How clinical practice recommendation are developed

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Disclosure

- Member of the GRADE working group
- No financial conflict of interest
This session

• Second of two sessions concerning the use of GRADE methodology in developing recommendations for practice guidelines:

  – How to grade the quality of evidence

  – How to move from evidence to recommendations
Goals and Objectives

1. Define the strength of recommendation

2. Discuss the factors that affect the grading of the strength of recommendation

3. Recommendation grading exercises
Case scenario

• You are sitting on a guideline panel assembled by the Lebanese Ministry of public health and asked to issue a recommendation to answer the following question:

Should home treatment vs. hospital treatment be used for patients with acute DVT of the leg?
Formulate question
Select outcomes
Rate importance
Outcomes across studies
Create evidence profile with GRADEpro
Rate quality of evidence for each outcome
Randomization increases initial quality

1. Risk of bias
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias

Grade down
High
Moderate
Low
Very low
Grade up

Outcome Critical
Outcome Critical
Outcome Important
Outcome Not important

Summary of findings & estimate of effect for each outcome

Systematic review

Guideline development

Formulate recommendations:
• For or against (direction)
• Strong or conditional (strength)

By considering the following factors:
- Problem
- Balance benefits/harms
- Resource use
- Equity
- Acceptability
- Feasibility

• “We recommend using...”
• “We suggest using...”
• “We recommend against using...”
• “We suggest against using...”
Goals and Objectives

1. Define the strength of recommendation

2. Discuss the factors that affect the grading of the strength of recommendation

3. Recommendation grading exercises
Grades of Recommendation Assessment, Development and Evaluation

www.gradeworkinggroup.org

2008 BMJ series

2011 JCE series

RATING QUALITY OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS

GRADE: an emerging consensus on rating quality of evidence and strength of recommendations

Guidelines are inconsistent in how they rate the quality of evidence and the strength of recommendations. This article explores the advantages of the GRADE system, which is increasingly being adopted by organisations worldwide.
Quality of evidence

• The extent to which we can be confident in the estimate of effect
Strength of recommendation

• The extent to which we can be confident that the desirable effects of an intervention outweigh the undesirable effects.
GRADE emphasizes the importance of the quality of evidence supporting a recommendation.
Importance of the quality of evidence

- Hormone replacement therapy in postmenopausal women
- Anti-arrhythmic agents in patients post heart attack
- Thrombolytic therapy in acute myocardial infarction
GRADE emphasizes the importance of the quality of evidence supporting a recommendation

“Evidence is never enough”
High quality evidence

Strong recommendation
Low quality evidence

Weak recommendation
Strength of recommendation

- A recommendation can have one of 2 strength:
  - Strong: panel is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects (or vice versa).
  - Conditional: panel concludes that the desirable effects of adherence to the recommendation probably outweigh the undesirable effects (or vice versa), but is not confident.
## Implications of strong and conditional recommendations

<table>
<thead>
<tr>
<th></th>
<th>Strong recommendation</th>
<th>Conditional recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>Most people in your situation would want the recommended course of action and only a small proportion would not</td>
<td>The majority of people in your situation would want the recommended course of action, but many would not</td>
</tr>
<tr>
<td><strong>Clinicians</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Policy makers</strong></td>
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## Implications of strong and conditional recommendations

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<td><strong>Clinicians</strong></td>
<td>Most patients should receive the recommended course of action</td>
<td>Be prepared to help patients to make a decision that is consistent with their own values</td>
</tr>
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<td><strong>Policy makers</strong></td>
<td></td>
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### Implications of strong and conditional recommendations

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<td><strong>Policy makers</strong></td>
<td>The recommendation can be adapted as a policy in most situations</td>
<td>There is a need for substantial debate and involvement of stakeholders</td>
</tr>
</tbody>
</table>
Goals and Objectives

1. Define the strength of recommendation

2. Discuss the factors that affect the grading of the strength of recommendation

3. Recommendation grading exercises
Determining strength of recommendation

- Quality of evidence
- Balance of benefits and harms
- Values and preferences
- Resource use
Quality of evidence

- The higher the quality of evidence → the more likely the recommendation will be strong

- The lower the quality of evidence → the more likely the recommendation will be conditional
Balance of benefits & harms

- **Benefits clearly outweigh downsides**: Strong recommendation for a given action
- **Benefits probably or a little outweigh downsides**: Weak recommendation for a given action
- **Downsides probably or a little outweigh benefits**: Weak recommendation against a given action
- **Downsides clearly outweigh benefits**: Strong recommendation against a given action
Balance of benefits & harms

• The larger the difference between benefits and harms → the more likely the recommendation will be strong

• The smaller the difference between benefits and harms → the more likely the recommendation will be conditional
Values and preferences

• The greater the variability and uncertainty in values and preferences → the more likely the recommendation will be conditional
Resource use

• Most of the interventions have resource implications: type, availability, amount

• Many of the resource implications are major

• Cost, opportunity cost
Resource use

• The higher the costs of an intervention – that is, the more resources consumed → the more likely the recommendation will be conditional
Determining strength of recommendation

- Quality of evidence
- Balance of benefits and harms
- Values and preferences
- Resource use
- Equity
- Feasibility
- Acceptability
Goals and Objectives

1. Define the strength of recommendation

2. Discuss the factors that affect the grading of the strength of recommendation

3. Recommendation grading exercises
WHO Rapid Advice Guidelines for pharmacological management of sporadic human infection with avian influenza A (H5N1) virus

Holger J Schünemann, Suzanne R Hill, Meetal Kakad, Richard Bellamy, Timothy M Uyeki, Frederick G Hayden, Yazdan Yazdanpanah, John Beigel, Tawee Chotpitayasunondh, Chris Del Mar, Jeremy Farrar, Tran Tinh Hien, Bülent Özbay, Norio Sugaya, Keiji Fukuda, Nikki Shindo, Lauren Stockman, Gunn E Vist, Alice Croisier, Azim Nagjdaliyev, Cathy Roth, Gail Thomson, Howard Zucker, Andrew D Oxman, for the WHO Rapid Advice Guideline Panel on Avian Influenza
PICO question

- **Population:** patients hospitalised with avian influenza (H5N1)
- **Intervention:** oseltamivir
- **Comparator:** No oseltamivir
- **Outcomes:**
  - Mortality
  - Morbidity
  - Antibiotic resistance

Should oseltamivir be used for treatment of patients hospitalised with avian influenza (H5N1)?
Summary of the evidence

- No clinical trial of oseltamivir for treatment of H5N1 patients.
- 4 systematic reviews and health technology assessments (HTA) reporting on 5 studies of oseltamivir in seasonal influenza
  - Hospitalization: OR 0.22 (0.02 – 2.16)
  - Pneumonia: OR 0.15 (0.03 – 0.69)
- 3 published case series
- Many in vitro and animal studies
- No alternative that is more promising at present
- 50 to 80% mortality
- Cost: ~ Euro 50 per treatment course
Judgments about the strength of a recommendation - oseltamivir for treatment of patients hospitalised with avian influenza (H5N1)

<table>
<thead>
<tr>
<th>Factors</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balance between desirable and undesirable</td>
<td>“The benefits are uncertain, but potentially large.”</td>
</tr>
<tr>
<td>Quality of the evidence</td>
<td>“The quality of the evidence is very low.”</td>
</tr>
<tr>
<td>Values and preferences</td>
<td>“All patients and care providers would accept treatment for H5N1 disease.”</td>
</tr>
<tr>
<td>Costs (resource use)</td>
<td>“The cost is not high for treatment of sporadic cases.”</td>
</tr>
</tbody>
</table>
What would you recommend?
Recommendation

In patients with confirmed or strongly suspected infection with avian influenza A (H5N1) virus, clinicians should administer oseltamivir treatment as soon as possible.

Schunemann et al., The Lancet ID, 2007
Recommendation

In patients with confirmed or strongly suspected infection with avian influenza A (H5N1) virus, clinicians should administer oseltamivir treatment as soon as possible.

Remarks: This recommendation places a high value on the prevention of death in an illness with a high case fatality. It places relatively low values on adverse reactions, the development of resistance and costs of treatment.

Schunemann et al., The Lancet ID, 2007
Recommendation

Remarks: Despite the lack of controlled treatment data for H5N1, this is a strong recommendation, in part, because there is a lack of known effective alternative pharmacological interventions at this time.

The panel voted on whether this recommendation should be strong or weak and there was one abstention and one dissenting vote.

Schunemann et al., The Lancet ID, 2007
PICO question

• **Population:** MSM and transgender persons
• **Intervention:** Consistent use of condoms during anal intercourse
• **Comparator:** No consistent use of condoms during anal intercourse
• **Outcomes:**
  - HIV infection
  - Other sexually transmitted infections
  - Quality of Life

Should condoms be consistently used (vs. not used) during anal intercourse in MSM and transgender persons?
# Summary of the evidence

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Consistent condom use</th>
<th>No condom use</th>
<th>Relative (95% CI)</th>
<th>Absolute</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV transmission (follow-up 1 years; Elisa with WB confirmation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5&lt;sup&gt;1&lt;/sup&gt;</td>
<td>observational studies</td>
<td>no serious limitations&lt;sup&gt;2&lt;/sup&gt;</td>
<td>no serious inconsistency&lt;sup&gt;3&lt;/sup&gt;</td>
<td>no serious indirectness&lt;sup&gt;4&lt;/sup&gt;</td>
<td>no serious imprecision&lt;sup&gt;5,6&lt;/sup&gt;</td>
<td>58/2168 (2.7%)</td>
<td>246/1726 (14.3%)</td>
<td>RR 0.34 (0.21 to 0.54)&lt;sup&gt;7,8&lt;/sup&gt;</td>
<td>94 fewer per 1000 (from 66 fewer to 113 fewer)</td>
<td>⊕⊕⊕Ο MODERATE CRITICAL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| STD transmission (follow-up 1 years; Culture or APTIMA Combo 2 (gonorrhea and chlamydia)<sup>9</sup>) |
| 1<sup>10</sup> | observational studies | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | 601/3859 (15.6%) | 831/3088 (26.9%) | RR 0.59 (0.54 to 0.62) | 113 fewer per 1000 (from 102 fewer to 124 fewer) | ⊕⊕ΟΟ LOW IMPORTANT |

| Quality of Life - not measured |
| 0 | - | - | - | - | - | none | - | - | - | - | IMPORTANTE |

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<sup>1</sup> No of observational studies:

- 5 for HIV transmission
- 1 for STD transmission

<sup>2</sup> Limitations for HIV transmission:

- No serious limitations

<sup>3</sup> Inconsistency for HIV transmission:

- No serious inconsistency

<sup>4</sup> Indirectness for HIV transmission:

- No serious indirectness

<sup>5</sup> Imprecision for HIV transmission:

- No serious imprecision

<sup>6</sup> Other considerations for HIV transmission:

- Strong association

<sup>7</sup> Relative risk for HIV transmission:

- RR 0.34

<sup>8</sup> 95% CI for HIV transmission:

- (0.21 to 0.54)

<sup>9</sup> Limitations for STD transmission:

- No serious limitations

<sup>10</sup> Inconsistency for STD transmission:

- No serious inconsistency

<sup>11</sup> Indirectness for STD transmission:

- No serious indirectness

<sup>12</sup> Imprecision for STD transmission:

- None

<sup>13</sup> Other considerations for STD transmission:

- None

<sup>14</sup> Relative risk for STD transmission:

- RR 0.59

<sup>15</sup> 95% CI for STD transmission:

- (0.54 to 0.62)
## Decision Table

<table>
<thead>
<tr>
<th>Factor</th>
<th>Explanation / Evidence</th>
<th>Judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of Evidence</td>
<td>Rated down for design as all included studies were observational. Rated up for high effect size (HIV incidence outcome only)</td>
<td>Moderate (HIV outcome) Low (STD outcome)</td>
</tr>
</tbody>
</table>
| Balance of Benefits vs. Harms | Consistent condom use reduced HIV transmission by 66%; if 1000 individuals practice this behaviour over 1 year:  
  • In low transmission settings (1.7% HIV incidence/yr) instead of 17 there will be 6 new infections  
  • In high transmission (9% HIV incidence/yr) instead of 90 there will be 31 new infections.  
Consistent condom use reduced STD transmission by 59%, if 1000 individuals practice this behaviour over 1 year:  
  • In low transmission settings (5.7% STD incidence/yr) instead of 57 there will be 33 new infections.  
  • In high transmission (10.4% STD incidence/yr) instead of 104 there will be 60 new infections.  
Quality of life considerations (Inconvenience / Decreased desire) not studied | Benefits clearly outweigh harms |
### Decision Table

<table>
<thead>
<tr>
<th>Factor</th>
<th>Explanation / Evidence</th>
<th>Judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Values and preferences</td>
<td><em>Per the Values and Acceptability preliminary report:</em> MSM believe condoms are useful for prevention and many advocate their distribution.</td>
<td>No major variability in values. Individual values might vary; panel placed a higher value on reduction of HIV/STI incidence relative to inconvenience/dislike.</td>
</tr>
<tr>
<td>Resource use</td>
<td></td>
<td>Not a major issue</td>
</tr>
</tbody>
</table>
What would you recommend?
## Recommendation

Using condoms consistently during anal intercourse is strongly recommended for MSM and transgender people over not using condoms.

*Strong recommendation, moderate quality of evidence*

## Complementary remarks

Water- and silicone-based lubricant use is key for the correct functioning of condoms during anal sex.
PICO question

- **Population:** MSM and transgender persons
- **Intervention:** Male circumcision
- **Comparator(s):** No male circumcision
- **Outcomes:**
  - HIV infection
  - Other sexually transmitted infections
  - Quality of Life

Should male circumcision be offered (vs. not offered) to MSM and transgender persons?
Summary of the evidence

• No randomised controlled trial data available to date

• Five new observational studies published since 2008

• Total number of studies with usable data, published and unpublished, all observational: 18
### Decision Table

<table>
<thead>
<tr>
<th>Factor</th>
<th>Explanation / Evidence</th>
<th>Judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of Evidence</td>
<td>No RCTs in MSM to study effect of adult male circumcision. Existing observational evidence is downgraded for design, heterogeneity, and imprecision.</td>
<td>Very low</td>
</tr>
<tr>
<td>Balance of Benefits vs. Harms</td>
<td>Current evidence suggests a potential benefit of adult male circumcision in terms of both HIV (OR 0.87, 95%CI 0.71-1.08 for all MSM irrespective of sexual role; OR 0.28, 95%CI 0.17-0.44 for MSM who practice insertive anal sex) and a non-significant positive effect on other STIs (RR range 0.86-0.90). Harms have not been studied but potentially include surgical complications, pain, and stigma (if circumcision offered only to MSM).</td>
<td>Benefits potentially outweigh harms</td>
</tr>
<tr>
<td>Values and Preferences</td>
<td><em>Per the Values and Acceptability preliminary report:</em> “With regard to adult male circumcision as an HIV prevention strategy, participants raised questions about relevance of circumcision in different cultural settings and adequacy to protect from HIV infection, and relevance to transgender people. Some felt the focus should be on education regarding sexual health rather than circumcision.”</td>
<td>Values and preferences generally against male circumcision</td>
</tr>
<tr>
<td>Resource Use</td>
<td>Significant resources needed for male circumcision in settings where it is not a standard intervention.</td>
<td>Significant concern</td>
</tr>
<tr>
<td>Feasibility</td>
<td>Significant concerns with feasibility of implementing a surgical intervention, especially within an already stigmatized population.</td>
<td>Significant concern</td>
</tr>
</tbody>
</table>
What would you recommend?
Recommendations

Not offering adult male circumcision to prevent HIV and STI acquisition is suggested over offering it to MSM and transgender people.

*Conditional recommendation; very low quality of evidence*

**Complementary remarks**

Further research is needed to examine the effect of adult male circumcision on preventing the acquisition of HIV and STIs among MSM who practise insertive versus receptive anal intercourse.
GLOBAL POLICY RECOMMENDATIONS

Increasing access to health workers in remote and rural areas through improved retention
PICO question

• **Population:** health workers in rural and underserved areas

• **Intervention:** adoption of public recognition measures (such as rural health days, awards and titles)

• **Comparator:** No adoption of public recognition measures

• **Outcomes:**
  – Availability
  – Competence
  – Responsiveness
  – Unintended effects

Should public recognition measures be adopted (vs. not adopted) for health workers in rural and underserved areas?
Summary of the evidence

Recognition from managers, peers and the public is one of the main motivating factors in health care and in other industries (95). But in the case of rural health, the evidence on public recognition comes mainly from case studies of individual health workers who have dedicated their lives to serving rural communities, for which they have received numerous public recognition awards (96-97). Whether these awards made them stay longer or whether intrinsic motivation factors contributed to their long-term service in rural areas is difficult to say. Nevertheless, it is likely that simple public recognition measures, such as titles, medals or awards can go a long way in raising the status and morale of rural health workers and thus contribute to their retention in these areas. Such public recognition measures are an occasion to focus attention on individual health workers and their achievements, thereby demonstrating political support for rural health workers and rural health work.
**Decision Table**

**Population:** health workers in rural or remote areas  
**Intervention:** adopt public recognition measures

<table>
<thead>
<tr>
<th>Factors</th>
<th>Decision</th>
<th>Explanation</th>
</tr>
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<tbody>
<tr>
<td>Quality of the evidence</td>
<td>High</td>
<td>• No direct evidence on improved retention.</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Low</strong></td>
<td>• Supportive evidence from a systematic review of qualitative studies shows that recognition is one of the main motivating factors for health workers.</td>
</tr>
<tr>
<td></td>
<td>Very low</td>
<td></td>
</tr>
<tr>
<td>Values and preferences</td>
<td><strong>No significant variability</strong></td>
<td>• All health workers value the recognition of their efforts, as this improves their morale and status.</td>
</tr>
<tr>
<td></td>
<td>Significant variability</td>
<td></td>
</tr>
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## Decision Table

<table>
<thead>
<tr>
<th>Benefits Advantages</th>
<th>Benefits clearly outweigh disadvantages</th>
<th>• Benefits: improved morale and status, particularly if through national rural health days.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Benefits and disadvantages are balanced</td>
<td>• Disadvantages: individual titles target only a small number of health workers.</td>
</tr>
<tr>
<td></td>
<td>Disadvantages clearly outweigh benefits</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>• Less resource-intensive</td>
<td>• Very limited resources needed for awards or for organizing public recognition events.</td>
</tr>
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<td></td>
<td>• More resource-intensive</td>
<td></td>
</tr>
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<td></td>
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<tr>
<td></td>
<td>• Yes, globally</td>
<td>• No major barrier foreseen.</td>
</tr>
<tr>
<td></td>
<td>• Yes, conditionally</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>• Local influence (mentionation)</td>
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</tbody>
</table>
What would you recommend?
Recommendation

• We recommend the adoption of public recognition measures (such as rural health days, awards and titles) at the local, national and international level for health workers in rural and underserved areas (strong recommendation, low quality evidence)
Final notes

• Conditional recommendations reflect either:
  – Low quality evidence
    ➔ need to push the research agenda
  – Balance of benefits and harms
    ➔ need to be weighted
  – Differing values and preferences
    ➔ need to consider the specific setting
Back to our question

• *Should home treatment vs. hospital treatment be used for patients with acute DVT of the leg?*
## Summary of Findings

### Home treatment compared to hospital treatment for patients with DVT


<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No of Participants (studies) Follow up</th>
<th>Quality of the evidence (GRADE)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects</th>
<th>Risk difference with Home treatment (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>1708 (6 studies)</td>
<td>★★★☆☆☆ LOW&lt;sup&gt;3,4,5,6&lt;/sup&gt;</td>
<td>RR 0.72 (0.45 to 1.15)</td>
<td>46 per 1000</td>
<td>13 fewer per 1000 (from 25 fewer to 7 more)</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>1769 (7 studies)</td>
<td>★★★☆☆☆ MODERATE&lt;sup&gt;3,4,5&lt;/sup&gt;</td>
<td>RR 0.65 (0.44 to 0.94)</td>
<td>76 per 1000</td>
<td>27 fewer per 1000 (from 5 fewer to 43 fewer)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1708 (6 studies)</td>
<td>★★★☆☆☆ LOW&lt;sup&gt;3,4,5,6&lt;/sup&gt;</td>
<td>RR 0.67 (0.33 to 1.36)</td>
<td>21 per 1000</td>
<td>7 fewer per 1000 (from 14 fewer to 8 more)</td>
</tr>
<tr>
<td>Quality of life</td>
<td>0 (3 studies&lt;sup&gt;1&lt;/sup&gt;)</td>
<td>★★★☆☆☆ LOW&lt;sup&gt;9,10&lt;/sup&gt;</td>
<td>Not estimable</td>
<td>See comment</td>
<td>See comment</td>
</tr>
<tr>
<td>Post thrombotic syndrome - not reported</td>
<td>-</td>
<td>See comment</td>
<td>Not estimable</td>
<td>See comment</td>
<td>See comment</td>
</tr>
</tbody>
</table>
Let’s go to the exercise

• Use the evidence to recommendation table
Thank you

Questions?