Outline

• Foundations of trustworthy guidelines
• AGREE II reporting checklist
• GRADE as applied to clinical practice guidelines
Acknowledgment

- This presentation draws on training material provided by the GRADE working group.
  - www.GradeWorkingGroup.org


- Key papers to read:
Trustworthy Guidelines

1. Transparent process
2. Conflict of interest – open and managed
3. Multidisciplinary
   - experts and key stakeholders
   - patients/consumers
4. Evidence from systematic review
5. Clear process for evidence → recommendations
6. Clearly articulated recommendations
7. Externally reviewed
8. Process for updating
9. Implementation – facilitators, barriers, resource implications ……
Foundations of trustworthy guidelines

The Grading of Recommendations Assessment, Development and Evaluation (short GRADE) working group began in the year 2000 as an informal collaboration of people with an interest in addressing the shortcomings of grading systems in health care. The working group has developed a common, sensible and transparent approach to grading quality (or certainty) of evidence and strength of recommendations. Many international organizations have provided input into the development of the GRADE approach which is now considered the standard in guideline development.
GRADE(ing) CPGs

The ultimate goal for the guideline group is to grade the recommendations.

Recommendations take into account:

- Overall quality of evidence:
  - Study bias; inconsistency; indirectness; imprecision other biases.
  - Magnitude of effect; dose-response; residual confounding.

- Importance; balance between harms and benefits; values and preferences; costs/resources.

  - Strong – “We recommend….”
  - Weak or conditional – “We suggest….”
GRADE is outcome-centric

The quality of evidence may vary with across the outcomes.

The study quality (risk of bias) is only one part of the assessment.
Formulating key questions and systemic review

Topic e.g. IgA nephropathy and IgA vasculitis

1. Key questions
   • Who should receive immunosuppressive therapy and who not?
   • What are the most effective immunosuppressive therapies to treat patients with IgA nephropathy?
   • What are the harms of immunosuppressive therapies in patients with IgA nephropathy? …………………etc.

2. PICO – population, intervention, comparator and outcomes for each question
   • Defines the scope of the systematic review
   • Identifies the critical outcomes
Hierarchy of Outcomes

1. Critically important outcomes
   - Evidence profiles and summary of findings tables
   - Overall quality determined by the most important outcome

2. Important but not critical outcomes
   - May not be included in evidence profiles
   - Should play little or not part in formulation of recommendations

3. Not important outcomes
   - Not included in evidence profiles
   - Should not be used to formulated recommendations
Hierarch of Outcomes

Critical for decision making

- All-cause mortality
- End-stage kidney disease (need for dialysis/ eGFR <15 ml/min/1.73m²)
- 50% loss of GFR
- Infection
- Malignancy

Important but not critical for decision making

- Complete remission (as defined by the investigator)
- Annual GFR loss (minimum 3 year follow-up required)

Low importance for decision making

- Urine/serum biomarkers

Patient important outcomes?
SONG-GN Project*
Fatigue, anxiety, quality of life, ability to work

* www.songinitiative.org
<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparator(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with IgA nephropathy</td>
<td>Immunosuppressive medication</td>
<td>Placebo/other immunosuppressive medication</td>
</tr>
<tr>
<td>Patients with IgA nephropathy</td>
<td>Non-immunosuppressive medication*</td>
<td>Placebo/other non-immunosuppressive therapies</td>
</tr>
<tr>
<td>Patient with IgAN in IgA vasculitis</td>
<td>Immunosuppressive therapy</td>
<td>Placebo/other immunosuppressive medication</td>
</tr>
</tbody>
</table>

OUTCOMES

**Critical**
- All-cause mortality
- End-stage kidney disease (need for dialysis/ eGFR <15 ml/min/1.73m²)
- 50% loss of GFR
- Infection
- Corticosteroid-related adverse events, in particular diabetes induction
- Malignancy

**Important**
- Complete remission (as defined by the investigator)
- Annual GFR loss (minimum 3 year follow-up required)
Systematic review

Guideline development

Formulate recommendations:
- For or against (direction)
- Strong or weak/conditional (strength)

By considering:
- Quality of evidence
- Balance benefits/harms
- Values and preferences

Revise if necessary by considering:
- Resource use (cost)

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
- 1. Large effect
- 2. Dose response
- 3. Confounders

Formulate question
Select outcomes
Rate importance
Outcomes across studies
Create evidence profile
Rate quality of evidence for each outcome

Summary of findings & estimate of effect for each outcome
Quality Assessment

Focus is on identifying factors that influence confidence in the magnitude of the effect.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Quality of evidence</th>
<th>Lower if…</th>
<th>Higher if…</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized trials</td>
<td>High</td>
<td>Study limitations (design and execution)</td>
<td>Large effect (e.g., RR 0.5)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>Inconsistency</td>
<td>Very large effect (e.g., RR 0.2)</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>Indirectness</td>
<td>Evidence of dose-response gradient</td>
</tr>
<tr>
<td></td>
<td>Very low</td>
<td>Imprecision</td>
<td>All plausible confounding would reduce a demonstrated effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Publication bias</td>
<td></td>
</tr>
</tbody>
</table>
Quality of evidence: beyond risk of bias

Definition: The extent to which the confidence in an estimate of the treatment effect is adequate to support a particular recommendation

Methodological limitations
Inconsistency of results
Indirectness of evidence
Imprecision of results
Publication bias

Risk of bias:
Allocation concealment
Blinding
Intention-to-treat
Follow-up
Stopped early etc.

Sources of indirectness:
Indirect comparisons
Patients
Interventions
Comparators
Outcomes
Evidence Profiles

• Provide a record of judgements made by the reviewers and/or guideline authors.

• Aim to provide transparency of review process and evaluation of quality of evidence for each outcome.

• Should be provided in a useable format for readers of guidelines.

• The link between recommendations and profiles should be clear.
  – Often poorly done

• KDIGO are using MAGICapp to provide transparency and make the links

• https://www.magicapp.org/
### Induction: Cyclophosphamide vs Induction: Azathioprine

**Patients with proliferative lupus nephritis**

**10 Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty in effect estimates</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td>5 years</td>
<td>Relative risk 1.39 (CI 95% 0.25 - 7.77) Based on data from 148 patients in 2 studies</td>
<td>107 per 1000</td>
<td>149 per 1000</td>
<td>Very Low Due to serious inconsistency, Due to very serious imprecision</td>
</tr>
<tr>
<td><strong>End stage kidney disease</strong></td>
<td></td>
<td>Relative risk 0.40 (CI 95% 0.15 - 1.07) Based on data from 144 patients in 2 studies Follow up: Mean 21 months.</td>
<td>125 per 1000</td>
<td>50 per 1000</td>
<td>Very Low Due to serious risk of bias, Due to very serious imprecision</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td></td>
<td>Relative risk 1.25 (CI 95% 0.27 - 5.88) Based on data from 57 patients in 1 studies Follow up: 18 months.</td>
<td>105 per 1000</td>
<td>131 per 1000</td>
<td>Very Low Due to serious risk of bias, Due to very serious imprecision</td>
</tr>
<tr>
<td><strong>Malignancy</strong></td>
<td></td>
<td>Relative risk 0.59 (CI 95% 0.13 - 2.63) Based on data from 144 patients in 2 studies Follow up: Mean 21 months.</td>
<td>54 per 1000</td>
<td>32 per 1000</td>
<td>Very Low Due to serious risk of bias, Due to very serious imprecision</td>
</tr>
<tr>
<td><strong>≥50% loss of GFR</strong></td>
<td></td>
<td>Relative risk (CI 95% - )</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Conceptualising quality

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
<th>Confidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>We are very confident that the true effect lies close to that of the estimate of the effect.</td>
<td>+++++</td>
</tr>
<tr>
<td>Moderate</td>
<td>We are moderately confident in the estimate of effect: The true effect is likely to be close to the estimate of effect, but possibility to be substantially different.</td>
<td>+++++○</td>
</tr>
<tr>
<td>Low</td>
<td>Our confidence in the effect is limited: The true effect may be substantially different from the estimate of the effect.</td>
<td>+++.○○</td>
</tr>
<tr>
<td>Very low</td>
<td>We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.</td>
<td>+++.○○○</td>
</tr>
</tbody>
</table>
Evidence to recommendations

<table>
<thead>
<tr>
<th>Strength of recommendation</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Strong</td>
<td>Weak</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality of evidence</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
<td>Moderate</td>
<td>Low</td>
<td>Very low</td>
</tr>
</tbody>
</table>
Strength of recommendation

“The strength of a recommendation reflects the extent to which we can, across the range of patients for whom the recommendations are intended, be confident that desirable effects of a management strategy outweigh undesirable effects.”
## Determinants strength

<table>
<thead>
<tr>
<th>Factors that can weaken the strength of a recommendation</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>❑ Lower quality evidence</td>
<td>The higher the quality of evidence, the more likely is a strong recommendation.</td>
</tr>
<tr>
<td>❑ Uncertainty about the balance of benefits versus harms and burdens</td>
<td>The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation is warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak recommendation warranted.</td>
</tr>
<tr>
<td>❑ Uncertainty or differences in patients’ values</td>
<td>The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak recommendation warranted.</td>
</tr>
<tr>
<td>❑ Uncertainty about whether the net benefits are worth the costs</td>
<td>The higher the costs of an intervention – that is, the more resources consumed – the less likely is a strong recommendation warranted.</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Grade</th>
<th>Evidence</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Benefits clearly outweigh harms or vice versa</td>
<td>Confident of size and direction of effect</td>
</tr>
<tr>
<td>1B</td>
<td>Benefits and harms closely balanced</td>
<td>Confident of direction but size less clear</td>
</tr>
<tr>
<td>1C</td>
<td>Serious limitations</td>
<td>Very serious limitations</td>
</tr>
<tr>
<td>1D</td>
<td>Serious limitations</td>
<td>Very serious limitations</td>
</tr>
<tr>
<td>2A</td>
<td>Benefits clearly outweigh harms or vice versa</td>
<td>Confident of size and direction of effect</td>
</tr>
<tr>
<td>2B</td>
<td>Benefits and harms closely balanced</td>
<td>Confident of direction but size less clear</td>
</tr>
<tr>
<td>2C</td>
<td>Serious limitations</td>
<td>Very serious limitations</td>
</tr>
<tr>
<td>2D</td>
<td>Serious limitations</td>
<td>Very serious limitations</td>
</tr>
</tbody>
</table>
When is a strong recommendation with low quality evidence justified?
<table>
<thead>
<tr>
<th>Situation</th>
<th>Certainty of evidence</th>
<th>Benefits</th>
<th>Harms</th>
<th>Values and preferences</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life threatening situation</td>
<td>Low or very low</td>
<td>Low or very low</td>
<td>Immaterial (very low to high)</td>
<td>Intervention may reduce mortality. No adverse events.</td>
<td>High value placed on uncertain but life preserving benefit</td>
</tr>
<tr>
<td>Uncertain benefit, certain harm</td>
<td>Low or very low</td>
<td>High or moderate</td>
<td>High or moderate</td>
<td>Possible but uncertain benefit. Substantial established harm</td>
<td>High value placed on avoiding adverse event over uncertain benefit</td>
</tr>
<tr>
<td>Potential catastrophic harm</td>
<td>Immaterial (very low to high)</td>
<td>Low or very low</td>
<td>Low or very low</td>
<td>Potential important harm, benefit variable</td>
<td>High value placed on avoiding increase in harm</td>
</tr>
<tr>
<td>Possibly equivalent – one clearly more risky or costly</td>
<td>Low or very low</td>
<td>High or moderate</td>
<td>Low or very low</td>
<td>Benefit similar (uncertain), but confident of differences in harms</td>
<td>High value placed on the reduction in harm</td>
</tr>
<tr>
<td>Equivalent benefits – one maybe more risky</td>
<td>High or moderate</td>
<td>Low or very low</td>
<td>Certain that benefit is similar, best estimate is one has more harms</td>
<td>High value placed on avoiding the harm</td>
<td>Strong recommendation against possibly more harmful (1C or 1D)</td>
</tr>
</tbody>
</table>
An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management

Recommendation: We recommend that patients with IPF should not be treated with cyclosporine A (strong recommendation, very low quality evidence).

Values: This recommendation places a high value on preventing side effects and cost and a low value on very low-quality evidence showing discordant results.

Remarks: (Vote: none for use, 18 against use, 4 abstentions, 9 absent.)
Recommendation 3: For patients with chronic noncancer pain with an active substance use disorder

**Strong recommendation AGAINST**

We recommend against the use of opioids

Research evidence Key info Rationale Practical info Decision Aids References Feedback (0)

Low quality evidence suggests a possible substantial increase in the very serious adverse outcomes of unintentional non-fatal overdose and death in patients with active substance abuse disorder using opioids. Compared to individuals without active substance use disorder, patients with chronic non-cancer pain and active substance use disorder are at higher risk for opioid use disorder (risk increases from 5.5% to 8.9%), non-fatal overdose (risk increases from 0.2% to 0.9% at <20 MED/day, with increasing risk at higher doses) and fatal overdose (risk increases from 0.1% to 0.5% at <20 MED/day, with increasing risk at higher doses). [29] Moderate quality evidence does not support an association between smoking status and opioid misuse (adjusted OR 1.29, 95%CI 0.97 to 1.7). [104][14][46][109]

In general, GRADE discourages strong recommendations when the quality of evidence for critical outcomes is low or very low. One paradigmatic situation in which strong recommendations may be warranted despite low or very low quality of evidence is when high quality evidence suggests modest benefits and low or very low quality evidence suggests the possibility of catastrophic harm. For recommendation 3, high quality evidence suggests modest benefit and low quality evidence suggests an elevated risk of serious harm.
Chapter 3: Steroid-sensitive nephrotic syndrome in children

3.1: Treatment of the initial episode of SSNS

3.1.1: We recommend that corticosteroid therapy (prednisone or prednisolone)* be given for at least 12 weeks. (1B)

3.1.1.1: We recommend that oral prednisone be administered as a single daily dose (1B) starting at 60 mg/m²/d or 2 mg/kg/d to a maximum 60 mg/d. (1D)

3.1.1.2: We recommend that daily oral prednisone be given for 4–6 weeks (1C) followed by alternate-day medication as a single daily dose starting at 40 mg/m² or 1.5 mg/kg (maximum 40 mg on alternate days) (1D) and continued for 2–5 months with tapering of the dose. (1B)

Rationale:

• Moderate quality evidence for administering prednisone
• Moderate quality evidence of a single daily dose for at least 4 weeks
• Essentially no evidence for dose (based on ISKDC recommendations)

Questions:

• Why the minimum and why the maximum doses? What are the benefits and harms? What are the values behind this part of the recommendation. If it cannot be described then should it be a 1 (strong) or a 2 (weak)?
Chapter 14: Treatment of anti-glomerular basement membrane antibody glomerulonephritis

14.1: Treatment of anti-GBM GN

14.1.1: We recommend initiating immunosuppression with cyclophosphamide and corticosteroids plus plasmapheresis (see Table 31) in all patients with anti-GBM GN except those who are dialysis-dependent at presentation and have 100% crescents in an adequate biopsy sample, and do not have pulmonary hemorrhage. (IB)

14.1.2: Start treatment for anti-GBM GN without delay once the diagnosis is confirmed. If the diagnosis is highly suspected, it would be appropriate to begin high-dose corticosteroids and plasmapheresis (Table 31) while waiting for confirmation. (Not Graded)

14.1.3: We recommend no maintenance immunosuppressive therapy for anti-GBM GN. (ID)

14.1.4: Defer kidney transplantation after anti-GBM GN until anti-GBM antibodies have been undetectable for a minimum of 6 months. (Not Graded)

Rationale:

- No clear statement on maintenance immunosuppression. This may be obvious to an expert but problematic for non expert reader e.g. patient.

Question – does this reflect:

- Futility of maintenance immunosuppression?
- Harms associated with maintenance immunosuppression?
- Both or other?
Summary

• GRADE provides an overarching framework to ensure that clinical practice guidelines:
  – are based on a systematic search for and evaluation of evidence
  – follow a transparent process for evaluation of evidence and formulation of recommendations
  – provide clear statements of the strength of recommendations and reliability/uncertainty of supporting evidence
  – provide clear statements of benefits and harms underpinning a recommendation
  – provide clear statements of values and preferences underpinning recommendations