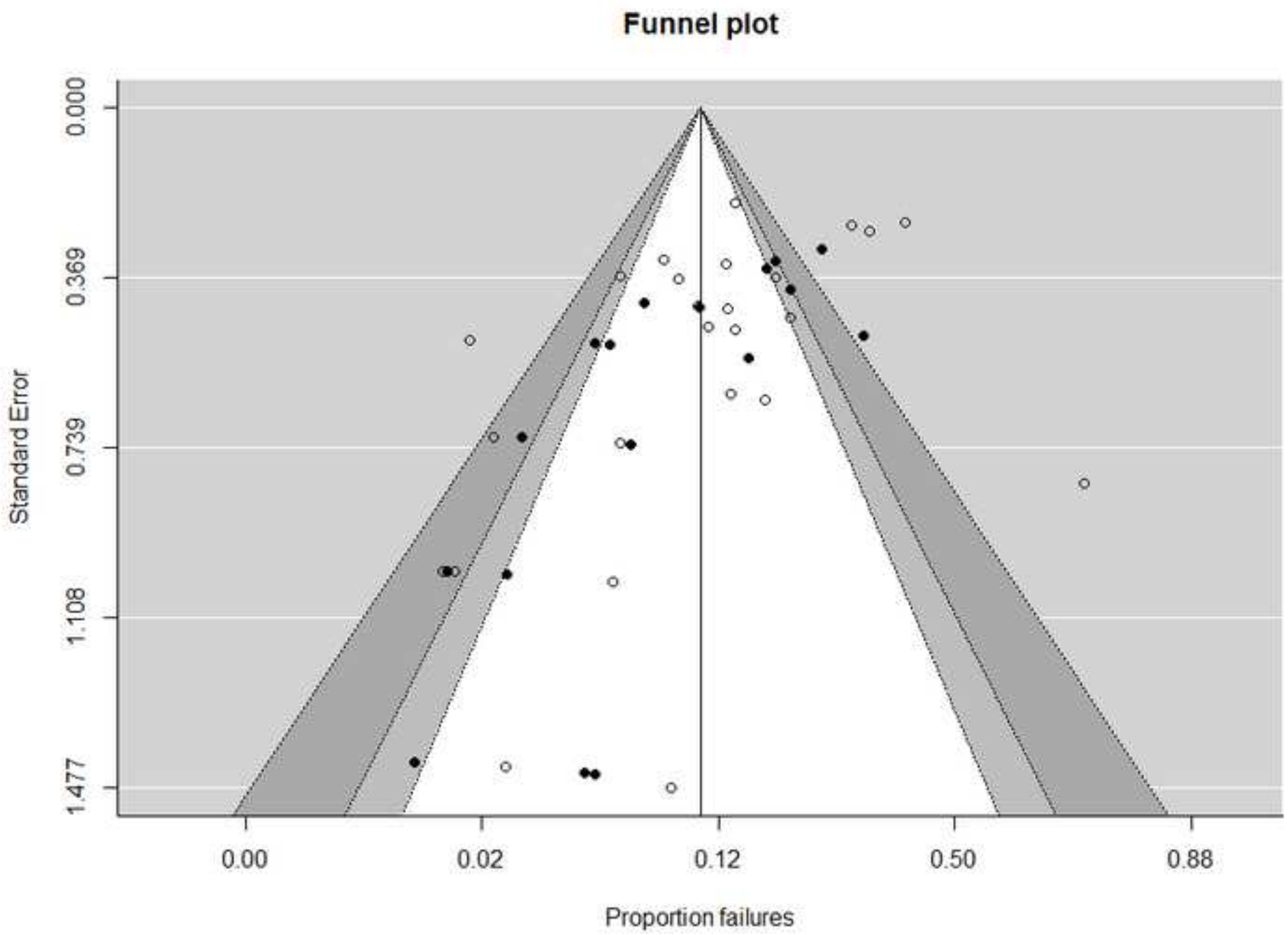

Figure 3b Contour enhanced funnel plot for treatment failure in IVOST or oral antibiotic regimens

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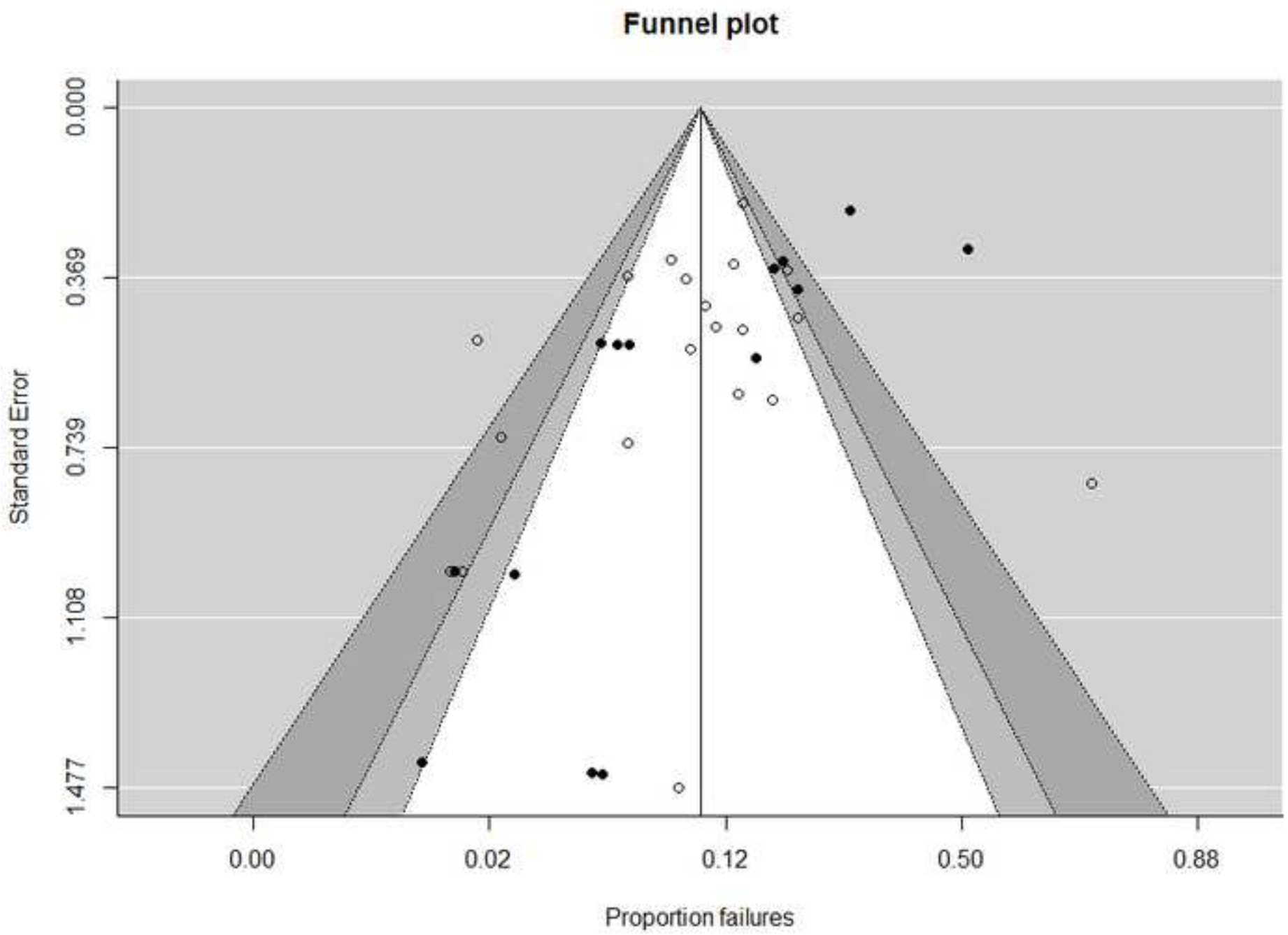

Table 1: Risk of bias tables

Randomised Controlled Trials

	Random Sequence Generation (selection bias)	Allocation Concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Brack et al, 2012	-	-	+	+	-	-
Cagol et al, 2009	-	-	+	+	?	?
Gupta et al, 2009	-	?	+	+	-	-
Klaassen et al 2000	-	?	-	-	-	-
Mullen et al, 1999	-	-	+	+	-	-
Orme et al, 2014	-	?	+	+	-	-
Paganini et al, 2003	-	-	+	+	-	-
Paganini et al, 2001	-	-	+	+	-	-
Paganini et al, 2000	-	-	+	+	-	-
Petrilli et al, 2000	?	?	+	+	-	-
Santolaya et al, 2004	?	?	+	+	-	-
Shenep et al, 2001	-	?	+	+	-	-
Varan et al, 2005	?	?	+	+	-	-

Key: - low risk of bias, ? unclear risk of bias, + high risk of bias

Prospective Observational cohorts

	Population of interest	Loss to follow-up	Prognostic factor	Outcome of interest	Potential confounders	Statistical analysis
Abbas et al, 2003	-	-	-	-	-	-
Aquino et al, 2000	-	-	-	-	-	-
Bash et al, 1994	-	-	-	-	-	-
Dommett et al, 2009	-	-	-	-	-	?
Doyle et al, 1996	-	-	-	-	-	-
Fernandez et al, 2012	-	-	-	-	-	-
Kaplinsky et al, 1994	-	?	-	-	-	-
Karthaus et al, 2000	-	-	-	-	-	-
Lau et al, 1994	-	-	-	-	?	-
Malik, 1997	-	-	-	-	-	-
Miedema et al, 2012	-	?	-	?	-	-
Mustafa et al, 1996	-	-	-	-	-	-
Paganini et al, 2001	-	?	-	-	-	-
Paganini, 2003	-	-	-	-	-	-
Paganini, 2000	-	-	-	-	-	-
Park et al, 2003	?	-	-	-	-	-
Petrilli et al, 2007	-	-	-	?	-	-
Phillips et al, 2006	?	-	-	-	-	-
Preis et al, 1993	?	-	-	?	-	-
Quezada et al, 2007	-	-	?	?	?	-
Sari et al, 2007	-	-	-	?	-	-
Shrestha et al, 2009	-	?	-	-	-	-
Tordecilla et al, 1998	-	?	?	?	-	-
Wiernikowski et al, 1991	?	-	-	-	-	-

Key: - low risk of bias, ? unclear risk of bias, + high risk of bias

Table 2~~1~~ Refusal to consent data (NA – not applicable)

Study	**Concept described**	**Refusal by parents**	**Refusal by physicians**	**Total number of episodes**	**Notes**
Brack et al, 2012	Enrolment	25	NA	93	
Doyle et al, 1996	Enrolment	5	NA	84	
Lau et al, 1994	Enrolment	5	NA	29	
Mullen et al, 1999	Enrolment	12	13	66	
Park et al, 2003	Enrolment	9	NA	39	Includes inability to take oral antibiotics
Quezada et al, 2007	Enrolment	3	9	34	First year of study only
Santolaya et al, 2004	Enrolment	2	NA	151	
Shenep et al, 2001	Enrolment	86	NA	286	
Orme et al, 2014	Confirmation following enrolment	6	7	50	
Quezada et al, 2007	Confirmation following enrolment	8	Included with parental refusal	67	
Wiernikowski et al, 1991	Confirmation following enrolment	2	NA	24	

Online Resource 1 Database search strategies