Building Global Research Collaboration in Critical Care

John C. Marshall, MD FRCSC
Critical Care Canada Forum
Toronto, CANADA
October 31, 2012

St. Michael’s Hospital
University of Toronto
• September 1989
• 20-25 intensivists
• Commitment to collaborate in multicentre clinical research in critical care
Dalteparin versus Unfractionated Heparin in Critically Ill Patients

The PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group

- 350 + members
- > 50 active research programs
- >120 publications
- Entirely self-funded
Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

John A. Myburgh, M.D., Ph.D., Simon Finfer, M.D., Rinaldo Bellomo, M.D., Laurent Billot, M.Sc., Alan Cass, M.D., Ph.D., David Gattas, M.D., Parisa Glass, Ph.D., Jeffrey Lipman, M.D., Bette Liu, Ph.D., Colin McArthur, M.D., Shay McGuinness, M.D., Dorrilyn Rajbhandari, R.N., Colman B. Taylor, M.N.D., and Steven A.R. Webb, M.D., Ph.D., for the CHEST Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group*
• 11 sites
• NIH-funded
• 5 papers in *New England Journal of Medicine*
Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis

Frank M. Brunekhorst, M.D., Christoph Engel, M.D., Frank Bloos, M.D., Ph.D., Andreas Meier-Hellmann, M.D., Max Ragaller, M.D., Norbert Weiler, M.D., Onnen Moerer, M.D., Matthias Gruendling, M.D., Michael Oppert, M.D., Stefan Grond, M.D., Dirk Olthoff, M.D., Ulrich Jaschinski, M.D., Stefan John, M.D., Rolf Rossaint, M.D., Tobias Welte, M.D., Martin Schaefer, M.D., Peter Kern, M.D., Evelyn Kuhnt, M.Sc., Michael Kiehntopf, M.D., Christiane Hartog, M.D., Charles Natanson, M.D., Markus Loeffler, M.D., Ph.D., and Konrad Reinhart, M.D., for the German Competence Network Sepsis (SepNet)

German Sepsis Network

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

Anders Perner, M.D., Ph.D., Nicolai Haase, M.D., Anne B. Guttormsen, M.D., Ph.D., Jyrki Tenhunen, M.D., Ph.D., Gudmundur Klenzenson, M.D., Anders Åneman, M.D., Ph.D., Kristian R. Madsen, M.D., Morten H. Møller, M.D., Ph.D., Jeanie M. Elkjær, M.D., Lone M. Poulsen, M.D., Asger Bendtsen, M.D., M.P.H., Robert Winding, M.D., Morten Steensen, M.D., Pawel Berezowicz, M.D., Ph.D., Peter Søe-Jensen, M.D., Morten Bestle, M.D., Ph.D., Kristian Strand, M.D., Ph.D., Jørgen Wiis, M.D., Jonathan O. White, M.D., Klaus J. Thomberg, M.D., Lars Quist, M.D., Jonas Nielsen, M.D., Ph.D., Lasse H. Andersen, M.D., Lars B. Holst, M.D., Katrin Thormar, M.D., Anne-Lene Kjældgaard, M.D., Maria L. Fabritius, M.D., Frederik Mondrup, M.D., Frank C. Pott, M.D., D.M.Sc., Thea P. Møller, M.D., Per Winkel, M.D., D.M.Sc., and Jørn Wetterslev, M.D., Ph.D., for the 6S Trial Group and the Scandinavian Critical Care Trials Group*
### Most Cited Papers in Critical Care

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Year</th>
<th>Focus</th>
<th>Citations/Yr</th>
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<tr>
<td>van den Berghe</td>
<td>NEJM</td>
<td>2001</td>
<td>Glucose</td>
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<td>NICE/SUGAR</td>
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<td>Van den Berghe</td>
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<td>Glucose</td>
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<td>PROWESS</td>
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<td>2001</td>
<td>APC</td>
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<td>2001</td>
<td>EGDT</td>
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<td>NEJM</td>
<td>2008</td>
<td>Glucose/Starch</td>
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<td>CORTICUS</td>
<td>NEJM</td>
<td>2008</td>
<td>Steroids</td>
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<td>Annane</td>
<td>JAMA</td>
<td>2002</td>
<td>Steroids</td>
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<td>TRICC</td>
<td>NEJM</td>
<td>1999</td>
<td>Transfusion</td>
<td>111.5</td>
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# Influence of Organizational Model on Study Impact

<table>
<thead>
<tr>
<th>Model</th>
<th>N</th>
<th>Median Citations/Year</th>
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<tbody>
<tr>
<td>Single site</td>
<td>96</td>
<td>5.6</td>
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<tr>
<td>2-5 sites</td>
<td>48</td>
<td>10.7</td>
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<tr>
<td>Ad hoc group</td>
<td>68</td>
<td>15.6 (^a)</td>
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<tr>
<td>Trials group</td>
<td>24</td>
<td>44.3 (^a,c)</td>
</tr>
<tr>
<td>Industry</td>
<td>75</td>
<td>12.0 (^b)</td>
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\(^a\) p<0.001 vs single site, \(^b\) p<0.01 vs single site, \(^c\) p<0.01 vs industry
Investigator-Led Critical Care Trials Groups
H1N1 Influenza
InFACT: a global critical care research response to H1N1

The H1N1 pandemic presents acute care researchers with an extraordinary challenge and an unprecedented opportunity. By early October, 2009, there had been more than 340 000 reported cases of H1N1 infection in 191 countries, with more than 4100 deaths. WHO initially projected that up to 2 billion people could become infected with the virus over the next 2 years. Although vaccination programmes and other factors should reduce this number, plausible estimates of the number of infected individuals who might benefit from admission to intensive care range from 200 000 to 10 million. Influenza killed at least 50 million people during the 1918 pandemic. Today, with antibiotics and antiviral agents, mechanical ventilation, and the supportive measures available in intensive care, most of those deaths could have been prevented.

The mortality for H1N1-infected patients admitted to intensive care ranges from 10 to 40% over the first month, and survivors spend a median of 2 weeks in the intensive care unit. To reduce this toll requires a better understanding of the epidemiology and clinical and treatment of severe H1N1 disease. In parallel, we will develop a biobank to facilitate studies of genetic susceptibility and clinical biology.

We are starting a programme of collaborative, investigator-led randomised trials of treatment strategies that target both the virus and the host response. Our initial three studies will evaluate inexpensive interventions that are available in both the developed and the developing world: corticosteroids and statins. They use adaptive designs to ensure that results can be quickly incorporated into practice, and that ineffective treatments are dropped. As measures of efficacy, they will measure survival of individual patients and the rapidity with which patients can be liberated from limited intensive-care resources.

We seek to reduce the consequences of severe H1N1 infection in the developed world, where available research infrastructure is most robust, and in the developing world, where the human toll is likely to be the greatest. To this end, we will catalogue international critical care capacity, and promote, mentor, and support clinical research activities in resource-poor areas.
Members

ANZICS CTG
ARDSNet
BRIC Net
CCCTG
CRISMA
Chinese CCTG
ESICM CTG
George Institute
GiViTI
Hellenic Sepsis Group
ICNARC
ICCTG
ICS UK CTG
LASI
Scandinavian CTG
Scottish CTG
SepNet
SOAP investigators
USCIITG

Executive

Derek Angus (Treasurer)
John Marshall (Chair)
Kathy Rowan (Secretary)
Steve Webb (Vice-chair)
The International Forum for Acute Care Trialists (InFACT) seeks to improve the care of acutely ill patients around the world through the promotion of high quality clinical research into the causes, prevention, and optimal management of acute, life-threatening illness.
International Severe Acute Respiratory Infections Consortium

- Priority for HIROS
- Supported by Wellcome Trust
- Links to WHO and funders
- Multiple international partners
- Strong ID/virology focus
ISARIC Working Groups

1. Global clinical trials    Derek Angus
2. Databases and metrics    Kathy Rowan
3. Biologic studies         Ken Baillie
4. Changing research       Steve Webb
A Global Adaptive Clinical Trial in Severe Acute Respiratory Infection

- Bayesian adaptive design
- Simple, plausible, inexpensive, and widely available interventions
- Run by national/regional CTGs
- Combined RCT/QI initiative
Applying the Model Elsewhere ...

- Fluids and hemodynamic support
- Prevention and treatment of nosocomial ICU-acquired infection
Multinational GWAS Study of Susceptibility to Severe H1N1

• Ken Baillie, Tim Walsh  Scotland

• Patients from 2009 H1N1 datasets

• Application to Wellcome Trust – October 2012
Outcome Measures Working Group

- Understanding of performance and limitations of existing metrics
- Identification of need for new outcome measures
- Formal process to test and validate these
- Inaugural meeting Amsterdam, May 2013
Global VOICES

A Virtual Organization of Intensive Care and Emergency Services

- Sentinel surveillance
- Representative observational studies
- Educational platform
ACCESS

- Understanding capacity for urban acute care
- Data from 120 cities in World Bank database
• Program track on investigator-led research

• InFACT retreat at game farm prior to meeting
Why does investigator-led research succeed?

- Investigator passion
- Friendship and collegiality
- Scientific rigour
Conclusions

• The foundation for global critical care collaborative research is strong

• The infrastructure is being built

• The prospects are exhilarating
Thank you!!