

Stem cells as therapy for necrotizing enterocolitis: a systematic review and meta-analysis of preclinical studies

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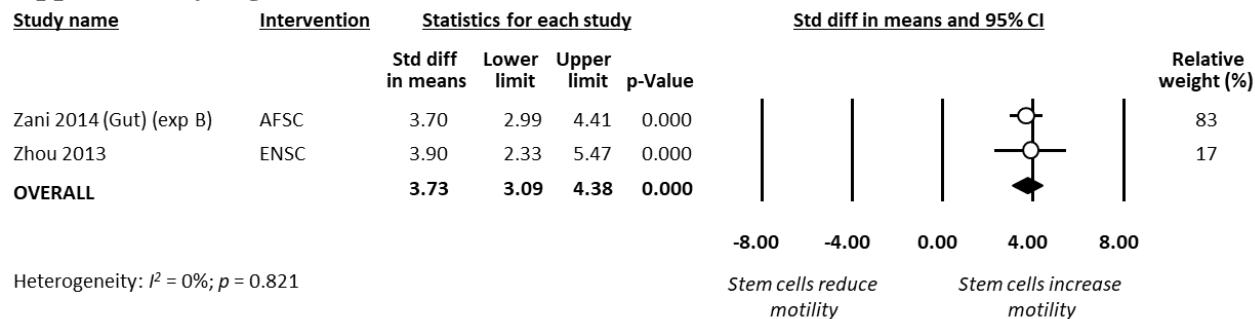
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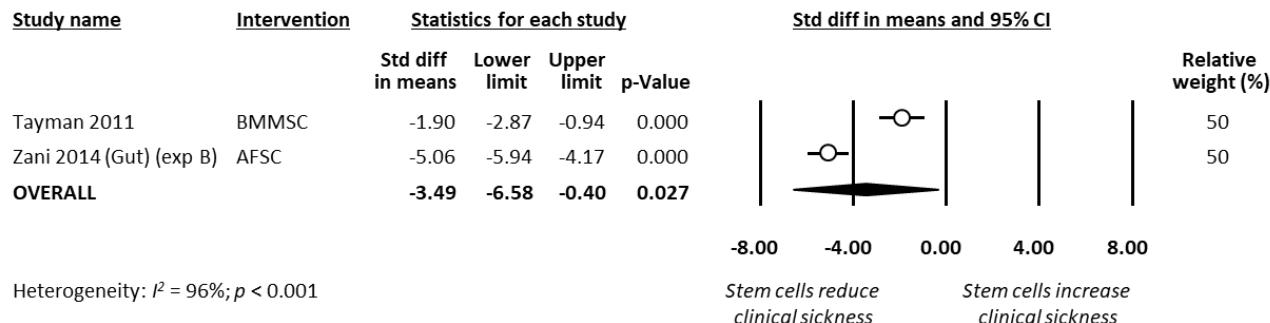
Supplementary Material

1 Supplementary Figures



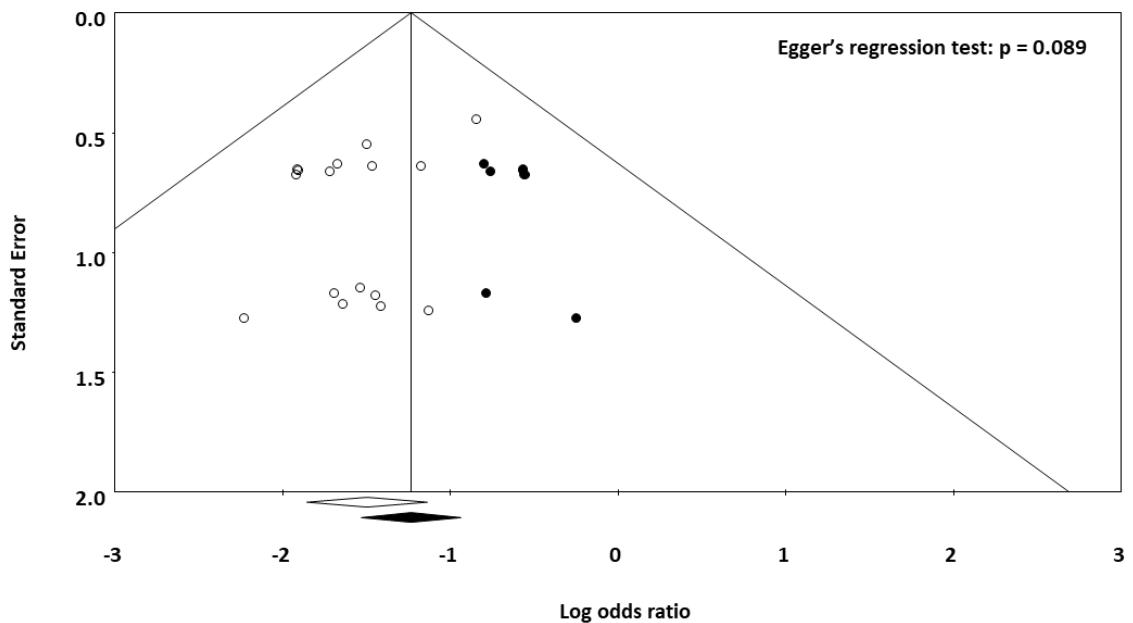
Supplementary Figure 1. Meta-analysis on stem cells and intestinal motility following necrotizing enterocolitis (NEC).

AFSC: amniotic fluid stem cells; ENSC: enteric neural stem cells.

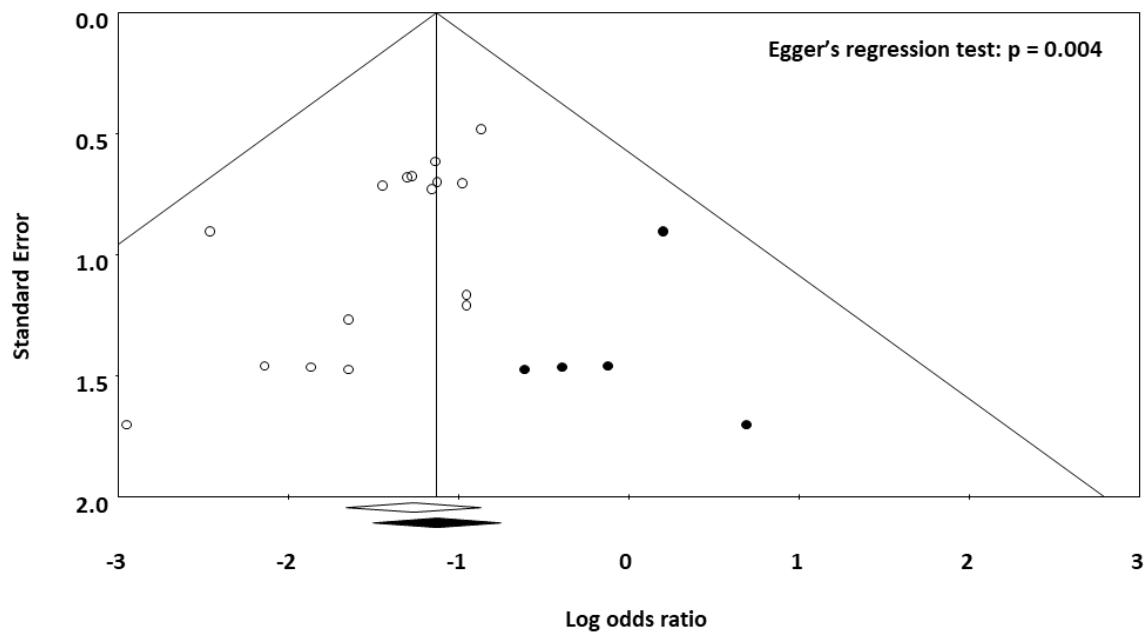


Supplementary Figure 2. Meta-analysis on stem cells and clinical sickness score following necrotizing enterocolitis (NEC).

AFSC: amniotic fluid stem cells; BMMSC: bone marrow mesenchymal stem cells.



Supplementary Figure 3. Funnel plot of publication bias of the analysis on stem cells/stem cell-derived products and incidence of any grade necrotizing enterocolitis (NEC). The white dots represent the sample studies and the black dots represent the studies that have been added by the trim-and-fill.



Supplementary Figure 4. Funnel plot of publication bias of the analysis on stem cells/stem cell-derived products and incidence of grade 3-4 necrotizing enterocolitis (NEC). The white dots represent the sample studies and the black dots represent the studies that have been added by the trim-and-fill.

2 Supplementary Tables

Supplementary Table 1. Sensitivity meta-analyses of stem cells and necrotizing enterocolitis, removing studies with non-rat animals and studies that use stem cell exosomes.

| Outcome | Result original meta-analysis | 95% CI | Sensitivity analysis | Result modified meta-analysis | 95% CI |
|-------------------------|-------------------------------|----------------|---|-------------------------------|----------------|
| Any grade NEC | OR 0.22 | 0.16 to 0.32 | Remove non-rat (i.e. mouse) study, Wei et al. 2015 | OR 0.20 | 0.13 to 0.29 |
| Grade 2 NEC | OR 0.44 | 0.27 to 0.71 | | OR 0.36 | 0.21 to 0.61 |
| Grade 3-4 NEC | OR 0.28 | 0.19 to 0.42 | | OR 0.26 | 0.17 to 0.40 |
| Intestinal permeability | SMD -3.48 | -3.90 to -3.05 | | SMD -3.55 | -4.05 to -3.05 |
| Any grade NEC | OR 0.22 | 0.16 to 0.32 | Remove interventions with stem cell exosomes | OR 0.23 | 0.15 to 0.35 |
| Grade 2 NEC | OR 0.44 | 0.27 to 0.71 | | OR 0.33 | 0.15 to 0.71 |
| Grade 3-4 NEC | OR 0.28 | 0.19 to 0.42 | | OR 0.30 | 0.19 to 0.47 |
| Intestinal permeability | SMD -3.48 | -3.90 to -3.05 | | SMD -3.59 | -4.06 to -3.11 |

NEC: necrotizing enterocolitis.

3 Systematic search

PubMED search: 1100 hits

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AND

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AND SYRCLE animal filter

EMBASE search: 530 hits

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AND

((exp Necrotizing Enterocolitis/ OR NEC.ti,ab,kw. OR exp Enterocolitis/ OR Pneumatosis Intestinalis.ti,ab,kw. OR exp newborn hypoxia/ OR Necrotizing.ti,ab,kw. OR Necrotize.ti,ab,kw. OR Necrotising.ti,ab,kw. OR Necrotise.ti,ab,kw. OR Necroticans.ti,ab,kw.) OR ((exp prematurity/ OR exp newborn disease/ OR infan*.ti,ab,kw. OR Neonatal Prematurity.ti,ab,kw. OR Extremely Preterm Infant*.ti,ab,kw. OR Newborn*.ti,ab,kw. OR Neonate*.ti,ab,kw. OR neonatal.ti,ab,kw. OR exp Low Birth Weight/ OR Decreased gestational age.ti,ab,kw. OR premature gestation.ti,ab,kw. OR prematurity.ti,ab,kw.) AND (exp intestine injury/ OR intestinal injury.ti,ab,kw. OR gut injury.ti,ab,kw. OR gastrointestinal.ti,ab,kw. OR Gastrointestinal Disease*.ti,ab. OR Cholera Infantum.ti,ab,kw. OR Functional Gastrointestinal Disorder*.ti,ab,kw. OR Intestinal Disease*.ti,ab,kw. OR intestinal inflammation.ti,ab,kw. OR gut ischaemia.ti,ab,kw. OR enterocolitis ulcerosa necroticans.ti,ab,kw. OR Enterocolitides.ti,ab,kw. OR exp pseudomembranous colitis/ OR Pseudomembranous Enterocolitis.ti,ab,kw. OR Pseudomembranous Enteritis.ti,ab,kw. OR Pseudomembranous Colitis.ti,ab,kw. OR Antibiotic Associated Colitis.ti,ab,kw. OR Antibiotic Associated Colitis.ti,ab,kw. OR Clostridium Enterocolitis.ti,ab,kw. OR exp neutropenic enterocolitis/ OR Neutropenic Enterocolitis.ti,ab,kw. OR typhlitis.ti,ab,kw. OR exp Pneumatosis Intestinalis/ OR Pneumatosis Intestinalis.ti,ab,kw. OR pneumatosis intestinalis.ti,ab,kw. OR exp Pneumoperitoneum/ OR exp Mesenteric Ischemia/ OR Mesenteric Ischemia*.ti,ab,kw. OR mesentery ischemia*.ti,ab,kw. OR Mesenteric Vascular Insufficiency.ti,ab,kw. OR Mesenteric Vascular Insufficiencies.ti,ab,kw. OR Ulcer*.ti,ab,kw.)))

AND **SYRCLE animal filter:** (exp animal experiment/ or exp animal model/ or exp experimental animal/ or exp transgenic animal/ or exp male animal/ or exp female animal/ or exp juvenile animal/ OR animal/ OR chordata/ OR vertebrate/ OR tetrapod/ OR exp fish/ OR amniote/ OR exp amphibia/ OR mammal/ OR exp reptile/ OR exp sauropsid/ OR therian/ OR exp monotreme/ OR placental mammals/ OR exp marsupial/ OR Euarchontoglires/ OR exp Afrotheria/ OR exp Boreoeutheria/ OR exp Laurasiatheria/ OR exp Xenarthra/ OR primate/ OR exp Dermoptera/ OR exp Glires/ OR exp Scandentia/ OR Haplorrhini/ OR exp prosimian/ OR simian/ OR exp tarsiiform/ OR Catarrhini/ OR exp Platyrrhini/ OR ape/ OR exp Cercopithecidae/ OR hominid/ OR exp hylobatidae/ OR exp chimpanzee/ OR exp gorilla/ OR exp orang utan/ OR (animal OR animals OR pisces OR fish OR fishes OR catfish OR catfishes OR sheatfish OR silurus OR arius OR heteropneustes OR clarias OR gariepinus OR fathead minnow OR fathead minnows OR pimephales OR promelas OR cichlidae OR trout OR trouts OR char OR chars OR salvelinus OR salmo OR oncorhynchus OR guppy OR guppies OR millionfish OR poecilia OR goldfish OR goldfishes OR carassius OR auratus OR mullet OR mullets OR mugil OR curema OR shark OR sharks OR cod OR cuds OR gadus OR morhua OR carp OR carps OR cyprinus OR carpio OR killifish OR eel OR eels OR anguilla OR zander OR sander OR lucioperca OR stizostedion OR turbot OR turbots OR

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Supplementary Material

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