Review Title
Efficacy and safety of mesenchymal stromal cell therapy in preclinical models of acute lung injury: a systematic review

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Conflicts of Interest
Duncan Stewart is President and CEO of Northern Therapeutics.
Shirley Mei is an employee of Northern Therapeutics.
Malcolm Macleod is a member of the UK Home Office Animals in Science Committee.
The remaining team members have no competing interests to declare.

Review Question
In preclinical studies of acute lung injury, do MSCs reduce death and the severity of acute lung injury as described by the American Thoracic Society preclinical acute lung injury consensus conference [1], and do they enhance pathogen clearance in infectious acute lung injury models?

Searches
Search strategies will be developed in conjunction with an information specialist and a librarian. Ovid MEDLINE®, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, and EMBASE Classic+ EMBASE. We will also search BIOSIS and Web of Science. The example strategy listed in the attached Appendix was used to search in MEDLINE and EMBASE. In addition, a manual review of the bibliographies of selected articles and relevant reviews will be performed.

Condition Being Studied.
Acute respiratory distress syndrome (ARDS) is a condition characterized by the presence of severe hypoxemia and diffuse radiographic infiltration. It is most commonly caused by infection, affects nearly 20 000 Canadians yearly and is associated with a mortality rate of 35 - 45% despite intensive care management and mechanical ventilation. ARDS is associated with an unchecked pro-inflammatory response that disrupts pulmonary endothelial and capillary epithelial integrity and results in fluid and protein accumulation within the lungs.

Mesenchymal stromal cells (MSCs) could represent a promising new therapy for ARDS. Evidence suggests that exogenously administered MSCs home to areas of inflammation, dampen pro-inflammatory responses, reduce pulmonary dysfunction, and increase bacterial clearance. Several preclinical studies examining MSCs in acute lung injury have been published, but the evidence for MSC therapy in this condition has not been systematically reviewed. A systematic review of preclinical evidence is essential to provide a detailed review of the efficacy of MSCs in preclinical acute lung injury and to aid the design of a future clinical trial.

Participants / Population
Inclusion: Preclinical in vivo models of acute lung injury that mimic the pathophysiology of human patients with ARDS. The American Thoracics Society consensus criteria for preclinical acute lung injury will be used as a reference [1]. Model of lung injury will include those caused by direct infection in the lung (e.g. intratracheal endotoxin or intratracheal bacteria), chemical or chemotherapeutic causes (e.g. bleomycin induced lung injury, oleic acid) and indirect or systemic infection (e.g. systemic endotoxin, cecal-ligation and puncture), trauma, shock (e.g. hemorrhagic), remote organ injury (e.g. pancreatitis), and ventilator induced lung injury.

Exclusion: In vitro studies and neonatal animal models of acute lung injury.

Interventions
Exclusion: Differentiated mesenchymal stromal cells (e.g. MSC differentiated to an endothelial cell); co-treatment with another therapy or cell type; mesenchymal stromal cells engineered to over or under express particular genes.

Comparator / Control
Animals that have had experimental acute lung injury induced but have not been administered MSCs.

Types of Studies to be Included
Eligible studies include controlled comparative studies (randomized, quasi-randomized, and non-randomized) of preclinical acute lung injury.

Outcomes:
Primary Endpoint:
Death (<2 days, 2-4 days, >4 days)

Secondary Endpoints:
Four key features of preclinical acute lung injury as defined by the American Thoracic Society [1]
1. Histologic evidence of lung injury (e.g. lung injury score)
2. Alteration of the alveolar capillary barrier (e.g. increased albumin in bronchoalveolar lavage fluid)
3. Inflammatory response (e.g. pulmonary neutrophils)
4. Measures of physiological dysfunction (e.g. increased alveolar – arterial gradient of oxygen concentration)

Bacterial clearance in infectious models of acute injury
All secondary endpoints will be analyzed in categories of time from induction of acute injury (<6 h, 6-24 h, >24 h)

Data Extraction
Two independent reviewers will review studies and extract data into standardized, piloted forms. Discrepancies will be resolved through discussion with the principal investigator.

Risk of Bias Assessment
Since no standardized and validated tool exists to evaluate risk of bias in preclinical studies, we will describe the biases using The Cochrane Risk of Bias Assessment Tool [2]. Items include concealment of allocation, random sequence generation, blinding of personnel and endpoint measurements, and completeness of endpoint reporting. Each criteria will be assigned a value of low, high, or unclear risk of bias for each included study.

Assessment of Construct and External Validity [3]
Construct validity will be assessed in relation to the extent the experimental systems models the clinical entity of ARDS. Elements to be recorded include type, age, gender of animals as well as any intercurrent illness or use of co-interventions (e.g. fluid resuscitation). External validity will be evaluated in relation to the replicability of the cause and effect relationship under varied conditions (e.g. use of a multicentre preclinical study).

Description of Reporting
We will describe the quality of reporting of included studies using elements of the ARRIVE Guidelines (Animal Research: Reporting in vivo Experiments) [4].

Strategy for Data Synthesis
Results from outcomes with discrete data (e.g. death) will be pooled and meta-analysis will be performed with inverse variance random effects modeling. Data will be expressed as odds ratios and 95 percent confidence intervals.
Dichotomous endpoints (e.g. death) from each included study will be pooled and described as odds ratios and 95% confidence intervals. A random effects modeling approach with the use of Forest plots for presentation of the data [5]. Continuous endpoints will be pooled using the ratio of weighted means method with inverse variance random effects modeling [6]. Statistical heterogeneity of included preclinical studies will be measured using the $I^2$ test with 95% uncertainty intervals [7]. An evaluation for the presence of publication bias will be conducted with funnel plot techniques, and Egger’s regression test [8].

Planned sensitivity analyses will examine heterogeneity of the primary endpoint death. These will be carried out according to risk of bias assessments. Several subgroup analyses to examine preclinical heterogeneity will be conducted on the primary endpoint death. These will include: definition of death, the type of animal model, animal age, sex, strain, presence of co morbidities, type and severity acute lung injury, MSC preparation, timing of administration of MSCs from induction of acute lung injury, route of MSC administration, type of controls, use of co-interventions, antibiotics, mechanical ventilation, single versus multi-centre study, and presence of an a priori sample size calculation. These subgroup analyses are exploratory and the results will be interpreted with caution.

A detailed version of this protocol has been submitted for publication.
Reference List


Appendix – Representative Search Strategy

Database: Embase Classic+Embase <1947 to 2013 June 05>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Search Strategy:

1  Mesenchymal Stem Cells/ (34040)
2  Mesenchymal Stem Cell Transplantation/ (8987)
3  Multipotent Stem Cells/ (5907)
4  Mesenchymal Stromal Cells/ (14974)
5  ((mesenchymal adj3 (stem or stroma$1 or progenitor*)) and (cell$1 or cell-induced)).tw. (44453)
6  (MSC or MSCs or ADMSC or ADMSCs or BM-MSC or BM-MSCs or BMD-MSC or BMD-MSCs or BM-MSCs or BM-MSCs or BMSC or BMSCs or HBMSC or HBMSCs or ABMSC or ABMSCs or MAPC or MAPCs).tw. (35768)
7  (((multipotent or multi-potent) adj3 (stem or stroma$1 or progenitor*)) and (cell$1 or cell-induced)).tw. (8725)
8  ((marrow* adj3 (stem or stroma$1 or progenitor*)) and (cell$1 or cell-induced)).tw. (43339)
9  (exp Bone Marrow Cells/ or Bone Marrow Transplantation/) and (exp Stem Cells/ or exp Stem Cell Transplantation/ or Stem Cell Nichel/)(77540)
10 (colony-forming unit fibroblast* or CFU-F$1).tw. (1415)
11 exp Mesoderm/cy [Cytology] (5943)
12 exp Adult Stem Cells/ (7455)
13 ((adult* adj3 (stem or stroma$1 or progenitor*)) and (cell$1 or cell-induced)).tw. (17001)
14 ((fibroblast-derived adj3 (stem or stroma$1 or progenitor*)) and (cell$1 or cell-induced)).tw. (40)
15 IPS cell$1.tw. (3176)
16 or/1-15 (174293)
17 exp Stem Cell Transplantation/ (128846)
18 exp Gene Therapy/ (96802)
19 Mesenchymal.tw. (116010)
20 (17 or 18) and 19 (11653)
21 16 or 20 (174617)
22 exp Adult Stem Cells/ (7455)
23 exp Lung/pa, pp [Pathology, Physiopathology] (73140)
24 ((lung$1 or pulmonary) adj3 (disease* or injur* or contusion* or embolism* or haemorrhag* or hemorrhag* or infection* or trauma*).tw. (338023)
25 exp Respiratory Distress Syndrome, Adult/ (34780)
26 (acute or adult) adj respiratory distress syndrome).tw. (24402)
27 (ARDS or ARDSS).tw. (17412)
28 (shock adj1 lung).tw. (1093)
29 exp Acute Lung Injury/ (9987)
30 (lung injur* adj1 acute).tw. (19950)
31 ali.tw. (9000)
32 exp Respiratory Insufficiency/ (113996)
33 ((respiratory or ventilatory) adj3 (insufficien* or deficien* or disturbance* or dysfunction* or depression or failure or paralys#s)).tw. (97062)
34 exp Systemic Inflammatory Response Syndrome/ (261293)
35 "inflammatory response syndrome" adj1 systemic).tw. (6469)
36 (sepsis or septic* or bacteremia or bacteraemia or endotoxic* or endotoxemi* or endotoxaemi*).tw. (293213)
37 exp Hyperoxia/ (9036)
38 hyperoxi*.tw. (16180)
39 exp Reperfusion Injury/ (64760)
40 ((pulmonary or lung$1 or nonpulmonary or non-pulmonary) adj3 (ischemi* or ischaemi* or reperfusion*)).tw. (4926)
41 exp Peritonitis/ (67720)
42 peritonitis.tw. (57018)
exp Pneumonia, Aspiration/ (14576)
((pneumonia or acid) adj1 aspiration).tw. (7192)
(mendelson$1 adj syndrome).tw. (485)
exp Oleic Acid/ (24465)
(oelic acid* or olate or 9-octadecenoic acid* or cis-9-octadecenoic acid*).tw. (35809)
exp Bleomycin/ (53023)
(bleomycin* or blanoxan or blenoxane or BLEO-cell or bleolem or bleomicin*).tw. (28063)
expl Endotoxins/ (117578)
exp Oleic Acid/ (24465)
(oleic acid* or oleate or 9-octadecenoic acid* or cis-9-octadecenoic acid*).tw. (35809)
exp Bronchoalveolar Lavage Fluid/ (56822)
(bronchoalveolar or broncho-alveolar or alveolar or bronchial or lung$1 or pulmonary or saline) adj1 lavage*).tw. (58750)
((intravenous or IV or intrapulmonary or intra-pulmonary or intrabronchial or intra-bronchial) adj1 bacter*).tw. (592)
exp Cecum/ (35563)
exp Ligation/ or exp Punctures/ or in.fs. (378628)
((cecum or cecal or coecum or caecum) adj3 (ligation* or puncture* or injur*)).tw. (5591)
exp Pancreatitis/ (118884)
Pancreatit*.tw. (104949)
or/22-56,60-63 (2787405)
21 and 64 (7053)
exp animal experimentation/ or exp models, animal/ or animals/ or mammals/ or vertebrates/ or exp fishes/ or exp amphibia/ or exp reptiles/ or exp birds/ or exp hyraxes/ or exp marsupialia/ or exp monotremata/ or exp scandentia/ or exp chiropteran/ or exp carnivora/ or exp cetacea/ or exp Xenarthra/ or exp elephants/ or exp insectivora/ or exp lagomorpha/ or exp rodentia/ or exp sirenia/ or exp Perissodactyla/ or primates/ or exp strepsirhini/ or haplorhiniform/ or exp tarsii/ or exp platyrhiniform/ or catarrhiniform/ or exp cercopithecidae/ or gorilla gorilla/ or pan paniscus/ or pan troglodytes/ or exp pongo/ or exp hylobatidae/ or hominidae/ (10693999)
exp Drug Evaluation, Preclinical/ (307089)
(preclinical* or pre-clinic*).tw. (125267)
or/66-69 (12371409)
65 and 70 (4094)
71 use prnz (2127)
exp mesenchymal stem cell/ (34040)
expl mesenchymal stem cell transplantation/ (8987)
expl multipotent stem cell/ (19308)
expl mesenchymal stroma cell/ (1120)
((mesenchymal adj3 (stem or stroma$1 or progenitor*)) and (cell$1 or cell-induced)).tw. (44453)
(MSC or MSCs or ADMSC or ADMAscs or BM-MSC or BM-MSCs or BMD-MSC or BMD-MSCs or BMDMSC or BMDMS cells or BMSC or BMSCs or HBMSC or HBMSCs or ABMSC or ABMSCs or ABMSCs or MAPCs or MAPCs).tw. (35768)
(((multipotent or multi-potent) adj3 (stem or stroma$1 or progenitor*)) and (cell$1 or cell-induced)).tw. (8725)
((marrow* adj3 (stem or stroma$1 or progenitor*)) and (cell$1 or cell-induced)).tw. (43339)
(exp bone marrow cell/ or exp bone marrow transplantation/) and (exp stem cell/ or exp stem cell transplantation/) (80630)
(colony-forming unit fibroblast* or CFU-F$1).tw. (1415)
adult stem cell/ (5119)
((adult* adj3 (stem or stroma$1 or progenitor*)) and (cell$1 or cell-induced)).tw. (17001)
((fibroblast-derived adj3 (stem or stroma$1 or progenitor*)) and (cell$1 or cell-induced)).tw. (40)
IPS cell$1.tw. (3176)
exp mesoderm/ (29049)
(cell or cytolog*).tw. (5284561)
87 and 88 (13805)
or/73-86,89 (182688)
exp stem cell transplantation/ (128846)
exp gene therapy/ (96802)
Mesenchymal.tw. (116010)
(91 or 92) and 93 (11653)
90 or 94 (182999)
exp lung/ (494458)
(patholog* or physiopatholog* or physio-patholog*).tw. (1276913)
96 and 97 (30655)
exp lung disease/ (1655002)
((lung$1 or pulmonary) adj3 (disease* or injur* or contusion* or embolism* or haemorrhag* or hemorrhag* or infection* or trauma*)).tw. (338023)
exp adult respiratory distress syndrome/ (34780)
((acute or adult) adj respiratory distress syndrome).tw. (24402)
ARDS or ARDSS).tw. (17412)
(shock adj1 lung).tw. (1093)
exp acute lung injury/ (9987)
(lung injur* adj1 acute).tw. (19950)
ali.tw. (9000)
exp respiratory failure/ (113996)
((respiratory or ventilatory) adj3 (insufficien* or deficien* or disturbance* or dysfunction* or depression or failure or paralys#s)).tw. (97062)
exp systemic inflammatory response syndrome/ (261293)
(*inflammatory response syndrome* adj1 systemic).tw. (6469)
(sepsis or septic* or bacteremia or bacteraemia or endotoxic* or endotoxemi* or endotoxaemi*).tw. (293213)
exp hyperoxial/ (9036)
hyperoxi*.tw. (16180)
exp reperfusion injury/ (64760)
((pulmonary or lung$1 or nonpulmonary or non-pulmonary) adj3 (ischemi* or ischaemi* or reperfusion*)).tw. (4926)
exp peritonitis/ (67720)
peritonitis.tw. (57018)
exp aspiration pneumonia/ (14576)
((pneumonia or acid) adj1 aspiration).tw. (7192)
(mendelson$1 adj syndrome).tw. (485)
exp oleic acid/ (24465)
(oleic acid* or oleate or 9-octadecenoic acid* or cis-9-octadecenoic acid*).tw. (35809)
exp bleomycin/ (53023)
(bleomycin* or blanoxan or blenoxane or BLEO-cell or bleolem or bleomicin*).tw. (28063)
exp endotoxin/ (117578)
(endotoxin* or ETX).tw. (72974)
exp lipopolysaccharide/ (77890)
(lipopolysaccharide* or lipo-polysaccharide* or LPS or lipoglycan*).tw. (173627)
exp lung lavage/ (58846)
((bronchoalveolar or broncho-alveolar or alveolar or bronchial or lung$1 or pulmonary or saline) adj1 lavage*).tw. (58750)

((intravenous or IV or intrapulmonary or intra-pulmonary or intrabronchial or intra-bronchial) adj1 bacter*).tw. (592)

exp cecum/ (35563)

exp ligation/ (65710)

exp puncture/ (113102)

133 and (134 or 135) (1215)

((cecum or cecal or coecum or caecum) adj3 (ligation* or puncture* or injur*)).tw. (5591)

exp Pancreatitis/ (118884)

Pancreatit*.tw. (104949)

exp animal experiment/ or exp animal model/ or animal/ or exp invertebrate Chordata/ or exp experimental animal/ or exp transgenic animal/ or exp male animal/ or exp female animal/ or exp juvenile animal/ or vertebrate/ or exp fish/ or exp amphibia/ or exp reptile/ or exp bird/ or mammal/ or exp hyrax/ or exp marsupial/ or exp monotremate/ or exp scardentia/ or placental mammals/ or exp bat/ or exp carnivora/ or exp cetacea/ or exp edentata/ or exp elephant/ or exp insectivora/ or exp lagomorph/ or exp rodent/ or exp sierenia/ or exp ungulate/ or primate/ or exp prosimian/ or haplorhin/ or exp tarsiiform/ or simian/ or exp platyrrhini/ or catarrhini/ or exp cercopithecidae/ or ape/ or exp hylotadidae/ or hominid/ or exp chimpanzee/ or exp gorilla/ or exp orang utan/ (10715704)

exp animal$1 or chordata or vertebrate* or fish$2 or amphibian* or amphibium* or reptile$1 or bird$1 or mammal* or dog or dogs or canine$1 or cat or cats or hyrax* or marsupial* or monotrem* or scardentia or bat or bats or carnivora* or cetacea or edentata* or elephant* or insect or insects or insectivore or lagomorph* or rodent$2 or mouse or mice or murine or murinae or muridae or rat or rats or pig or pigs or piglet$1 or swine or rabbit$1 or sheep$1 or goat$1 or horse$1 or equus or cow or cows or cattle or calf or calves or bovine or sirenia or ungulate$1 or primate$1 or prosimian* or haplorhin* or tarsiiform* or simian* or platyrrhini or catarrhini or cercopithecidae or ape or apes or hylotadidae or hominid* or chimpanzee* or gorilla* or orangutan* or monkey or monkeys or ape or apes).tw. (8398088)

(preclinical* or pre-clinical*).tw. (124960)

or/143-145 (12204975)

142 and 146 (4183)

147 use emczd (2045)

72 or 148 (4172)

remove duplicates from 149 (3064)