Minesh Khashu
Consultant Neonatologist
&
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@mkrettiwt @SIGNECconf

#SIGNEC2018
signec.org
Good Housekeeping

FIRE EXIT

Don’t switch off!

WARNING
ACRONYMS AHEAD

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• Has surgeons operating on the tiniest patients

• Has a survival of only about 50% if requiring surgery

• Has, despite 6 decades of research, eluded us in terms of causation

• Has become the major cause of preterm mortality & morbidity
First we had each other,
Then we made you,
We were happy to have everything,
But then we sadly lost you.

Remembrance
Plan

- Aim & Learning outcomes
- Introduction to SIGNEC
- Defining NEC
- Experts by lived experience, new developments, QI, Global NEC day
- Key take home messages

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Aim & Learning Outcomes

01

Improve understanding of:
* Difficulties in terms of defining NEC
* Family experience esp. long term
* Recent advances & implications for clinical practice
* Potential new therapies/diagnostics
* QI

02

Improve understanding of aim/objectives of SIGNEC
SIGNEC includes neonatologists, paediatricians, surgeons, dieticians, transfusion medicine specialists, epidemiologists, basic science researchers, nurses, trainees and other healthcare professionals with an interest in NEC and healthcare improvement.
The aim is to facilitate knowledge sharing, networking and collaboration to optimise research and improvements in practice
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Make a difference by sharing your thoughts and passion and contributing your expertise
GENETICS & IMMUNOLOGY

GESTATIONAL AGE
- TLR4
- TGF b2
- T cell ontogeny

GENETICS e.g. POLYMORPHISMS

INFECTION/INFLAMMATION
- TIMING OF INFLAMMATION
  - FECAL vs TISSUE MICROBIOME
  - ABSOLUTE PHYLA vs DIVERSITY

ENVIRONMENT

MICROBIOME

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NEC has been a very tough nut to crack

Once we get to the bottom of this, it has the potential to open up new frontiers in our understanding of disease
NEVER DOUBT THAT A SMALL GROUP OF THOUGHTFUL, COMMITTED, CITIZENS CAN CHANGE THE WORLD; INDEED, IT IS THE ONLY THING THAT EVER HAS.

Margaret Mead
• Prof. David Hackam

• Prof. Kate Costeloe

Session 1

1330-1800
the Defining Moment
Necrotizing enterocolitis (NEC) is a leading cause of mortality and morbidity in preterm newborns.

About 30-50% of preterm babies who require surgery for NEC do not survive.

There has been significant research into NEC including pathophysiology and biomarkers, but little has translated into progress in managing NEC.

Despite 60 years of research, our understanding of the causation of NEC has not improved enough to change outcomes.
“UNLESS SOMEONE LIKE YOU CARES A WHOLE AWFUL LOT, NOTHING IS GOING TO GET BETTER. IT’S NOT.”

-Dr. Seuss
Is There a Problem?
What Is the Problem?
What Causes the Problem?
What Keeps you from Solving the Problem?

How do We Feel About This?
Are You Going to be Part of the Problem, or Part of the Solution?

What could you do to make a small improvement?
Who or what do you need for that?
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What could you do to make a small improvement?
Who or what do you need for that?
Critical Barriers

- Lack of appropriate definitions
- Lack of appropriate datasets
- Lack of capacity to gain insights from data
Three critical steps

1. Clarification and consensus of case definitions for various ANIDs to be used clinically, in epidemiology and in research.

2. Strategic integration of this consensus into neonatal databases to harmonise case definitions, data fields and core datasets locally and globally to create big data.

3. Integration of machine learning to test features, extract new unknown features and validate case definitions (Predictive modelling).
Why?

This will enable objective data insights, delineate ANID subsets and improve specificity and sensitivity of diagnostic tools.

It is important to highlight that this has far reaching potential to ongoing innovation and progress for many diagnostic and treatment modalities.
Why now?

• Neurology, oncology, cardiology, diabetes and dermatology are rapidly advancing their field through better workflow, Real World Data (RWD) capturing, and advanced data analytics.

• The application of advanced statistical modelling within machine learning (ML) has been a strategic advancer for these fields.

• Applying ML to NEC research can be a pivotal enabler to assist in formulating a case definition(s) for individual Acquired Neonatal Intestinal Diseases (ANID), exploring the possibility of different subsets and validating diagnostic tools and treatments.
However, none of this will be possible until we have agreed global definition(s) for NEC and related conditions.
Is when we define NEC properly & start using AI
Beyond what ifs...

• A major discovery in our understanding of NEC pathogenesis may significantly transform the NEC landscape

• We do not know if and when a breakthrough moment will be here

• Till then the best approach would be to break down the problem of NEC into risk subgroups, a similar approach that has helped advance diagnosis and management for diabetes and multiple sclerosis

• This may help in delineating the pathogenesis of the various subsets and by using ML for analysis, we may reach that breakthrough moment much earlier and more cost effectively
The analysis and big data demands of this will be intense, but it is worth our while to take this path
Building Consensus

• An international consensus-determined guidance on definition(s) is long overdue to enable harmonization

• Consensus is difficult as there is significant inter-expert variability

• Looking at other areas of medicine for inspiration, Multiple Sclerosis (MS) faced a similar challenge to NEC as a condition lacking biomarkers for differentiation
• By agreeing on a case definition and structuring workflow, as a ‘diagnostic decision tree’, neurologists where not just able to improve identification of MS but create clean databases to deploy ML for further research insights.

• A decision tree provided critical thinking to identify red flags, highlighted differential features systematically though interpretation of MRI imaging and exclusion determined there is no better explanation than MS.
A similar problem was found in retinopathy of prematurity (ROP) where a machine learning approach was utilised to not only overcome inter-expert variability but to utilise it to improve diagnostics and aid consensus.

Bolon-Canedo et al 2015, achieved this through focussing agreement around features and performing objective feature extraction with ML. Then with ML it was measured against a ROP dataset and feedback given on the feature performance to achieve consensus among experts.
Next Steps 2

• Once NEC data bases are streamlined, ML and artificial neural networks would be the next stage to help ongoing validation and refinement of case definitions

• This technology is designed not only to cope with big data but uses ensemble modelling of various statistical models to continuously evolve and mould itself for the specific challenge (disease model) at hand

• A lot of NEC research investment is still vested on the discovery of biomarkers. But the mounting evidence is that ensemble modelling is needed to enable validation of biomarkers

• Biomarkers need algorithmic incorporation of clinical and visual presentation to improve accuracy and differentiation

• ML can be a key enabler and NEC disease modelling should be a strategic avenue for research
Preprocessing Data

Data collection
Workflow and data fields derived from Clinical Decision Tree

Raw Data

Labels
- Definition of NEC subsets
- Definition of NLD*

Machine Learning

Training data set → Learning algorithm → Final model

Types of Learning

Supervised learning → Unsupervised learning

Classification
- Support vector machines
- Nearest neighbor
- Naïve bayes
- Discriminant analysis

Regression
- Linear regression GLM
- SVR, GPR
- Neural networks
- Ensemble methods
- Decision trees

Clustering
- kMeans, kMedoids, Fuzzy, C-Means
- Hierarchical
- Gaussian mixture
- Neural networks
- Hidden Markov model

Dimensionality reduction

Prediction

New Data

Labels
• These key strategies have long-term implications with significant ongoing Return on Investment for future research, not just for NEC or neonatal care but all of medicine.

• Medical research as a whole, has a big problem ahead. The trajectory of costs for clinical trials are unsustainable, and the complexity of clinical care and conditions is making it less and less likely to obtain answers through traditional means.

• Despite the investment of time and resources traditional methods often provide limited insight and application for clinical practice.
The adoption of today's digital technologies and advances in data processing offer a unique opportunity to revolutionise human research with significant improvements in time, cost, and the quality of data collected.

The critical question is whether the neonatal community is open and willing to take advantage of these advancements.
Margaret Hamilton, lead software engineer of the Apollo Project, stands next to the code she wrote by hand and that was used to take humanity to the moon. [1969]
“Education is every day and everywhere, the only thing you have to pay is attention.”

Tim Fargo
Data is every day and everywhere, the only thing you have to pay is attention.

Every baby, every day on a neonatal unit is providing data.
Can improved NEC definitions/datasets and artificial intelligence insights help us conquer NEC?

Yes!
Are we ready to integrate 3 critical steps?

- Clean datasets
- Define better NEC and other ANIDs
- Machine Learning/AI