Some patients benefit, others don’t – how to fix it?

Anders Perner
Treat all kinds of patients with limited evidence base

Investigator-initiated trials
...and a few industry ones

Research funding
NNF and Fresenius Kabi
Discussion points...

- All interventions used in healthcare should be safe and effective
- Pressure to implement without good evidence
- ...resulting in benefit, waste and harm
- Why aren’t some benefiting and who are they?
- How may we help these patients?
MODERN MEDICINE HAD TO START SOMEWHERE
The first chemo...
Intensive care
Implemented without RCTs
The implementation pressure...

- Pressure to do something
- Hope
- Neophilia
- Physiological rationing
- Focus on effects – less on side-effects
- Success measured by surrogate markers
- Screening
- Neophilia
- Cultural pressure to do something
- Growth
- Industry
- Politics
- Patient groups

Healthcare
Good evidence for patient’s treatments?

• Interventions in clinical guidelines based on good evidence...

1. Cardiology 8%  
   JAMA 2019;321:1069-80

2. Oncology 6%  
   JCO 2011; 29:186–91

3. Critical care 10%  
   ICM 2018; 44:1189–91

4. Sepsis 8%  
   ICM 2017; 43:304–77
No change over time !!!
Benefit vs. harm
Harm

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hydroxyethyl Starch 130/0.42 versus Ringer’s Acetate in Severe Sepsis

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Hydroxyethyl starch increased....
1-in-13 died of hydroxyethyl starch
>500 medical reversals: an RCT shows an intervention to be no better or worse than prior standard care

- Critical care
  - Hydroxyethyl starch*
  - Dopamine*
  - HFO ventilation*
  - Intensive insulin*
  - Steroids in traumatic brain injury*
  - High tidal volume ventilation*
  - Supra-normal oxygen delivery*
  - Oral chlorhexidine*
  - IV fluid boluses in kids wo access to ICU*
  - Inhaled nitric oxide
  - Early parenteral nutrition
  - Early enteral nutrition in shock
  - PCT-guided Ab-escalation
  - Early goal-directed therapy
  - Albumin for resuscitation
  - Albumin substitution
  - Early dialysis
  - High-dose dialysis
  - Activated protein C
  - Liberal blood transfusion
  - Intra-aortic balloon pump
  - Pulmonary artery catheter
  - Levosimendan
  - Hypothermia to 33°C
  - Pantoprazole prophylaxis
  - Immunonutrition
  - Mechanical DVT prophylaxis
  - Liberal oxygen therapy

- Surgery & Anaesthesia
  - Off pump cardiac surgery*
  - Minimally invasive surgery in cervix cancer*
  - Lymphadenectomy in PET-neg c. ovary
  - Stapled hemorrhoidopexy
  - Decompressive cranietomy in traumatic brain injury
  - Knee arthroscopy
  - Vertebroplasty
  - Fusion surgery for lumbar spinal stenosis
  - Adenoidectomy
  - Robotic surgery
  - Negative pressure dressings for open fractures
  - Mechanical bowel preparation for colorectal surgery
  - Sedative premedication for general anaesthesia
  - Postoperative AB for acute calculous cholecystitis
  - Liberal transfusion in cardiac surgery
  - High perioperative oxygen fraction
  - Levosimendan in cardiac surgery

- Internal medicine
  - PIP/Tazo for ESBL infections*
  - Anti-psychotics for dementia*
  - Opioids for chronic pain
  - Prophylactic IV fluid before IV contrast
  - Early mobilisation in stroke
  - Prolonged IV antibiotics for complex bone infections
  - Platelet transfusion in ICH pts on antiplatelet therapy
  - Prophylactic ICD in non-CAD heart failure
  - Prolonged IV antibiotics for endocarditis
  - Prophylactic NAC before IV-dye contrast
  - Co-administration of Fucidin for staphylococci
  - Routine oxygen for stroke
  - Routine oxygen for MI
  - Ab-prophylaxis in stroke pts with dysphagia

*increased mortality

Inspired by VINAY PRASAD
Waste in health care

20 - 40%
Why aren’t some benefiting?

• The cost and complexity of clinical trials
Who don’t benefit

• Those with...
  – Acute illness
  – Multimorbidity
  – Lower or higher age
  – Pregnancy
  – Rare diseases
  – Less ‘marketed’ diseases
  – Not fitting the frameworks promoted

• Everyone needing ‘standard care’...
  – Oxygen, IV fluids, nutrition, antibiotics, analgesics, transfusion
  – ...and nursing care, physio, psychosocial support, surgery, invasive procedures...
Acknowledge the problem
Reduce the complexity and cost of clinical trials
1M Euro

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Better models for collaboration
patients – clinical academia –
industry
Public investments in clinical trials
Danish governmental grants for medical research 2012-16
THE FUTURE OF HEALTHCARE IS PRECISION MEDICINE
Investments in ‘smart’ trials
A ‘true’ learning healthcare system

RCT result

- Exploration of results
- Clinical uptake
- Harmonization of care
- New clinical baseline
- Improved geno- and phenotyping
- New RCT designed
- Randomized Embedded Multi-factorial Adaptive Platform trials
Randomized
Embedded
Multifactorial
Adaptive
Platform trials
For patient treatment to be safe and effective...

- Acknowledge the problems
- Reduce trial cost and complexity – we need more trials
- Better models for fair collaboration – patients – clinical academics – industry
- Public investments in trials
- Invest in ‘smart’ trials and ‘true’ learning healthcare