**Supplemental Information**

**Search Strategy:**

Date of searches August 10th, 2017.

Databases: Pubmed, Embase, Web of Science, Scopus

**PubMed**

(C. diff infection OR clostridium difficile infection OR CDI OR clostridium difficile associated infection OR CDAD) AND (pediatric OR paediatric OR children OR infants OR adolescent) AND (Risk OR Risk Factor OR Predictor OR Marker) Filters: Publication date from 1974/01/01 to 2017/08/09

= 830 references

**Embase**

(C diff infection OR clostridium difficile infection OR CDI OR clostridium difficile associated infection OR CDAD) AND (pediatric OR paediatric OR children OR infants OR adolescent) AND (Risk OR Risk Factor OR Predictor OR Marker)

= 859 references

**Web of Science**

Clostridium difficile AND pediatric AND risk

= 150 references

**Scopus:**

Clostridium difficile AND pediatric AND risk. Search in: Title, Abstract, Keywords

= 193 references

**Supplemental Figure 1:**

**1A**: Funnel Plot of the association between antibiotic exposure and *C. difficile* infection (CDI). Dashed line indicates pooled relative risk of 2.14.



**1B**: Funnel plot of the association between proton-pump inhibitors and *C. difficile* infection (CDI). Dashed line indicates pooled relative risk of 1.33.



**Supplemental Table 1:** Modified Newcastle-Ottawa Scale Scores for included studies

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **First Author** | **Year Published** | **Study Design** | **Selection** | **Comparability** | **Outcome** | **Total** |
| **Representativeness of exposed cohort** | **Representativeness of non-exposed cohort** | **Ascertainment of exposure** | **Demonstration that outcome of interest was not present at start of the study** | **Study controls for age** | **Study controls for any additional factor** | **Assessment of outcome from secure records** | **Follow-up length adequate for outcome to occur** | **Follow up period clearly reported** |
| Nylund | 2011 | RC | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |
| Guo | 2012 | PC | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 7 |
| Hojsak | 2012 | RC | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 7 |
| De Blank | 2013 | RC | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |
| Price | 2013 | RC | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 8 |
| Boyle | 2015 | RC | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |
| Santiago | 2015 | RC | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 8 |
| Pant | 2016 | RC | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| **First Author** | **Year Published** | **Study Design** | **Selection** | **Comparability** | **Exposure** | **Total** |
| **Case definition adequate** | **Representativeness of cases** | **Selection of controls** | **Definition of controls** | **Study controls for age** | **Study controls for any additional factor** | **Ascertainment of exposure** | **Same method of ascertainment for cases and controls** | **Non-response rate similar for both groups** |
| Pascarella | 2009 | RCC | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 7 |
| Turco | 2010 | RCC | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |
| Brown | 2015 | RCC | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 8 |
| Ciricillo  | 2016 | RCC | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |
| Finnerty | 2016 | RCC | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |
| Karaaslan | 2016 | RCC | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 8 |
| Daida | 2017 | RCC | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |

**Supplemental Table 2: Other risk factors not included in meta-analysis**

|  |  |  |
| --- | --- | --- |
| **Risk factor** | **Reference** | **Adjusted OR/HR/RR (95%CI)** |
| Age |  |  |
| Age, per additional year | Guo *et al.*  | RR: 1.06 (1.00-1.12) |
| Age, per additional year | Karaaslan *et al.* | OR: 0.72 (0.6-0.79) |
| Age 4-6 years (ref = 0-3 years) | Daida *et al.* | OR: 0.07 (0.01-0.41) |
| Age >7 years (ref = 0-3 years) | Daida *et al.* | OR: 0.11 (0.02-0.54) |
| Race |  |  |
| Black (reference = white) | Nylund *et al.* | RR: 0.63 (0.58-0.68) |
| Black ALL patients (ref= white ALL) | De Blank *et al.* | HR: 0.346 (0.081–1.478) |
| Hispanic (ref = white) | Nylund *et al.* | RR: 0.78 (0.74-0.83) |
| Asian ALL patients (ref = white ALL) | De Blank *et al.* | HR: 3.190 (1.390-7.309) |
| American Indian ALL patients (ref = white ALL) | De Blank *et al.* | HR: 0.700 (0.050-9.886) |
| Other (ref = white) | Nylund *et al.* | RR: 0.85 (0.77-0.94) |
| Other ALL patients (ref = white ALL)  | De Blank *et al.* | HR: 0.595 (0.182-1.951) |
| Antibiotics exposure |  |  |
| Received 2-3 different abx (ref = received 1) | Guo *et al.* | RR: 0.644 (0.248-1.676) |
| Received >3 different abx (ref = received 1) | Guo *et al.* | RR: 3.808 (1.271-11.409) |
| Antibiotics, per additional day of exposure | Price *et al.* | RR: 1.04 (1.02-1.06) |
| Aminoglycosides | De Blank *et al.* | HR: 1.357 (1.053-1.749) |
| Aminoglycosides in ALL patients | De Blank *et al.* | HR: 1.786 (1.079-2.956) |
| Penicillin in CNS tumor patients | De Blank *et al.* | HR: 3.195 (1.056-9.671) |
| Cephalosporin 3rd generation | De Blank *et al.* | HR: 1.518 (1.177-1.959) |
| Cephalosporin 3rd generation in OS and EWS | De Blank *et al.* | HR: 4.417 (1.230-15.860) |
| Cephalosporin 3rd generation in CNS tumors | De Blank *et al.* | HR: 2.306 (1.120-4.746) |
| Cephalosporin 3rd generation | Guo *et al.* | RR: 1.918 (0.524-7.019) |
| Cephalosporin 4th generation | De Blank *et al.* | HR: 2.383 (1.839-3.089) |
| Cephalosporin 4th generation in ALL | De Blank *et al.* | HR: 2.166 (1.306-3.592) |
| Cephalosporin 4th generation in AML | De Blank *et al.* | HR: 2.272 (1.434-3.599) |
| Cephalosporin 4th generation in OS and EWS | De Blank *et al.* | HR: 4.935 (1.272-14.635) |
| Cephalosporin 3rd or 4th generation | Brown *et al.*  | OR: 0.827 (0.358-1.779) |
| Macrolides  | Guo *et al.* | RR: 0.635 (0.282-1.431) |
| Carbapenem  | Guo *et al.* | RR: 2.958 (1.108-7.899) |
| Carbapenem in CNS tumors | De Blank *et al.* | HR: 3.123 (1.146-8.515) |
| Metronidazole | Guo *et al.* | RR: 0.629 (0.219-1.809) |
| Vancomycin  | Guo *et al.* | RR: 0.924 (0.875-0.976) |
| Gastric acid suppression  |  |  |
| Outpatient acid suppression | Brown *et al.* | OR: 1.017 (0.464-2.230) |
| Outpatient H2RA | Brown *et al.* | OR: 4.583 (1.450-14.488) |
| Immunosuppressive drugs |  |  |
| Chemotherapy | Brown *et al.* | OR: 0.794 (0.325-1.939) |
| Chemotherapy for 0-7 days in CNS tumors | De Blank *et al.* | HR: 2.906 (1.435-5.295) |
| Chemotherapy for 8-14 days  | De Blank *et al.* | HR: 1.942 (1.491-2.529) |
| Chemotherapy for 8-14 days in ALL | De Blank *et al.* | HR: 2.603 (1.317-5.147) |
| Chemotherapy for 8-14 days in AML | De Blank *et al.* | HR: 2.248 (1.253-4.033) |
| Cytarabine, per additional gram | Price *et al.* | RR: 1.01 (0.97-1.06) |
| Corticosteroids | Brown *et al.* | OR: 0.720 (0.367-1.413) |
| Corticosteroids, per additional day | Price *et al.* | RR: 1.02 (0.99-1.06) |
| Immunosuppressive therapy | Brown *et al.* | OR: 0.515 (0.264-1.006) |
| Recent hospitalization |  |  |
| Hospitalization in last 3 months | Ciricillo *et al.* | RR: 2.51 (0.55-11.39) |
| Recent healthcare contact | Guo *et al.* | RR: 0.016 (0.002 – 0.131) |
| Length of current stay, per additional day | Guo *et al.* | RR: 1.051 (1.015-1.087) |
| PICU stay  | Karaaslan *et al.* | OR: 15.6 (3.2-75.8) |
| Hematology/Oncology unit stay | Karaaslan *et al.* | OR: 7.8 (2.0-29.9) |
| Comorbidities |  |  |
| Comorbidities | Guo *et al.* | RR: 1.645 (0.76–3.561) |
| Comorbidities | Santiago *et al.* | RR: 40 (6.8–232.2) |
| IBD | Nylund *et al.* | RR: 11.42 (10.16-12.83) |
| IBD | Pascarella *et al.* | OR: 3.3 (1.5-7.6) |
| Solid organ transplant | Nylund *et al.* | RR: 4.53 (3.92-5.24) |
| Solid organ transplant | Pant *et al.* | RR: 6.6 (6.0-7.3) |
| Hematopoietic stem cell transplant | Nylund *et al.* | RR: 3.31 (2.87-3.82) |
| Neoplastic disease | Nylund *et al.* | RR: 3.10 (2.89-3.31) |
| Solid organ tumors | Karaaslan *et al.* | OR: 6.1 (2.4-15.7) |
| Lymphoma (ref = leukemia) | De Blank *et al.* | HR: 0.98 (0.669-1.436) |
| Non-CNS solid tumors (ref = leukemia) | De Blank *et al.* | HR: 1.467 (1.105-1.948) |
| CNS tumors (ref = leukemia) | De Blank *et al.* | HR: 1.073 (0.741-1.553) |
| Other malignancies (ref = leukemia) | De Blank *et al.* | HR: 1.434 (0.98-2.10) |
| Hematologic disorder | Nylund *et al.* | RR: 2.50 (2.34-2.66) |
| HIV infection | Nylund *et al.* | RR: 4.09 (3.16-5.30) |
| Fungal infection | Nylund *et al.* | RR: 2.71 (2.39-3.07) |
| Bacterial infection | Nylund *et al.* | RR: 1.84 (1.74-1.94) |
| Bacteremia | Price *et al.* | RR: 2.33 (1.21-4.48) |
| Sterile site infection | Price *et al.* | RR: 2.92 (1.54-5.55) |
| Fever, per additional day | Price *et al.* | RR: 1.05 (1.02-1.08) |
| Cystic fibrosis | Nylund *et al.* | RR: 2.65 (2.22-3.17) |
| Pancreatitis | Nylund *et al.* | RR: 2.86 (2.41-3.39) |
| Nasogastric/gastrostomy tube placement | Guo *et al.* | RR: 3.031 (1.011-9.089) |
| Gastrostomy | Nylund *et al.* | RR: 2.00 (1.67-2.39) |
| Liver disease | Nylund *et al.* | RR: 2.04 (1.80-2.32) |
| Malnutrition | Nylund *et al.* | RR: 2.39 (2.14-2.67) |
| Malnutrition | Karaaslan *et al.* | OR: 7.0 (1.3-36.7) |
| Renal disease | Nylund *et al.* | RR: 2.09 (1.99-2.19) |
| SLE | Nylund *et al.* | RR: 2.06 (1.58-2.68) |
| GERD | Nylund *et al.* | RR: 1.97 (1.76-2.20) |
| Cardiac disease | Nylund *et al.* | RR: 1.38 (1.23-1.56) |
| Congenital heart disease | Karaaslan *et al.* | OR: 4.5 (1.1-18.6) |
| Appendicitis | Nylund *et al.* | RR: 1.46 (1.28-1.66) |
| Asthma | Nylund *et al.* | RR: 0.54 (0.49-0.59) |
| Obesity | Price *et al.* | RR: 2.79 (1.24-6.28) |
| Prior ventilator use in OS and EWS  | De Blank *et al.* | HR: 0.855 (0.154-4.744) |
| Prior pressor use in OS and EWS | De Blank *et al.* | HR: 3.724 (0.680-20.400) |
| Prior ventilator and pressor use in OS and EWS | De Blank *et al.* | HR: 34.969 (4.709-259.703) |
| Laboratory parameters |  |  |
| Hemoglobin | Guo *et al.* | RR: 3.207 (1.4-7.343) |
| WBC  | Guo *et al.* | RR: 2.875 (1.308-6.317) |
| Neutropenia  | Price *et al.* | RR: 1.24 (0.59-2.61) |
| Neutropenia | Daida *et al.* | OR: 1.11 (1.01-1.22) |
| Neutropenia > 15 days | Price *et al.* | RR: 2.84 (1.27-6.34) |
| CRP | Guo *et al.* | RR: 5.286 (2.594-10.774) |
| Albumin | Guo *et al.* | RR: 7.493 (3.104-18.088) |
| IgG | Guo *et al.* | RR: 1.852 (0.716-4.793) |
| IgA | Guo *et al.* | RR: 0.952 (0.313-2.898) |
| Other  |  |  |
| Midwest region of USA (ref = northeast) | Nylund *et al.* | RR: 0.94 (0.86-1.02) |
| Southern region of USA (ref = northeast) | Nylund *et al.* | RR: 0.80 (0.76-0.85) |
| Western region of USA (ref = northeast) | Nylund *et al.* | RR: 1.08 (1.02-1.15) |
| Metropolitan area (ref = rural) | Nylund *et al.* | RR: 1.42 (1.29-1.59) |
| Public insurance (ref = private) | Nylund *et al.* | RR: 0.80 (0.76-0.85) |
| Uninsured (ref = private) | Nylund *et al.* | RR: 0.80 (0.73-0.88) |
| HCUP year 2000 (ref = 1997) | Nylund *et al.* | RR: 1.07 (0.98-1.16) |
| HCUP year 2003 (ref = 1997) | Nylund *et al.* | RR: 1.35 (1.25-1.46) |
| HCUP year 2006 (ref = 1997) | Nylund *et al.* | RR: 1.87 (1.74-2.01) |
| Sharing ward with CDI patient | Daida *et al.* | OR: 1.60 (0.31-8.14) |
| Clinical assessment scale (author-derived) | Santiago *et al.* | RR: 0.8 (0.7-0.9) |
| NSAIDS | Guo *et al.* | RR: 9.0 (3.232-25.061) |

Ref = reference group

Abx = antibiotics

ALL = acute lymphoblastic leukemia

AML = acute myeloid leukemia

OS = osteosarcoma

EWS = Ewing sarcoma

IBD = inflammatory bowel disease

SLE = systemic lupus erythematosus

GERD = gastroesophageal reflux

WBC = white blood count

HCUP = Healthcare Utilization Project

CDI = *Clostridium difficile* infection

|  |  |  |  |
| --- | --- | --- | --- |
| **Section/topic**  | **#** | **Checklist item**  | **Reported on page #**  |
| **TITLE**  |  |
| Title  | 1 | Identify the report as a systematic review, meta-analysis, or both.  | 1 |
| **ABSTRACT**  |  |
| Structured summary  | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.  | 3 |
| **INTRODUCTION**  |  |
| Rationale  | 3 | Describe the rationale for the review in the context of what is already known.  | 4 |
| Objectives  | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).  | 4 |
| **METHODS**  |  |
| Protocol and registration  | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.  | 5 |
| Eligibility criteria  | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.  | 5 |
| Information sources  | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.  | 5 |
| Search  | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.  | 5 |
| Study selection  | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).  | 5-6 |
| Data collection process  | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.  | 5 |
| Data items  | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.  | 6 |
| Risk of bias in individual studies  | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.  | 7 |
| Summary measures  | 13 | State the principal summary measures (e.g., risk ratio, difference in means).  | 6 |
| Synthesis of results  | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.  | 6 |

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|  |  |  |  |
| --- | --- | --- | --- |
| **Section/topic**  | **#** | **Checklist item**  | **Reported on page #**  |
| Risk of bias across studies  | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).  | 7 |
| Additional analyses  | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.  | 6 |
| **RESULTS**  |  |
| Study selection  | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.  | Fig. 1 |
| Study characteristics  | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.  | Table 1 |
| Risk of bias within studies  | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).  | Supp. 1 |
| Results of individual studies  | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.  | Figs. 2-4 |
| Synthesis of results  | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.  | 8-9 |
| Risk of bias across studies  | 22 | Present results of any assessment of risk of bias across studies (see Item 15).  | N/A |
| Additional analysis  | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).  | 8 |
| **DISCUSSION**  |  |
| Summary of evidence  | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).  | 9-10 |
| Limitations  | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).  | 11-12 |
| Conclusions  | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.  | 12 |
| **FUNDING**  |  |
| Funding  | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.  | 1 |

*From:*  Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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

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