Causes of Sudden Death:

Neonatal Reasons

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No conflict of interest to declare
Sudden death – Neonatal reasons

Neonatal death: first **28** days of life

Early neonatal death: first **7** days of life (included in *perinatal death*)

Sudden and/or unexpected death or collapse: the death of an infant in which the mode and cause of death or collapse are not immediately obvious prior to investigation.

- **47%** of deaths among children under five were newborns in 2017.
- Neonatal mortality rates: **1.6 – 87.6‰**
  - **1.6 - 3.6‰** in the western world – **10‰** in Jordan in 2017

  Sustainable Development Goals (SDG) target: **12‰** by 2030

- The majority ~ **77%** of the neonatal deaths are concentrated in the first day and week.

  *WHO 2017  UNICEF Global Data 2018*

Sudden unexpected early neonatal death rate: **0.008 – 0.1 /1,000** livebirths in Australia

*Pediatr Res. 2016*
Sudden /unexpected neonatal death

Neonatal Causes  (variable rates between countries)

Excluding:
very low birth weight – extreme prematurity = not unexpected

• Infection – (involving sepsis, pneumonia or meningitis)
• Congenital abnormality /isolated or incl. chromosomal or nonchromosomal genetic disorders
• Cardiac disease
• Pulmonary disease
• Metabolic diseases (IEM)
• Other
• Undetermined due to limited investigation /
/Unexplained despite ancillary tests and investigation ≈ SIDS
Infection
Sepsis, Pneumonia, Meningitis/meningoencephalitis

• in utero (transplacentally or through membranes)
• during delivery (intrapartum) HSV, HIV, hepatitis B / bacteria
• from external sources after birth (postpartum)
  from mother directly or through breastfeeding (eg, HIV, CMV)
  from contact with family or visitors, health care practitioners,
  or the hospital environment (numerous organisms)

• Bacteria are the principal pathogens.
  group B strept, E.coli, Listeria monocytogenes, Klebsiella, gonococci,
  chlamydiae and many others

• Viruses (HSV, CMV, RSV, adenovirus) or fungi cause some cases.
Neonatal pneumonia  early or late onset

diffuse inflammatory infiltrations
Neonatal pneumonia
Late Neonatal Chlamydia Pneumonia

eosinophils
TORCH infections

Congenital Toxoplasmosis

toxo- cysts in the liver

**Incidence of death from congenital toxoplasmosis in 0-4-year-old children in Japan**

yearly neonatal death rate from congenital toxoplasmosis = 0.29%

_Pediatr Int. 2014_
CMV encephalitis
CMV encephalitis

polymicrogyria
Fungi causing pneumonia, meningoencephalitis, or disseminated infection

Candida, aspergillus, mucor

LUNGS

granulomatous reaction
Fungal infection

LUNGS

interstitial mononuclear inflammatory infiltrates - giant cell macrophages
perivascular microabscesses  giant cells
Fungal infection

BRAIN

extensive necrosis

thrombosed vessels
mucor hyphae
Congenital abnormality
unrecognised by prenatal control

Heart defects

• Transposition of Great Arteries – noncorrected
• Hypoplastic Left Heart Complex
• Interrupted Aortic Arch
• Tetralogy of Fallot / critical pulmonary stenosis
Cardiac disease

Neonatal myocardial infarction

*Associated with*

- cardiac or coronary artery malformations
- coagulopathy / thromboembolism of coronary artery
- perinatal asphyxia
- post infectious (e.g. enteroviral myocarditis)
- erythroblastosis / fetal anemia

(myocardial necrosis and calcifications post enteroviral myocarditis)
Cardiac disease
Arrhythmogenic myocardial diseases

Cardiomyopathies

Histiocytoid cardiomyopathy

- cardiomegaly, severe cardiac arrhythmias or sudden death, and the presence of histiocyte-like cells within the myocardium
- presents as SIDS in infancy – 1 in 5 cases (20%) diagnosed within 30 days of birth
- mtDNA mutation in MT-CYB gene identified

Hypertrophic cardiomyopathy – postneonatal age
very rarely the cause of sudden neonatal death
(compound heterozygosity)
Histiocytoid cardiomyopathy

nests of foamy histiocyte-like cells with a granular cytoplasm containing lipid droplets and abundant atypical mitochondria

https://www.researchgate.net/publication/315471736_Histiocytoid_cardiomyopathy_/figures
Left ventricular non-compaction cardiomyopathy (LVNC) presenting as dilated cardiomyopathy

Masson tr.

Spongiform myocardium

trabecular sinusoids in the L. ventricular myocardium
Cardiac disease

Arrhythmogenic myocardial diseases

Channelopathies (Long QT syndrome—LQTS, Brugada syndrome—BrS, Catecholaminergic Polymorphic Ventricular Tachycardia—CPVT and Short QT syndrome—SQTS)

“Cardiac ion channelopathies” are not detectable during a standard postmortem examination.
It is thought that may create the vulnerable infant and thus contribute to SIDS (or SND).

Evidence

• clinical correlations between the long QT syndrome and SIDS

• genetic analyses in cohorts of SIDS victims (“molecular autopsy”) have revealed a large number of mutations in ion channel-related genes linked to inheritable arrhythmogenic syndromes.
LUNGS

Congenital Pulmonary Hypoplasia / Persistent Pulmonary Hypertension

Acute respiratory distress soon after birth – early neonatal death
Congenital Pulmonary Hypoplasia

**Primary**
genetic syndromes/chromosomal defects – or reflects underlying **Congenital Alveolar Dysplasia**

**Secondary**
abnormal thoracic cavity +/- mediastinal shift
- diaphragmatic hernia / CAM

abnormal fetal breathing movements
- CNS or neuromuscular disorders

abnormalities of fetal lung fluid and lung fluid pressure
- oligohydramnios

**CHD with poor pulmonary blood flow**
- pulmonary stenosis
Primary Pulmonary Hypoplasia

Congenital Alveolar Dysplasia

Developmental disorder – growth arrest at the saccular stage

term infant
Congenital Pulmonary Hypoplasia

**Primary**

genetic syndromes/chromosomal defects – or reflects underlying Congenital Alveolar Dysplasia

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**Combined lung weight to body weight ratio** < 0.012

**Radial alveolar count** < 5

CHD with poor pulmonary blood flow
- pulmonary stenosis
diaphragmatic hernia

CPH following oligohydramnios

https://ars.els-cdn.com/content/image/1-s2.0-S1726490111003315-gr5_lrg.jpg
Pulmonary hypoplasia + Kidney disease

Scenario

• women not been followed prenatally
• few cases unsuspected at prenatal US

Postnatal diagnoses in this group include:

• bilateral renal agenesis
• polycystic renal disease
• congenital urethral obstruction

Death from pulmonary hypoplasia or renal failure
Pulmonary hypoplasia in ARPKD
Pulmonary hypoplasia + Skeletal dysplasia

Secondary to severe thoracic constriction or Primary

Lethal in the early neonatal period
Skeletal ciliopathies

JEUNE ATD

Short-Rib ± Polydactyly

+ extraskeletal findings
• Spondylocostal / spondylothoracic dysostoses (Jarcho-Levin phenotype)
Persistent Pulmonary Hypertension of the Newborn (PPHN)

PPHN is the failure of the normal circulatory transition that occurs after birth.

- **marked pulmonary hypertension**
- **right-to-left shunting of blood at the foramen ovale and ductus arteriosus**
- **hypoxemia**
- **asphyxia**
Secondary to

1. Acute pulmonary vasoconstriction due to acute perinatal events
   parenchymal lung disease / asphyxia/ hypothermia/ hypoglycemia
   (e.g. alveolar hypoxia secondary to meconium aspiration syndrome, respiratory distress syndrome, or pneumonia)

2. Hypoplasia of the pulmonary vascular bed (commonly seen with congenital diaphragmatic hernia or oligohydramnios, uncommonly with CAM)

3. Congenital Heart Defect (left-to-right shunt VSD, AV canal, patent DA, AP window / TGA / Obstructive cardiopathy TAPVR, MS, HLHS, cardiomyopathy)

Idiopathic (10% - impaired pulmonary relaxation after birth in the absence of parenchymal lung disease or CHD)
   constriction or premature closure of the DA in utero, which can occur after exposure to aspirin or NSAIDs during the third trimester.

Semin Fetal Neonatal Med 2017
PPHN

Endothelial proliferation, intimal fibrosis, medial hypertrophy
PPHN
PPHN

Alveolar capillary dysplasia

- thickened alveolar walls with centrally located alveolar capillaries
- misalignment of congested pulmonary veins and venules adjacent to the hypertrophied pulmonary arteries and arterioles
PPHN

Alveolar capillary dysplasia / MPV

AVC/MPV is a genetic disorder characterized by abnormal vascular development in the lung.

FOXF1

Typically associated with multiple extrapulmonary malformations (CHD, intestinal malrotation, GU tract, others)

short “honeymoon” period of wellness followed by severe PPHN

M. Dishop. Diffuse Developmental Lung Disorders. ECP 2017
Genetic Surfactant Deficiency

present in the first hours, days, or weeks of life with acute respiratory distress and imaging findings that mimic hyaline membrane disease

-diffuse alveolar epithelial hyperplasia
-abundant alveolar proteinosis material
-increased foamy macrophages

alveolar proteinosis
Neonatal Acute Liver Failure

NALF
• neonatal iron storage disease
• inborn errors of metabolism
• infection

Hepatic necrosis
almost always in the context of congenital viral infection

HSV, enterovirus ECHO, adenovirus
Neonatal haemochromatosis / Neonatal iron storage disease

**Phenotype:**
severe liver disease in the newborn accompanied by extrahepatic siderosis

**Siderosis:** liver, exocrine pancreas, myocardium, thyroid, minor salivary glands et al. (≠ spleen)  
**thyroid > pancreas**

**Etiopathogenesis**

**GALD:** gestational alloimmune liver disease  
80% recurrence

*Rarely ( < 2% )*

**non-GALD:** perinatal infection, bile acid synthesis defect, mitochondrial DNA depletion (DGUOK mutations), trisomy 21, other syndromes

*J Clin Exp Hepatol 2013*
Neonatal haemochromatosis / Neonatal iron storage disease

Liver
small, nodular,
bile-stained,
fibrotic or cirrhotic

dominant features:
- marked loss of hepatocytes
- severe panlobular parenchymal fibrosis
- hepatocyte siderosis
Inborn Errors of Metabolism

IEM associated with SID + neonatal presentation

26 individual entities

Aminoacid and Peptide metabolism
- Urea cycle disorders
- Organic acidurias
- Other aminoacid disorders /non-organic acidurias
- Tyrosinemia type 1
- Nonketotic hyperglycinemia

Glycogen storage disorders
- GSD Ia (von Gierke)
- GSD II (Pompe)
- GSD IV (Andersen/lethal neonatal type)

Fatty acid and ketone body metabolism
- Disorders of carnitine transport and carnitine cycle
- Disorders of mitochondrial fatty acid oxidation

Mitochondrial respiratory chain disorders
- Point mutations of mtDNA
- Complex IV deficiency

0.9–6% of all SID cases involve IEM.

Metaanalysis

Of 43 IEMs associated with SID:
- 26 can already present during the neonatal period,
- treatment is available for at least 32,
- 26 can currently be identified by the analysis of acylcarnitines and amino acids in dried bloodspots (DBS).

Neonatology 2016
Fatty Acid Oxidation Defects

- diffuse macro- and micro-vesicular steatosis
- persistent extramedullary hemopoiesis

medium chain acyl-CoA dehydrogenase deficiency
think of

- Glutaric aciduria II
- Mitochondrial disorder
- Peroxisomal disorder

Cortical cysts – glomerular and tubular
mtDNA mutation

Degeneration and neovascularisation in the brainstem
GSD type IV
32/40w
Floppy baby – suspicion of perinatal asphyxia and HIE

Polyglucosan bodies
PAS (+)
PAS-diast (+)
AB (-)
Hales reactive
IEM

- Low incidences and aspecific symptoms and signs cause an under-diagnosis of IEMs

- Clinical symptoms may mimic perinatal asphyxia

- The application of combined metabolite screening and DNA-sequencing techniques facilitate fast identification and maximal diagnostic yield.
Other causes of sudden neonatal death or collapse

Rh incompatibility

Hypovolemia/hemorrhage

- **Fetomaternal hemorrhage** – anaemia /no hydrops
  Kleihauer test + /
  Placenta suggestive (multiple IV thrombi – delayed villous maturation)

- **Subgaleal (subaponeurotic) hemorrhage** (vacuum extraction on underlying bleeding disorder)

- **Rupture of subcapsular liver hematoma**
  Subcapsular liver hematoma associated with birth trauma, coagulopathies, malpresentation, extreme prematurity, anoxia, sepsis, and a variety of invasive procedures of the neonate.

  Rupture into the peritoneum has a 75% mortality rate.

*BMJ Case Rep 2013*
Other Genetic syndromes

Pierre – Robin sequence in Treacher - Collins syndrome causing airway obstruction

Severe opisthognathia / mandibular hypoplasia + U-shaped cleft of soft palate
TGA

TGA + (poly)asplenia + situs inversus/ambiguous = Heterotaxy disorder – Ivemark syndrome

Lipoid/aplastic pancreas → Total pancreatic insufficiency
Sudden unexpected neonatal death in the first week of life: autopsy findings from a specialist centre.

**OBJECTIVE:**
Sudden unexpected early neonatal death (SUEND) in the first week of life shares features with sudden unexpected death in infancy (SUDI) but is not included as SUDI, which is limited to post-perinatal deaths. The aim of this study was to review SUEND autopsies performed in a single specialist centre over a 10-year period, (1996-2005).

**METHODS:**
Retrospective analysis of >1500 consecutively performed paediatric autopsies performed by paediatric pathologists at one centre conducted according to a standard protocol including ancillary investigations. SUENDs were identified and autopsy findings reviewed.

**RESULTS:**
Of 1516 post-mortem examinations, 180 were first-week neonatal deaths, 55 (31%) presenting as SUEND. Thirty-two (58%) were explained following autopsy, whilst the remainder were unexplained; most deaths during sleep were associated with adult co-sleeping. Around 40% of explained deaths were associated with undiagnosed congenital abnormalities, mainly congenital heart disease. In addition, there were nine infection-related deaths and three deaths from unsuspected metabolic disease (fatty acid oxidation defects).

**CONCLUSION:**
There are distinct differences between SUEND and SUDI, with significantly more explained deaths in the former and a much greater proportion due to congenital abnormalities and metabolic disease.
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Specific diagnosis</th>
<th>No. of cases</th>
<th>No. of deaths</th>
<th>Abnormal neurology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Failure to establish safe skin to skin</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Accidental asphyxia during breastfeeding or skin-to-skin contact</td>
<td>Asphyxia related to position found—carer’s chest, bed sharing, father’s arms</td>
<td>11</td>
<td>6</td>
<td>1</td>
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<tr>
<td><strong>Fatal or potentially fatal conditions (lack of recognition)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cardiac disease</td>
<td>HLHS, TGA, interrupted aortic arch, myocardial infarction, critical pulmonary stenosis</td>
<td>9</td>
<td>3</td>
<td>0; DK 3</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Pneumonia, meningitis</td>
<td>5</td>
<td>5</td>
<td>NA</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Congenital lactic acidemia, urea cycle defect</td>
<td>3</td>
<td>3</td>
<td>NA</td>
</tr>
<tr>
<td>Hypovolemia</td>
<td>Subgaleal hemorrhage, placenta praevia with placental loss</td>
<td>2</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td>Airway abnormality</td>
<td>Prolapsed epiglottis with laryngomalacia (requiring supraglottoplasty)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Genetic</td>
<td>Chromosome 2 interstitial duplication adjacent to terminal deletion</td>
<td>1</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>PPHN</td>
<td></td>
<td>10</td>
<td>1</td>
<td>1</td>
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<tr>
<td><strong>Unexplained cause of death/collapse</strong></td>
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<tr>
<td>SIDS</td>
<td>SIDS</td>
<td>4</td>
<td>4</td>
<td>NA</td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Total number is 49 as one baby with PPHN had confirmed sepsis.

ALTE, acute life-threatening event; DK, don’t know; HLHS, hypoplastic left heart syndrome; NA, not applicable; PPHN, persistent pulmonary hypertension of the newborn; SIDS, sudden infant death syndrome; SUEND, sudden unexpected early neonatal death; TGA, transposition of the great arteries.
Unlike SUDI in the older infant, the etiology of life-threatening events in the neonatal group may be identified in the majority.

Cardiac disease, sepsis, persistent pulmonary hypertension, IEM, are the commonest identifiable neonatal causes of sudden or unexpected death according to some studies.

Ancillary investigations are essential.
References

10. Wilders R. Cardiac Ion Channelopathies and the Sudden Infant Death Syndrome. ISRN Cardiol. 2012
Thank you