Clinical Practice Guideline Development – A Pain in the Academic Lessons from pDCD

Matthew Weiss, M.D., Pediatric Intensivist, Québec, Québec
Bram Rochwerg, M.D., Intensivist, McMaster University, Hamilton
CCCF Deceased Donation Forum, November 1, 2016
Affiliations

Canadian Blood Services (MW & BR)
Centre mère-enfant Soleil du CHU de Québec-Université Laval (MW)
Transplant Québec – Donor Physician (MW)
McMaster University & GRADE Working Group (BR)
«Je ne soigne pas l’homme en général, je soigne l’individu en particulier.»

Claude Bernard, MD
Lyon, 1813-1878
pDCD CPG Development Membership

• Steering Committee
  • Matthew Weiss
  • Laura Hornby
  • Bram Rochwerg
  • Sam Shemie
  • Amber Appleby
  • Sylvia Torrance
  • William Witteman

• Implementation
  • Karen Dryden-Palmer
  • Steering Committee members

• CBS Support and Administration
  • Stephanie Currie-McCarragher
  • Clay Gillrie
  • Sophie Gravel
  • Lisa McCarthy-Tamblyn
  • Debbie White
  • Kimberly Young

• WLST
  • Catherine Farrell*
  • Jill Barter
  • Meagan Mahoney
  • Michael van Manen
pDCD CPG Development Membership

• Ante and Post Mortem
  • Mary Bennett*
  • Ram Singh*
  • Alf Conradi
  • Deepak Manhas
  • Samara Zavalkoff

• Death Determination
  • Sonny Dhanani*
  • Allon Beck
  • Laura Hornby
  • Meagan Mahoney
  • Christopher Tomlinson

• Cardiac pDCD
  • Ben Sivarajan*
  • Keith Barrington
  • Anne Dipchand
  • Darren Freed

• Neonatal pDCD
  • Michael van Manen*
  • Keith Barrington
  • Kevin Coughlin
  • Deepak Manhas
  • Christopher Tomlinson
pDCD CPG Development Membership

- **Eligibility and Impact**
  - Aviva Goldberg*
  - Allon Beck
  - Anne Dipchand
  - Valerie Langlois

- **Ethics and Legal**
  - Rebecca Greenberg*
  - Daniel Buchman*
  - Kevin Coughlin
  - Cynthia Cupido
  - Roseanne Dawson
  - Aviva Goldberg
  - Cheryl Mack

- **Society Partners**
  - CPS
  - CCCS
  - CACCN
  - CST

- **Patient Partners**
  - Emile Therien
  - Jennifer Woolfsmith

- **External Reviewer**
  - Tom Nakagawa
Impetus for pDCD CPGs
Canadian Environment - pre pDCD CPGs

• 2006 DCD guidelines silent on pediatric specific issues
  • Also done in the pre-GRADE era
• Only Sick Kids and CHEO had active programs
• No national guidance or transparent analysis of pediatric medical or ethical concerns
DCD in Practice

- In the UK 170% increase in total DCD donation from 2007 - 2014
- American hospitals must have a DCD plan in place for accreditation
- One factor in increase from 66 to 134 pediatric DCD cases 2007 - 2013
- pDCD represented 8% of Canadian pediatric donors in 2014*
  
*preliminary Canadian Blood Services data

NHS Organ Donation and Transplantation Report 2014/15
So what’s going on?
A Vocal Minority

Donating Hearts after Cardiac Death — Reversing the Irreversible

Robert M. Machin, Melody R. Silverman, Adam L. Mintz

Donation after cardiocirculatory death: a call for a moratorium pending full public disclosure and fully informed consent

Ari R Joffe, Joe Carcillo, Natalie Anton, Allan deCaen, Yong Y Han, Michael J Bell, Frank A Maffei, John Sullivan, James Thomas and Gonzalo Garcia-Guerra

Controversy: Death: Ethical issues and institutional process

C.H. Harrison and P.C. Laussen
The Majority View


PROMETHUS

PROMETHUS

Policy Statement

Ethical Controversies in Organ Donation After Circulatory Death

Thomas A. Narayama, Ron Shapiro, John C. Balistreri, Mary R. Trudel, John M. Tavalline, Maryam Valapour, Lori West, David Zasas, and Scott D. Halpern; on behalf of the American Thoracic Society Health Policy Committee

1) Hornby et al. CCM 2010; 2) Dhanani et al. CCM 2014
Rigorous CPGs?
2005 DCD Forum

• Pros -
  • True expert input
  • Broad based participation
  • Highly impactful

• Cons -
  • Done in the pre-GRADE/AGREE era
  • No formal evidence assessment
  • No mechanism for updating
• Started with a broad scoping review of the topic
• Convened a forum on the topic to:
  • Define scope of project
  • Clarify questions that required addressing
• Organized working groups with diverse expertise
• Created professional society partnerships

Pediatric Donation After Circulatory Determination of Death: A Scoping Review*

Matthew J. Weiss, MD^{1,2,3,4}; Laura Hornby, MSc^{5,6}; William Witteman, MIS^{2}; Sam D. Shemie, MD^{7,8,9}
Now to GRADE the Evidence

• GRADE is designed to answer questions through RCTs
• Recommends use of best available evidence, but pDCD evidence low or very low quality
• Qualitative data does not fit cleanly into GRADE tables
• Many questions were not even answerable with numbers
Bram Rochwerkg to the Rescue!
How panels usually view the methodologist
But ultimately it's better to work together...
.....to overcome misinformation and non-evidence based recommendations
Evolution of Guideline Methodology

• In 2008, US Congress asked the IOM to study best methods for developing clinical practice guidelines
• Resulted in 8 standards for trustworthy guidelines
8 Tenets of Believable Guidelines

1. Transparency
2. COI Declaration and Management
3. Stakeholders represented in Guideline Development Committee
4. Systematic reviews performed to summarize evidence
5. Evidence foundation evaluation and rating of strength of recommendation
6. Careful articulation of recommendation
7. External Review
8. Updating at regular intervals
GRADE is most widely used framework that includes all IOM components
Formulate question
Select outcomes
Rate importance of outcomes
Systematic Review (outcomes across studies)
Evidence Profile (GRADEpro)

1. Pooled estimate of effect for each outcome
2. Quality of evidence for each outcome

Start
RCT
observational
high
low

Low rate
Low rate
Low rate
Low rate
Low rate

High
Moderate
Low
Very low

Formulate recommendations
- For or against an action
- Strong or weak (strength)

Strong or weak:
- Quality of evidence
- Balance benefits/downsides
- Values and preferences
- Resource use (cost)

Wording
- “We recommend...” | “Clinicians should...”
- “We suggest...” | “Clinicians might...”
- unambiguous
- clear implications for action
- transparent (values & preferences statement)
GRADE Misconceptions

#1 - GRADE can’t be applied to questions without RCT evidence
Misconception #1 - GRADE Application to Lower Quality Evidence

**PICO Question**: Should a formal prediction tool vs no formal tool (clinical judgement alone) be used for predicting time of death within 30 mins of WLST?

No RCTs, 2 Observational Trials
Grading System for Actionable Questions

- high quality  RCT
- intermediate
- low  observational
- very low
Evidence: high or low quality?

- study design/study ROB
  - Cochrane ROB tool
  - NOS tool
- consistency
- directness (to the question asked)
- imprecision
- reporting bias
Moving Up

• extremely strong, consistent association; no plausible threats to validity, up 2 grades
  – insulin in diabetic ketoacidosis
  – antibiotics in septic shock

• strong, consistent association with no plausible confounders up 1 grade
# GRADE Application to Lower Quality Evidence

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Impact</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>False positive rates (predicted to die within time, but did not)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 observational studies</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>False negative rates (missed donation opportunity)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 observational studies</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>True positive rates (correctly predicts death within time)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 observational studies</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>True negative rates (correctly predicts patient will not die within time)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 observational studies</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
</tbody>
</table>
Misconception #2 – GRADE is not applicable when the direct evidence is lacking

• Good Practice Statements

We recommend antibiotics for Strep pneumonia

We recommend intensivists examine their patients
Good Practice Statement

i) Is the statement clear and actionable?
ii) Is the message really necessary?
iii) Is the net benefit large and unequivocal?
iv) Is the evidence difficult to collect and summarize?
v) If a public health guideline, are there specific issues that should be considered (eg, equity)
vi) Have you made the rationale explicit?
vii) Is this better to be formally GRADEd?
Misconception #3 – GRADE only considers the evidence of benefits and harms

**PICO Question**: Should regional oxygenation perfusion techniques be used for improving organ outcomes in controlled pDCD?
Evidence-to-Decision Considerations

- Quality of the evidence
- Balance between desirable and undesirable effects
- Costs
- Feasibility
- Acceptability
- Impact on Health Equity
- Values and preferences
GRADE Application can be a lot of work

- Potentially true
- But – the pay off including...
  - Representative panels with appropriate COI management
  - Transparent rationales & judgments
  - Explicit linkage to the evidence base with systematic evaluation of the certainty of evidence
  - Consideration of all relevant factors
  - Clear and actionable direction to clinicians

LEADS TO MORE TRUSTWORTHY (& PUBLISHABLE) RESULTS
The Recommendations
Canadian pDCD Recommendations

• Process generated
  • 65 GPSs
  • 7 actionnable recommendations
    • 3/7 justified a recommendation
    • 4/7 resulted in no recommendation
• Extensive list of research priorities
Actionable Recommendations

• We suggest 5 minutes of hands off observation of arrest of circulation prior to determination of death. (conditional recommendation, very low certainty in evidence)

• No recommendation is made regarding the universal administration of heparin in pDCD.
Cardiac pDCD

- Retrieval and transplantation of the heart in pDCD is consistent with the dead donor rule, as death is based on the permanent cessation of circulation.

- Considering the lack of published experience in cardiac pDCD:
  - Cardiac transplant programs should establish criteria for acceptance of heart donation, *ex vivo* cardiac protocols, and heart allocation in pDCD.
Research Agenda

• Need better understanding of inclusion and exclusion criteria for potential donors
• Need better research into risks and benefits of ante mortem treatments
• Need to understand Canadian donor potential
• Need better understanding of family experience
Limitations

• Relatively novel application of GRADE concepts – multiple GPSs
• Evidence base was low to very low quality
• Limited patient partner input
• Potential bias from the sponsor
Immediate Impact

• Four successful pDCD organ recoveries and transplantations since start of our process
• Multiple programs developed or under development
• First case of multi-organ pDCD in Québec May 2016
Future Impact

• Future Canadian Blood Services CPGs will use process
• Better tracking of deceased donation data under development, including pediatric specific monitoring
• Checklists and other KT tools under development
Canadian Blood Services Professional Education Website


Canadian Blood Services' professional education website is the trusted source for health-care professional education materials. We provide vital resources on transfusion of blood components, and donation and transplantation of organs and tissues. Explore our clinical guidelines, leading practices, courses, upcoming events and more.

https://professionaleducation.blood.ca/en
One last controversy
Appropriate Halloween Costume?
Thanks, Questions?