Reporting Heterogeneity of Treatment Effect in Critical Care Trials

CCCF, Toronto
November 1, 2016

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Disclosures

• Grant Support
  • NHLBI

• Consulting
  • Alexion
  • Asahi Kasei
  • Boehringer Ingelheim
  • GlaxoSmithKline
  • Regeneron
Outline:

• Examples of heterogeneity of treatment effect (HTE) and why it matters

• Recommendations for reporting HTE is Critical Care Trials
Three decades of failed trials for “sepsis”

• >100 studies no durable benefit overall or in traditionally defined subgroups
  • Anti-LPS (Polyclonal Ab, HA-1A, E5)
  • Anti-TNF or anti-IL-1 strategies
  • IVIG, Interferon gamma, GCSF
  • Growth hormone
  • Soluble PLA$_2$, elastase, and PAF Inhibitors
  • Heparin, antithrombin
  • Ibuprofen
  • APC for all severe sepsis and lower risk severe sepsis
  • Tissue factor pathway inhibitor (Opal ESICEM 2009)
  • Phospholipid emulsion (Dellinger CCM 2009)
  • TLR-4 antagonist (Tidswell CCM 2010, Opal, 2012)
  • APC for persistent septic shock (Ranieri & Thompson, 2012)

There must be a better way....
“If the patient would have been enrolled in the study had she been there—that is, she meets all the inclusion criteria, and doesn't violate any of the exclusion criteria—there is little question that the results are applicable.”

Guyatt  JAMA 1994
Can overall results of clinical trials be applied to all patients?

P M Rothwell

<table>
<thead>
<tr>
<th>Relative risk reduction</th>
<th>Absolute risk reduction</th>
<th>Cases treated per</th>
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On average:
Always operate and never give aspirin

By risk:
If low, give aspirin; if high, operate
Efficacy and Safety of Recombinant Human Activated Protein C for Severe Sepsis

Gordon R. Bernard, M.D., Jean-Louis Vincent, M.D., Ph.D., Pierre-Francois Laterre, M.D., Steven P. LaRosa, M.D.,
Drotrecogin alfa (activated) administration across clinically important subgroups of patients with severe sepsis

E. Wesley Ely, MD, MPH; Pierre-François Laterre, MD; Derek C. Angus, MD, MPH; Jeffrey D. Helterbrand, PhD; Howard Levy, MBBCh, PhD; Jean-François Dhainaut, MD, PhD; Jean-Louis Vincent, MD, PhD; William L. Macias, MD, PhD; Gordon R. Bernard, MD; for the PROWESS Investigators

Consistent treatment effect in nearly all traditionally defined subgroups

Conclusion: always give eligible patients drotrecogin alfa (Xigris)
FDA Approved Xigris for High Risk Severe Sepsis (eg. APACE II > 25)
What explains heterogeneity of treatment by disease severity?

- Higher event rates -> more power to see same relative risk reduction
- More favorable risk benefit for drugs with toxicity
- More “inflammation” in higher risk subset -> more therapeutic opportunity (*higher absolute and relative risk reduction*)
- ...

...
Why did traditional subgroup analyses fail to see heterogeneity of treatment effect?
• Conventional subgroup analyses are typically inadequate to detect large and clinically important differences in treatment effects
  • One variable at a time -> limits spectrum
  • Underpowered
• Multivariate risk stratification identifies important treatment differences (if substantial heterogeneity exists) and are superior to traditional subgroup analyses
Limitations of Applying Summary Results of Clinical Trials to Individual Patients
The Need for Risk Stratification

Typical Patient
• 4% → 3% (25% RRR)
• 1% harm
• No overall effect

Average Patient
• 8% → 6% (25% RRR)
• 1% harm
• 8% → 7% (12.5% RRR)

Assume: Constant RRR (25%) and harm in 1% of patients

JAMA, September 12, 2007
Drotrecogin alfa (activated) administration across clinically important subgroups of patients with severe sepsis

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<table>
<thead>
<tr>
<th></th>
<th>Favors drotrecogin alfa (activated)</th>
<th>Favors placebo</th>
<th>28-Day Mortality, %</th>
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Interpret “average effects” and traditional subset analyses with caution!
Heterogeneity of Treatment Effects Complicates the Interpretation of Both “Positive” and “Negative” Trials
Examined treatment effects across deciles of baseline risk using 7,255 nonsurgical ventilated ICU patients

- **Average mortality 39.8%**
- 10,000 simulations of 2,500 patient “clinical trials”
  - **RRR 15 or 20%; Fatal AEs in 3%**
- Considered “Positive” if an overall mortality benefit was detected
“Positive” Trial Simulations

Assumptions = 20% RRR; Fatal AEs 3/100; n=2,500
“Negative” Trial Simulations

15% RRR;Fatal AEs 3/100; n=2,500
“...this work suggests a single average treatment effect from an RCT might be a misleading guide to physicians for their use of a given treatment in an individual patient

...among patients who meet enrollment criteria, some patients will generally have a much greater absolute risk reduction from treatment ... treatment may even increase the risk of death in some.

...the ICU may be a pre-eminent site within which improved analyses and reporting of clinical trials can lead to more effective and efficient decisions, and smarter patient care.”
Additional Examples from Cardiovascular Medicine
Risk Prediction Models to Guide Treatment Decisions

- TIMI Risk Score for NSTEMI
- AHA/NHLBI Cholesterol Risk Calculator
- SPARC - Stroke Prevention in Atrial Fibrillation Risk Calculator
- “DAPT Score” for anti-platelet Rx following PCI
- …
Can we develop a similar approach for guiding treatment decisions for:

- Steroid Therapy for ARDS or Septic Shock?
- Duration of antibiotics (beyond PCT)?
- Transfusion thresholds for PRBC?
- Activated Protein C … did we prematurely abandon APC?

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### Table 3. Pragmatic Recommendations to Examine Heterogeneity of Treatment Effect by Baseline Risk of Death in a Trial with Mortality as Outcome

- Collect prerandomization data for an existing, well-validated severity of illness score (e.g., APACHE, SAPS) for the RCT’s primary outcome. If existing scores are not deemed adequate to the population under study, collect relevant data points to develop an internally validated risk score (22). This is referred to as the baseline risk of death score.
- As primary subgroup analysis, present absolute rates of the primary outcome stratified by quintile of baseline risk of death score.
- Test the statistical significance of the HTE as by testing the statistical significance of the interaction on the absolute scale between the baseline risk of death as a continuous variable and the treatment (recognizing that this is likely underpowered in a single trial, as most subgroups are).
Thank you

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