H1N1 pathology:

1. Encephalitis

<http://pediatrics.aappublications.org.ezproxy1.library.usyd.edu.au/content/129/4/e1068.short>

* Autoantibodies against NDMA elevated or positive in cerebrospinal fluid
* Normalized in the 3 follow-up studies

1. Hemophagocytic lymphohistiocytosis

<http://journals.lww.com/jpho-online/Abstract/2011/03000/Hemophagocytic_Lymphohistiocytosis_Associated_With.12.aspx>

1. Alveolar edema caused by disruption of epithelial cell junctions

<http://erj.ersjournals.com/content/early/2016/01/07/13993003.01282-2015>

* Flooding of alveolar lumen with proteinaceous oedema fluid, erythrocytes and inflammatory cells
* H1N1 in seeded in vitro human alveolar resulted in barrier damage, damage to epithelial cells occurred independently of endothelial cells (which were pro-inflammatory and pro-coagulant)
* Barrier damage associated with loss of **claudin-4**

1. Pneumonia and Acute respiratory distress syndrome (ARDS)

<http://journals.lww.com/co-criticalcare/Abstract/2011/02000/H1N1__viral_pneumonia_as_a_cause_of_acute.12.aspx>

1. Fulminant myocarditis (case study)

<http://www.sciencedirect.com/science/article/pii/S1109966616300768?np=y&npKey=633d29d038cfd1b9cbe6db1915c483f2cd05d2d2f4eb10955cb4733b2cc78f84>

* Myocardial involvement in influenza reported in up to 10% of cases
* Symptoms include fulminant myocarditis, cardiogenic shock, arrhythmias, atrioventricular blocks, congestive heart failure, cardiac tamponade, disseminated intravascular coagulation, etc.
* Elevated inflammatory markers (CRP, WBC, fibrinogen) and cardiac enzymes (CK-MB 335, troponin I)

1. Another case study

<http://rc.rcjournal.com/content/55/5/623.short>

* Fevers, progressive shortness of breath, cough
* Myocardial infarction and hemoptysis
* Diffuse erythema and bleeding and alveolar hemorrhage

1. Diffuse alveolar damage (DAD) induced acute respiratory failure

<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0166184>

* Increased expression of AQP3, AQP5, NaKATPase in DAD group
* Decreased expression of ENaC in DAD group
* No difference in protein expression and AQP1 expression between DAD and normal group

<http://www.atsjournals.org/doi/abs/10.1164/rccm.200909-1420OC>

* DAD present in 20 individuals
* 6 associated with necrotizing bronchiolitis, 5 showed extensive hemorrhage

1. Histopathological findings

<http://www.sciencedirect.com.ezproxy1.library.usyd.edu.au/science/article/pii/S0344033810002633>

http://www.sciencedirect.com.ezproxy1.library.usyd.edu.au/science/article/pii/S0344033810002633

<http://www.atsjournals.org/doi/abs/10.1164/rccm.200909-1420OC>

* Cytopathic effect in alveolar cells
* As well as necrosis
* Epithelial hyperplasia, squamous metaplasia of large airways
* Expression of TLR-3 and IFN-yamma
* Large amounts of CD8+ Tcells, granzyme B+ within lung tissue

<http://www.sciencedirect.com/science/article/pii/S0002944010600739?np=y&npKey=44a8ba7100e0df7f947e34db67ad1091a6cf17cf033f44191ca26234ca5c8ea9>

http://www.sciencedirect.com/science/article/pii/S0210569111002944

<http://www.nejm.org/doi/full/10.1056/NEJMc0907171#t=article>

* Epithelium necrosis
* hemmorrhage
* Inflammation and edema of lung
* Diffuse alveolar damage, hyaline membranes, inflammation, fibrosis
* No signs of myocarditis or encephalitis however not all samples had heart/brain samples available.
* Viral distribution
  + Epithelial cells in airways, sub
* Alveolar damage associated with viral antigen localization in T2 pneumocytes and alveolar lining cells
* Increased deaths associated with obesity and asthma – perhaps immunological factors and these medial conditions affect the outcome

1. C4D depoisition – marker of complement activation mediated by immune complexes

<http://www.nature.com/nm/journal/v17/n2/abs/nm.2262.html>

* Widened interalveolar septa, interstitial hemorrhages
* Abundant intra-alveolar edema
* Deposition of hyaline membranes
* Infiltration of mononuclear cells
* Lungs showed hyperplasia, detachment of T2 pneumocytes into lumen
* Fatal cases showed interstitial edema, desquamation of T2 pneumocytes and mononuclear cell infiltration
* H1N1 mainly detected in epithetlial cells of bronchioles, occasionally in respiratory epithelial cells
* IFN alpha higher in nasopharyngeus vs. tracheal

1. Increased IL-17, Th-17 mediators and IL-17 responsive cytokines in S-OIV H1N1 infected patients serum samples

<http://www.nature.com/cr/journal/v22/n3/abs/cr2011165a.html>

<http://www.atsjournals.org.ezproxy1.library.usyd.edu.au/doi/abs/10.1164/rccm.200909-1420OC>

* expression of TLR3, IFN-y, CD8+ T-cells, Granzyme B+ cells within lung tissue
* main pathological changes localized to lungs

Epidemiology

<http://journals.lww.com/pccmjournal/Citation/2012/09000/H1N1_in_Japanese_children_More_data_but_even_more.35.aspx>

* Insignificant results due to small sample (8 patient sample), but on better mortality in jap children

<http://www.scielo.br/scielo.php?pid=S0103-51502016000400805&script=sci_arttext>

* Comorbidities associated with H1N1 (11 patient sample)

H1N1 pathology **IN MICE**

1. ARDS (acute respiratory distress syndrome)

<http://onlinelibrary.wiley.com.ezproxy1.library.usyd.edu.au/doi/10.1111/j.1750-2659.2012.00414.x/full>

* Shows low PaO2: FiO2 ratios in affected mice, suggesting it can be used to track ARDS development
* Also suggests that the mouse model of H1N1 (at a lethal dose of mouse-adapted virus) validly also shows ARDS
* Progressive increase in pulmonary edema also found
* Conducted in 8-12w/o BALB/cAnNCr mice

<http://ajplung.physiology.org/content/311/6/L1160>

* Reduced surfactant phospholipids in ATII cells, abnormal ultrastructure of ATII cell lamellar bodies
* Altered ATII cell surface lipid metabolism, resulting in surfactant dysfunction and development of ARDS

1. CXCL4 is immunoprotective for mice against Influenza A virus in development of lung injury and neutrophil mobilization once inflamed

<http://www.nature.com.ezproxy1.library.usyd.edu.au/mi/journal/vaop/ncurrent/full/mi20171a.html>

* Chemokine (C-X-C motif) ligand 4 (CXCL4), also known as platelet factor 4 (PF4), is primarily stored in platelet α-granules and released upon activation of platelet aggregation. Research concerning the biological function of CXCL4 has revealed that this protein has a role in suppressing hematopoiesis, platelet aggregation and wound repair, inhibiting endothelial cell proliferation and angiogenesis, and regulating immune and inflammatory responses.6, 7 Although CXCL4 was the first member of the CXC chemokine family to be identified, purified CXCL4 has no chemotactic activity for neutrophils in vitro.6 Basically, this protein binds to C-X-C motif chemokine receptor 3 (CXCR3) and glycosaminoglycans but not the neutrophil chemotaxis receptor CXCR2.7 Nevertheless, other studies have found that CXCL4 can enhance neutrophil adherence to endothelial cells and facilitate neutrophil exocytosis to release myeloperoxidase and lysozyme.7 With regard to immunoregulation, CXCL4 also shows a cellular immune effect in facilitating neutrophil recruitment to inflamed tissues,8, 9, 10, 11, 12 promoting the activation, proliferation, and differentiation of monocytes,13, 14 natural killer cells,15 dendritic cells,16 and T cells.17, 18
* 10-12 weeks CXCL4-/- and wilt type C57BL/6 intranasally infected with H1N1 PR8

1. Interleukin 6 (IL-6) important in immune response to influenza pathogenesis

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5338329/>

* IL-6 deficient mice had higher lethality, reduced body weight, higher fibroblast accumulation, lower ECM turnover compared to wild-type
* IL6 deficiency produced increase TGF-beta in fibroblasts (may improve survival)
* IL6 crucial for lung repair, reducing fibroblast accumulation, promotes epithelial cell survival, increased macrophage recruitment, enhanced phagocytosis of viruses
* TGF beta involved in acute lung injury, promotes ENaC internalization (causing edema)
* Influenza stimulates Toll-like receptor 3 (TLR3) which activates TGF beta causing cell death through Avbeta6 integrin

1. Ribavirin and reduning protects mice against pneumonia

<http://www.sciencedirect.com/science/article/pii/S0254627216300255>

* All mice died in control, combined treatment had 100% survival but just reduning had 10%
* Reduced lung edema (from wet-to-dry ratios) compared to untreated group
* Reduced IL6 and IL10 in combined treatment

OTHER PAPERS (not h1n1 related directly)

1. Imipramine improves epithelial barrier function in acute lung injury (ALI) model

<http://journals.lww.com/ccmjournal/Citation/2016/12001/1053___IMIPRAMINE_IMPROVES_ALVEOLAR_EPITHELIAL.1014.aspx>

* Attenuates lung edema, improves (by reducing) wet/dry ratio compared to controls

1. Lung regeneration after infection

<http://www.sciencedirect.com/science/article/pii/S0092867411011731>

* P63 expressing stem cells in bronchiolar epithelium undergo rapid proliferation, radiate to interbronchiolar regions of alveolar ablation
* Once at interbronchiolar region, these cells form KRT5+ pods, begin to express aoveoli biomarkers, possibly reconstituting the alveolar-capillary network
* Human distal airway stemcells assemble alveoli-like structures in vitro – possibly therapy to acute and chronic airway disease

1. Toll-like Receptor 4 and Oxidative Stress involved ina cute lung injury

<http://www.sciencedirect.com/science/article/pii/S0092867408003401>

* Many flus lethal due to respiratory distress syndrome
* TLR4 mutants show natural resistance to acid0induced acute lung injury ALI) – suggests TLR4 involved in pathogenesis
* TLR4-TRIF-TRAF6 signaling controls ALI severity
* OxPAPC [oxidized phospholipid] identified to induce lung injury and cytokine production by lung macrophages via TLR4-TRIF
* OxPL – is it formed in H1N1? It is formed in H5N1… <http://www.sciencedirect.com/science/article/pii/S0210569111002944>
* Deletion of ncf1 imrpvoes severeity of ALI – meaning our immune response possibly makes ALI worse

1. Comparison of pathologies

<http://www.sciencedirect.com.ezproxy1.library.usyd.edu.au/science/article/pii/S0188440909001842>