
Search strategy: MEDLINE (PubMed)
1. Search "Crohn Disease"[Mesh]
2. Search crohns
3. Search crohn
4. Search crohn's
5. Search ileitis
6. Search Regional Enteritis
7. Search Granulomatous Enteritis
8. Search Inflammatory Bowel Disease 1
9. Search ileocolitis
10. Search 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. Search infliximab [Supplemental concept]
12. Search infliximab
13. Search remicade
14. Search inflectra
15. Search remsim
16. Search avakin
17. Search revellex
18. Search 11 or 12 or 13 or 14 or 15 or 16 or 17
19. Search "Adolescent"[Mesh]
20. Search "Child"[Mesh]
21. Search "Infant"[Mesh]
22. Search "Pediatrics"[Mesh]
23. Search infant*
24. Search infancy
25. Search newborn*
26. Search baby*
27. Search babies
28. Search neonat*
29. Search preterm
30. Search prematur*
31. Search postmatur*
32. Search child*
33. Search kid
34. Search kids
35. Search toddler
36. Search toddler *
37. Search adoles*
38. Search teen*
39. Search boy
40. Search boys
41. Search girl *
42. Search pediatric*
43. Search paediatric*
44. Search 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
45. Search 10 and 18 and 44

Search Strategy: Embase
1. exp Crohn disease /
2. crohns.mp.
3. crohn.mp.
4. crohn's.mp.
5. ileitis.mp.
6. Regional Enteritis.mp.
7. Granulomatous Enteritis.mp.
8. Inflammatory Bowel Disease 1.mp.
9. ileocolitis.mp.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. infliximab /
12. remicade.mp.
13. infliximab.mp.
14. inflectra.mp.
15. remsim.mp.
16. avakine.mp.
17. revellex.mp.
18. 11 or 12 or 13 or 14 or 15 or 16 or 17
19. exp child/
20. exp adolescent /
21. exp infant /
22. pediatrics / or exp neonatology /
23. infant .mp.
24. infancy.mp.
25. newborn* .mp.
26. baby* .mp.
27. babies.mp.
28. neonat*.mp.
29. preterm*.mp.
30. prematur*.mp.
31. postmatur*.mp.
32. child*.mp.
33. kid.mp.
34. kids.mp.
35. toddler.mp.
36. toddler*.mp.
37. adoles*.mp.
38. teen*.mp.
39. boy.mp.
40. boys.mp.
41. girl*.mp.
42. pediatric*.mp.
43. paediatric*.mp.
44. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
45. 10 and 18 and 44

Note: [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

**Search Strategy: CENTRAL**

1. crohns.mp.
2. crohn.mp.
3. crohn's.mp.
4. Ileitis.mp.
5. Regional Enteritis.mp.
7. Inflammatory Bowel Disease.mp.
8. Ileocolitis.mp.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. remicade.mp.
11. inflectra.mp.
12. remsima.mp.
13. infliximab.mp.
14. 10 or 11 or 12 or 13
15. infant*.mp.
16. infancy.mp.
17. newborn*.mp.
18. baby*.mp.
19. babies.mp.
20. neonat*.mp.
21. preterm*.mp.
22. prematur*.mp.
23. postmatur*.mp.
24. child*.mp.
25. kid.mp.
26. kids.mp.
27. toddler.mp.
28. toddler*.mp.
29. adole*.mp.
30. teen*.mp.
31. boy.mp.
32. boys.mp.
33. girl*.mp.
34. pediatric*.mp.
35. paediatric*.mp.
36. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
37. 9 and 14 and 36
38. crohns.mp.
39. crohn.mp.
40. crohn's.mp.
41. Ileitis.mp.
42. Regional Enteritis.mp.
43. Granulomatous Enteritis.mp.
44. Inflammatory Bowel Disease.mp.
45. Ileocolitis.mp.
46. 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45
47. remicade.mp.

48. inflectra.mp.
49. avakin.mp.
50. revellex.mp.
51. remsima.mp.
52. infliximab.mp.
53. 47 or 48 or 49 or 50 or 51 or 52
54. infant*.mp.
55. infancy.mp.
56. newborn*.mp.
57. baby*.mp.
58. babies.mp.
59. neonat*.mp.
60. preterm*.mp.
61. prematur*.mp.
62. postmatur*.mp.
63. child*.mp.
64. kid.mp.
65. kids.mp.
66. toddler.mp.
67. toddler*.mp.
68. adole*.mp.
69. teen*.mp.
70. boy.mp.
71. boys.mp.
72. girl*.mp.
73. pediatric*.mp.
74. paediatric*.mp.
75. 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74
76. 46 and 53 and 75

Note: [mp=title, original title, abstract, mesh headings, heading words, keyword]

**Search Strategy: ClinicalTrials.gov**

Advanced Search was selected.
The following search terms were entered:
Condition: crohn
Intervention: infliximab
Age group: child (birth - 17 years)

**Search Strategy: EU Trials Register**

Advanced Search was selected.
The following search terms were entered: infliximab
AND crohn
The following filters were applied: Age group - Children and Adolescent


Search Strategy: WHO International Clinical Trials Registry Platform
Advanced Search as selected. Trials in both Searches 1 and 2 were included in screening process.

Search 1:
- infliximab AND crohn in Title
- “Search for clinical trials in children” checked

Search 2:
- Crohn in Condition
- infliximab in Intervention
- “Search for clinical trials in children” checked

After Search 1 and 2 were completed, duplicate entries were merged.

Search Strategy: Conference proceedings
Abstracts from the following conferences were identified through the respective conference websites, if available.
1. Digestive Diseases Week (American):
   http://www.ddw.org/
2. Canadian Digestive Disease Week (Canadian):
   http://www.cag-acg.org/annual-conference-cddw
3. United European Gastroenterology Week (European):
   https://www.ueg.eu/week/
4. Advances in Inflammatory Bowel Disease
   (Crohn’s & Colitis Foundation):
   http://www.advancesinibd.com/
5. European Crohn’s and Colitis Organisation (ECCO):
   https://www.ecco-ibd.eu/publications/congress-abstract-s/

Search Strategy: Regulatory documents
Regulatory documents from FDA and EMA were searched:
- EMEA
  Search terms: active substance or common name: infliximab
  Pediatric decisions searched
- FDA
  Search terms: search by drug name: infliximab

Search Strategy: Manufacturer clinical trials
Searched “infliximab” in Janssen Clinical Trials Registry.

Search Strategy: Reference lists
Hand-searching of reference lists of relevant systematic reviews and included articles occurred after title and abstract screening and full-text screening.
Appendix 2: Outcome definitions from individual trials. Note: Reference numbering here is based on the reference list in the main article. For details about each study, see Table 1 in the main article.

**Endoscopic remission (complete MH)**
- Endoscopic lesion severity score using 10-cm visual analogue scale, 0 = healed, 10 = very severe disease (Baldassano et al. [2003]44)
- HBI < 5, ESR < 20 mm/h, and/or fistula closure, completely weaned from steroids (Ruemmele et al. [2009]44)
- CDEIS ≤ 3 (Luo et al. [2017]45)
- CDEIS score = 2 (Muhammed et al. [2014]41)
- Disappearance of ulcerations, multiple erosions, bleeding, and friability (grade 0 - complete normalization) (Olbjorn et al. [2014]49)
- SES-CD score = 0, no ulcers or other mucosal lesions like erosion and inflammation (Kang et al. [2016]41)
- SES-CD = 0–1, no signs of active inflammation of any colonic segment or in terminal ileum (Nuti et al. [2016]26)

**Partial mucosal healing**
- Disappearance of ulcerations, multiple erosions, bleeding, and friability (grade 1 - light hyperemia and granularity) (Olbjorn et al. [2014]49)
- Reduction of 50% in SES-CD from baseline, no endoscopic healing, no variation or worsening of SES-CD (Nuti et al. [2016]26)

**Clinical remission**
- PGA of inactive disease at every assessment point during follow-up (0–1, 1–2, 2–3 years) while receiving IFX without concomitant CS use or surgery (Hyams et al. [2009]40)
- PCDAI < 10 or modified CDAI < 150 (Baldassano et al. [2003]39)
- PCDAI ≤ 10 (Lee et al. [2015],44 Hyams et al. [2007],44 Kang et al. [2016],41 Luo et al. [2017]49)
- PCDAI ≤ 10 and CS-free (Walters et al. [2014]29)
- PCDAI ≤ 10 and no symptoms related to CD (Nuti et al. [2016]26)
- Inactive disease for ≥ 2 years follow-up on a 3-point scale based on PCDAI/PGA scores (Wauters et al. [2016]26)
- PCDAI ≤ 10 and free of surgery (Hyams et al. [2013]32)
- Initial PCDAI perirectal subscore of 5 or 10 decreasing to 0 (Crandall et al. [2009]39)

**Clinical response**
- PGA of mild or inactive disease at every assessment point during follow-up (0–1, 1–2, 2–3 years) while receiving IFX without concomitant CS use or surgery (Hyams et al. [2009]40)
- ≥ 10 point improvement in PCDAI or ≥ 70 point reduction in modified CDAI (Baldassano et al. [2003]39)
- Initial perirectal subscore of 10 decreasing to 5 (Crandall et al. [2009]39)
- Decrease from baseline in PCDAI score of ≥ 15 points, with total score ≤ 30 (Hyams et al. [2007]40)
- PCDAI reduction ≥ 15 or final PCDAI ≤ 10 (Lee et al. [2015],44 Luo et al. [2017],42 Chen and Luo [2016]47)
- PCDAI reduction ≥ 15 (Nuti et al. [2016]26)

Definitions: CD = Crohn disease, CDEIS = Crohn Disease Endoscopic Index of Severity, CS = corticosteroid, ESR = erythrocyte sedimentation rate, HBI = Harvey–Bradshaw Index, IFX = infliximab, MH = mucosal healing, PCDAI = Pediatric Crohn Disease Activity Index, PGA = physician global assessment, SES-CD = Simple Endoscopic Score for Crohn Disease.

Appendix 3 (Part 1 of 3): Risk of bias in individual studies and across studies (see Table 1 for reference numbering).

Part A. Risk of bias in individual randomized controlled trials, assessed with the Cochrane risk-of-bias tool.

Part B. Risk of bias across randomized controlled trials, assessed with the Cochrane risk-of-bias tool.

Appendix 3 (Part 2 of 3): Risk of bias in individual studies and across studies (see Table 1 for reference numbering).

<table>
<thead>
<tr>
<th>Study</th>
<th>Representativeness of the exposed cohort</th>
<th>Selection of the non-exposed cohort</th>
<th>Ascertainment of exposure</th>
<th>Demonstration that outcome of interest was not present at start of study</th>
<th>Comparability of cohorts on the basis of the design of analysis</th>
<th>Assessment of outcome</th>
<th>Adequacy of follow-up of cohorts</th>
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</tr>
</tbody>
</table>

Part C. Risk of bias in individual prospective cohort studies, assessed with the Ottawa–Newcastle tool.

Appendix 3 (Part 3 of 3): Risk of bias in individual studies and across studies (see Table 1 for reference numbering).

<table>
<thead>
<tr>
<th>Category</th>
<th>Bias Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representativeness of the exposed cohort</td>
<td>Low</td>
</tr>
<tr>
<td>Selection of the non exposed cohort</td>
<td>Low</td>
</tr>
<tr>
<td>Ascertainment of exposure</td>
<td>Low</td>
</tr>
<tr>
<td>Demonstration that outcome of interest was not present at start of study</td>
<td>Unclear</td>
</tr>
<tr>
<td>Comparability of cohorts on the basis of the design or analysis</td>
<td>Low</td>
</tr>
<tr>
<td>Assessment of outcome</td>
<td>Low</td>
</tr>
<tr>
<td>Was follow-up long enough for outcomes to occur</td>
<td>High</td>
</tr>
<tr>
<td>Adequacy of follow up of cohorts</td>
<td>Low</td>
</tr>
</tbody>
</table>

Part D. Risk of bias across prospective cohort studies, assessed with the Ottawa–Newcastle tool.