Guidelines: harnessing the evidence

Maurizio A. Leone,
SCDU Neurologia, Head and Neck Dept.
“Maggiore della Carità” Hospital,
Novara, Italy

maurizio.leone@maggioreosp.novara.it

Disclosures

Travel reimboursement and research funding from Merck-Serono, Dompe-Idec, TEVA

I did not receive funds related to guideline production and evaluation

Associate editor, European Journal of Neurology

President: Italian Association of Neuroepidemiology 2011-2014

Learning objectives

To be able to explain:

1. Why we need guidelines
2. How to formulate a question that can be answered (PICO)
3. Where to find guidelines
4. The architecture of guideline construction
5. How to critically appraise different guidelines

Q to audience

- Involved in critical evaluation of GL?
- Involved in developing GL?
- Using GL at least once a week in your clinical practice?
- Never using GL?
- Heard about GRADE before this conference?

CLINICAL SCENARIO

John M, 27 years-old, is admitted to the ER on sunday night. The Emergency Service was called by the owner of the pub where John was drinking a beer. They say he was drowsy, but at arrival to the hospital John is alert and conscious. The neuro and general examination is normal, except a tongue bite. Unfortunately no witness is available. Family and personal history are negative for seizures and syncope. Blood examination is normal, except prolactin twice the baseline. A CT scan is normal and an EEG, performed 12 hours later, shows epileptic abnormalities.

John is diagnosed as a first epileptic generalized tonic-clonic seizure and discharged without any antiepileptic therapy.

CLINICAL SCENARIO

John M, 27 years-old, is admitted to the ER on sunday night. The Emergency Service was called by the owner of the pub where John was drinking a beer. They say he was drowsy, but at arrival to the hospital John is alert and conscious. The neuro and general examination is normal, except a tongue bite. Unfortunately no witness is available. Family and personal history are negative for seizures and syncope. Blood examination is normal, except prolactin twice the baseline. A CT scan is normal and an EEG, performed 12 hours later, shows epileptic abnormalities.

John is diagnosed as a first epileptic generalized tonic-clonic seizure and discharged without any antiepileptic therapy.

Diagnosis - what is the probability that John had an epileptic seizure ?
(predictive value of tongue bite, prolactin, EEG/repeated EEG, ...)

CLINICAL SCENARIO

John M, 27 years-old, is admitted to the ER on sunday night. The Emergency Service was called by the owner of the pub where John was drinking a beer. They say he was drowsy, but at arrival to the hospital John is alert and conscious. The neuro and general examination is normal, except a tongue bite. Unfortunately no witness is available. Family and personal history are negative for seizures and syncope. Blood examination is normal, except prolactin twice the baseline. A CT scan is normal and an EEG, performed 12 hours later, shows epileptic abnormalities.

John is diagnosed as a first epileptic generalized tonic-clonic seizure and discharged without any antiepileptic therapy.

Diagnosis - what is the probability that John had an epileptic seizure ?
(predictive value of tongue bite, prolactin, EEG/repeated EEG, ...)

Therapy - when to start antiepileptic therapy ?
Which drug ?
How long ?

CLINICAL SCENARIO

John M, 27 years-old, is admitted to the ER on sunday night. The Emergency Service was called by the owner of the pub where John was drinking a beer. They say he was drowsy, but at arrival to the hospital John is alert and conscious. The neuro and general examination is normal, except a tongue bite. Unfortunately no witness is available. Family and personal history are negative for seizures and syncope. Blood examination is normal, except prolactin twice the baseline. A CT scan is normal and an EEG, performed 12 hours later, shows epileptic abnormalities.

John is diagnosed as a first epileptic generalized tonic-clonic seizure and discharged without any antiepileptic therapy.

Diagnosis - what is the probability that John had an epileptic seizure ?
(predictive value of tongue bite, prolactin, EEG/repeated EEG, ...)

Therapy - when to start antiepileptic therapy ?
Which drug ?
How long ?

Prognosis - what is John's probability to have a relapse ?
.. and to reach a seizure-free period ? ... or to die ?

We need evidence (about the accuracy of diagnostic tests, the power of prognostic markers, the comparative efficacy and safety of interventions, etc.) about 5 times for every in-patient. Sackett et al. Evidence based medicine: what it is and what it isn't. BMJ 1996;312:71

Foreground questions: Clinical decision-making, history taking, examining, diagnosing, and therapeutic intervening.

"Background" questions (about the disorder, test, treatment, ...) have 2 components:

a. Root* + Verb: "What causes ..."
b. Condition: "... stroke?"

* Who, What, Where, When, Why, How

Formulate a clinical question that can be answered

1st part	Population	Clinical characteristics of the patient or of the reference patients population
2nd part	Intervention	Therapy: drug / device / procedure Diagnosis: test
	Comparator	Alternative clinical act (placebo / no therapy / other therapy / other test)
3rd part	Outcome	Clinical outcome of interest (to be increased/reduced)
	Time	Time dimension of the observation of the outcome

Starting antiepileptic therapy (immediate vs. deferred)

Components: PICO(T)

- Population
- Intervention
- Control
- Outcome
- T (Time)

Population

In patients with a first epileptic seizure,

Starting antiepileptic therapy (immediate vs. deferred)

Components: PICO(T)

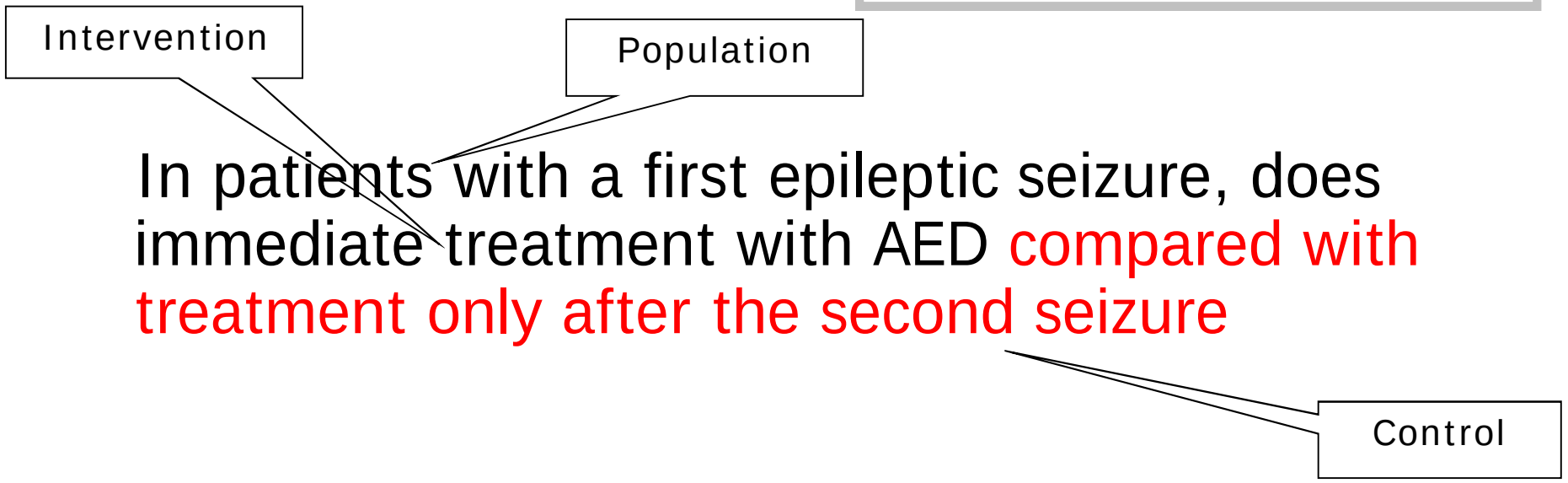
- Population
- Intervention
- Control
- Outcome
- T (Time)

In patients with a first epileptic seizure, does immediate treatment with AED

Starting antiepileptic therapy (immediate vs. deferred)

Components: PICO(T)

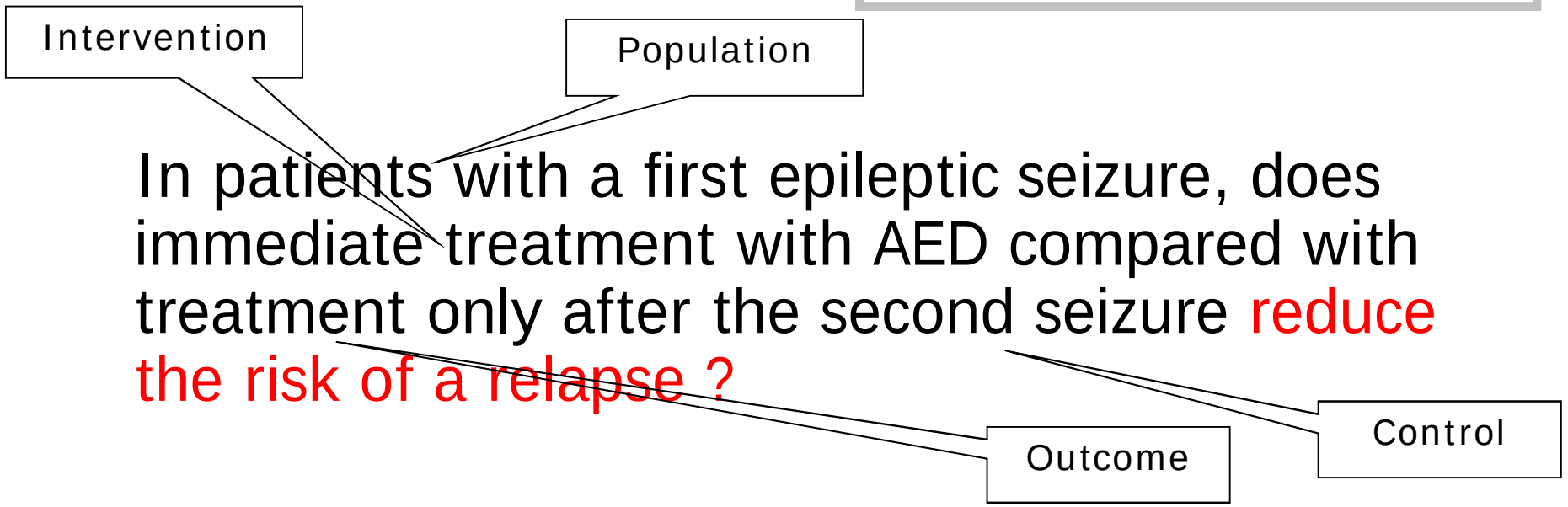
- Population
- Intervention
- Control
- Outcome
- T (Time)



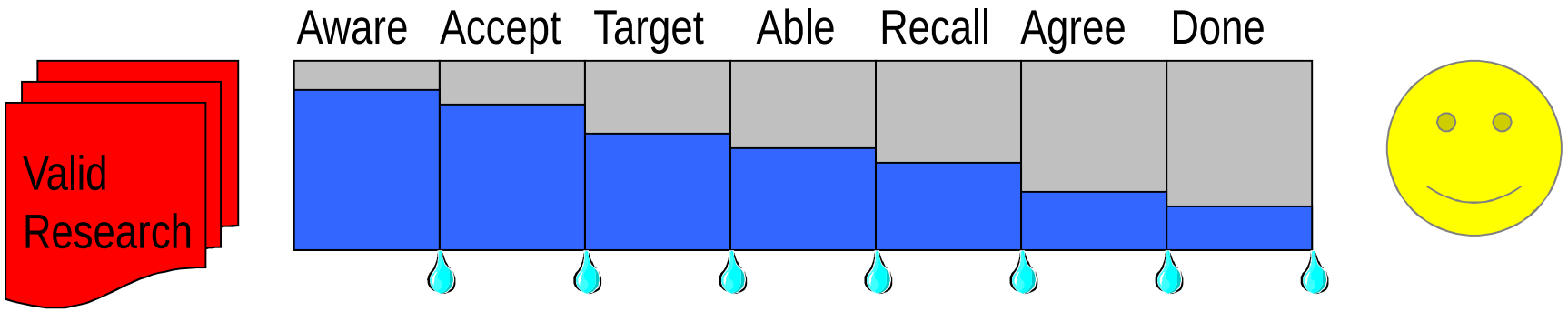
Starting antiepileptic therapy (immediate vs. deferred)

Components: PICO(T)

- Population
- Intervention
- Control
- Outcome
- T (Time)

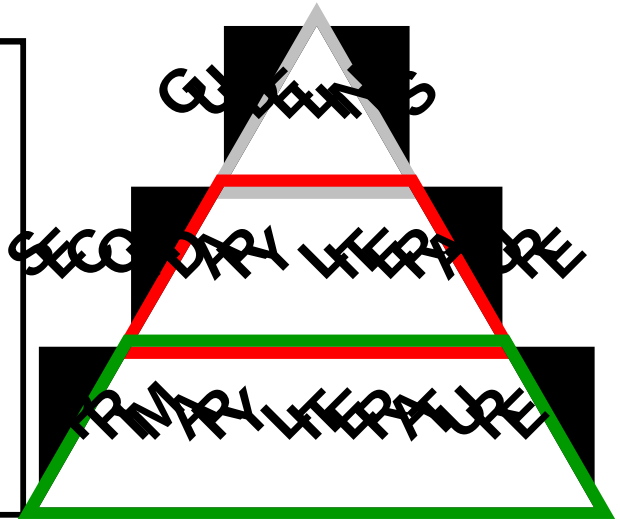


The leaky pipeline from research to practice



Steps from evidence generation to clinical application

1. generation of evidence from research
2. evidence summary and synthesis
3. forming clinical policy
4. application of policy
5. individual clinical decisions



Glasziou and Haynes, ACP JC; 2005: 7-9, modified

Guidelines are:

- Recommendations of clinical practice,
- produced through a systematic process,
- to assist physicians and patients
- in deciding which are the most appropriate method of care
- in specific clinical circumstances.

Aims: To ensure the highest degree of appropriateness of the interventions, reducing the possible variability in clinical decisions

Where to find guidelines?

Guideline Data Banks:	
National Guideline Clearinghouse www.guideline.gov	Guidelines Advisory Committee (Canada)
International Guidelines Database Guidelines International Network	TOP-Towards Optimized Practice (Canada)
CMA Infobase Canadian Medical Association	Sistema Nazionale Linee Guida (Italy)
Biblio Data Banks: NATIONAL LIBRARY OF MEDICINE EMBASE	HAS - Haute Autorité de Santé (France)
National Agencies:	Guia Salud (Spain)
Australian National Health and Medical Research Council	Institute for Quality and Efficiency in Health Care, WHO
New Zealand Guidelines Group	The Finnish Medical Society Duodecim
National Institute for Clinical Excellence NICE (UK)	Scientific Societies:
Scottish Intercollegiate Guidelines network SIGN	EFNS EUROPEAN FEDERATION OF NEUROLOGICAL SOCIETIES

Architecture of guideline development

Select topic

Build a team

Formulate clinical questions

Evidence
- a. Find
- b. Abstract
- c. Analyze
- d. Grade/Rate

Develop Recommendations

Validate

Disseminate

European Journal of Neurology 2005, 12: 575-581

EFNS TASK FORCE

EFNS guideline on the diagnosis and management of alcohol-related seizures: report of an EFNS task force

The EFNS Task Force on Diagnosis and Treatment of Alcohol-Related Seizures
Members of the Task Force: G. Bråthen[a], E. Ben-Menachem[b], E. Brodtkorb[a], R. Galvin[c], J. C. Garcia-Monco[d], P. Halasz[e], M. Hillbom[f], M. A. Leone[g] and A. B. Young[h]

[a]Department of Neurology and Clinical Neurophysiology, Trondheim University Hospital, Trondheim, Norway; [b]Institute of Clinical Neuroscience, SU/Sahlgrenska Hospital, Gothenburg, Sweden; [c]Department of Neurology, Cork University Hospital, Wilton, Cork, Ireland; [d]Servicio de Neurología, Hospital de Galdakao, Galdakao (Vizcaya), Spain; [e]National Institute of Psychiatry and Neurology, Epilepsy Center, Budapest, Hungary; [f]Department of Neurology, Oulu University Hospital, Oulu, Finland; [g]Clinica Neurologica, Ospedale Maggiore della Carità, Novara, Italy; and [h]Castle Craig Hospital, Blyth Bridge, West Linton, Peeblesshire, UK

European Journal of Neurology 2010, 17: 1124–1133 doi:10.1111/j.1468-1331.2010.03151.x
EFNS GUIDELINES/CME ARTICLE

Guidelines on management of low-grade gliomas: report of an EFNS–EANO* Task Force

R. Soffietti[a], B.G. Baumert[b], L. Bello[c], A. von Deimling[d], H. Duffau[e], M. Frénay[f], W. Grisold[g], R. Grant[h], F. Graus[i], K. Hoang-Xuan[j], M. Klein[k], B. Melin[l], J. Rees[m], T. Siegal[n], A. Smits[o], R. Stupp[p] and W. Wick[q]

Level of evidence	Source of evidence	Grade of recom.
I	Systematic reviews, RCTs	A
II	Cohort studies	B
III	Case-control studies	B
IV	Case series	C
V	Expert opinion	D (Good Practice Point)

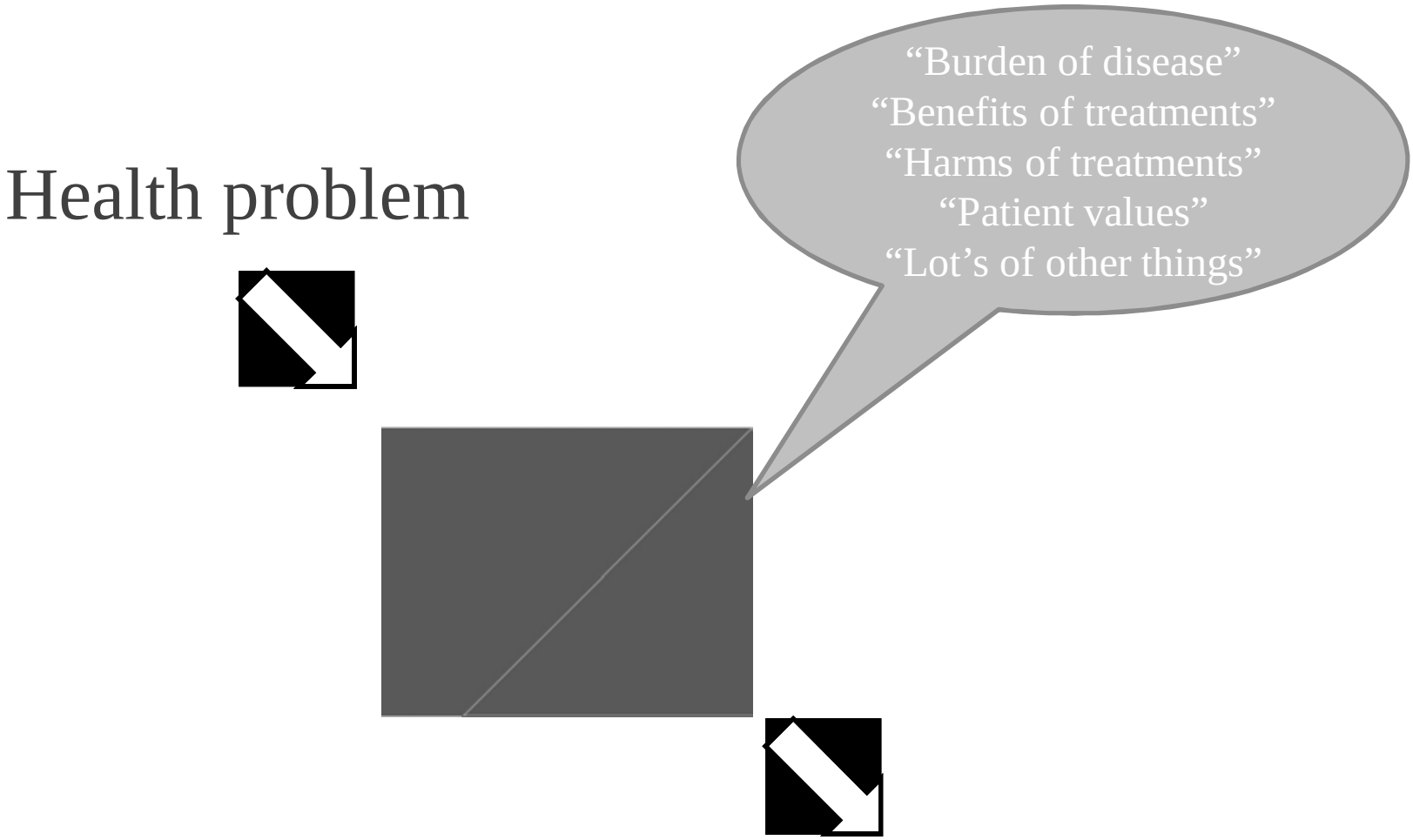
Clinical question: In pts with low-grade gliomas, …	Type of studies	Level of evidence	Grade of recom.	Recommendation "……"
does total/near total resection (compared to partial) decrease the incidence of recurrence and the risk of malignant transformation ?	Several obs cohort studies	III	B	Surgical resection represents the first treatment option, with the goal to maximally resect the tumour
when surgery is unfeasible, is biopsy indicated ?	No studies	V	GPP	When surgery is not feasible, a biopsy should be performed to obtain an histological diagnosis
in pts. with recurrence, is chemioterapy (vs. no) useful to increase the response rate?	Several obs cohort studies	II	B	Chemiotherapy is an option for patient with recurrence after surgery and radiation therapy
does high-dose radiation compared to low-dose reduce the risk of death at 2 years?	2 RCTs	I	A	A total RT dose of 50.4-54 Gy (low-dose) represents the current standard of care
does prophylactic antiepileptic therapy compared to no therapy reduce the risk of seizure ?	1 SR	I	A	Prophylactic AEDs must not be used before any epileptic seizures have occurred

Concerns with current guidelines

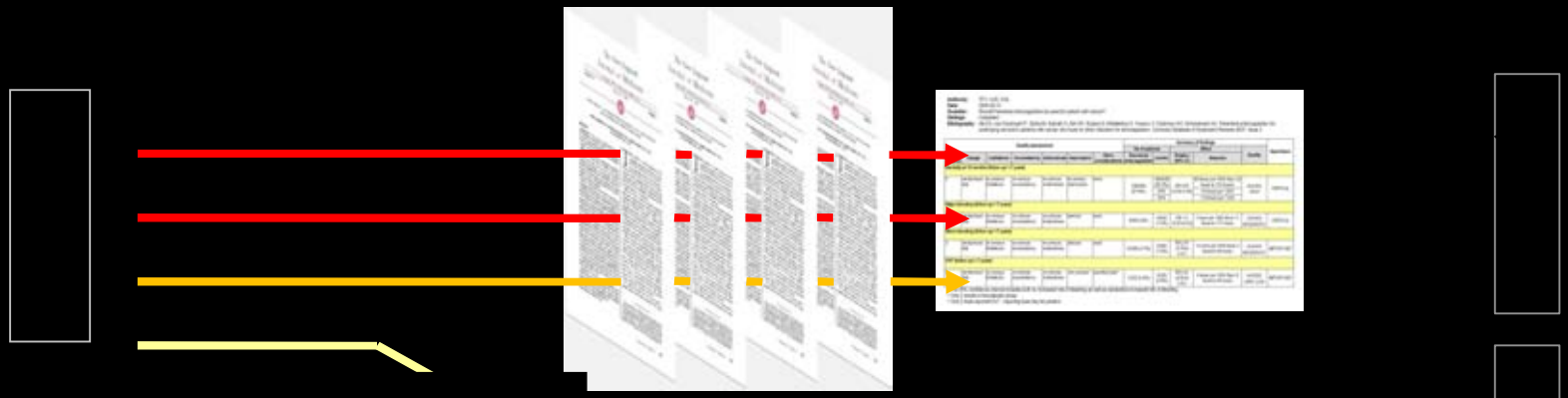
- Too many guidelines have become marketing and opinion-based pieces (... consensus papers rather than guidelines)
- About half of the recommendations are based on level C = expert opinion
- Older approaches have limitations:
  - confuse quality of evidence with strength of recommendations
  - lack well-articulated conceptual framework
  - criteria and procedures not transparent
  - focus on single outcomes
- Great variability of guidelines
- Clinicians do not use guidelines

Grades of Recommendation Assessment, Development and Evaluation

GRADE

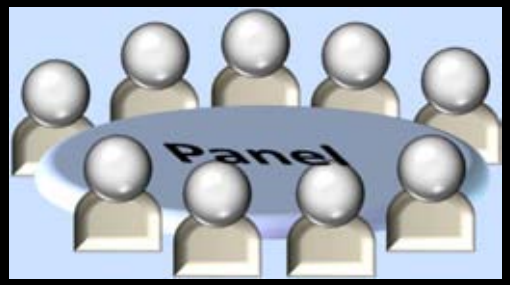


Courtesy of G. Gartlehner, the Austrian Cochrane Branch



Systematic

Guideline d



Courtesy of G. Gartlehner, the Austrian Cochrane Branch

Quality assessment criteria

Quality of evidence	Study design
High	Randomized trial
Moderate	
Low	Observational study
Very low	

Lower if...
Study limitations
Inconsistency
Indirectness
Imprecision
Publication bias

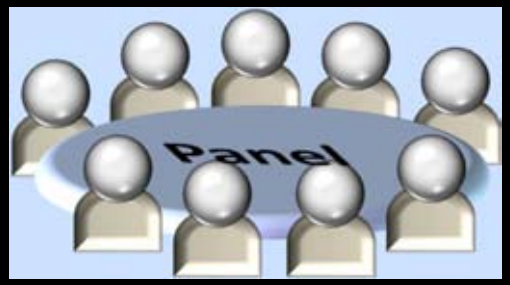
Higher if...
Large effect (e.g., RR 0.5) Very large effect (e.g., RR 0.2)
Evidence of dose-response gradient
All plausible confounding would reduce a demonstrated effect

Quality of the evidence

⨁⨁⨁⨁ High	We are very confident that the true effect lies close to that of the estimate of the effect
⨁⨁⨁™ Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⨁⨁™ ™ Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⨁™ ™ ™ Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Systematic

Guideline d



Courtesy of G. Gartlehner, the Austrian Cochrane Branch

Developing recommendations

Sequential assessment of the quality of evidence

Desirable effects
- health benefits
- less burden
- savings

Undesirable effects
- harms
- more burden
- costs

Evaluation of values and preferences

Formulationg recommendations (strong/weak for/against)

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.

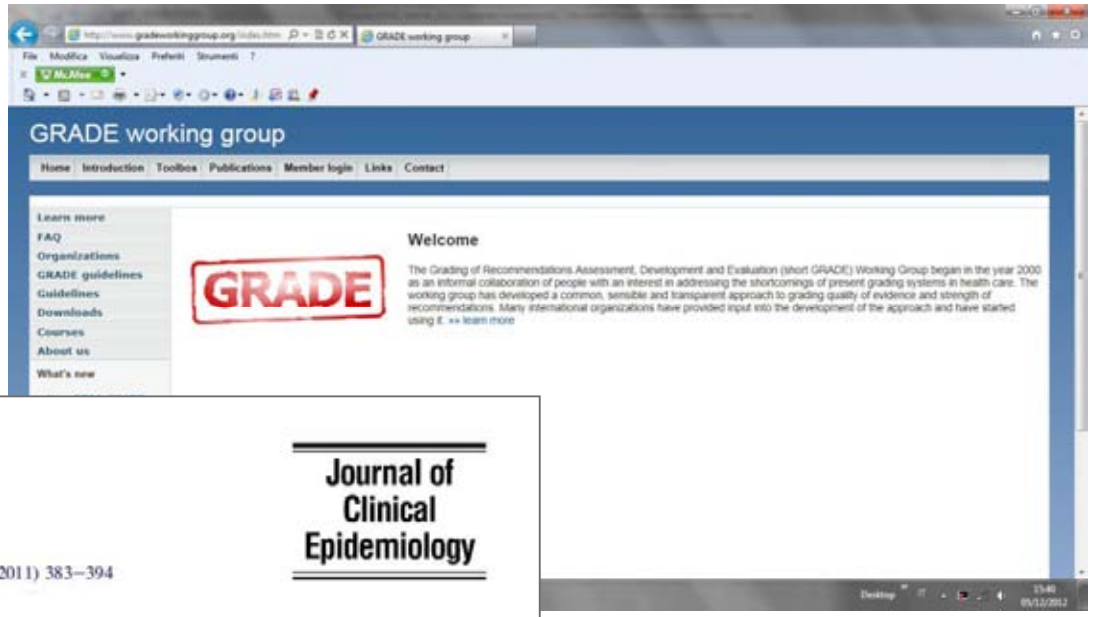
Implications of a strong recommendation

- Patients: Most people in this situation would want the recommended course of action and only a small proportion would not
- Clinicians: Most patients should receive the recommended course of action

Implications of a weak recommendation

- Patients: The majority of people in this situation would want the recommended course of action, but many would not
- Clinicians: Be more prepared to help patients to make a decision that is consistent with their own values/decision aids and shared decision making

Tools



ELSEVIER

Journal of Clinical Epidemiology 64 (2011) 383–394

Journal of Clinical Epidemiology

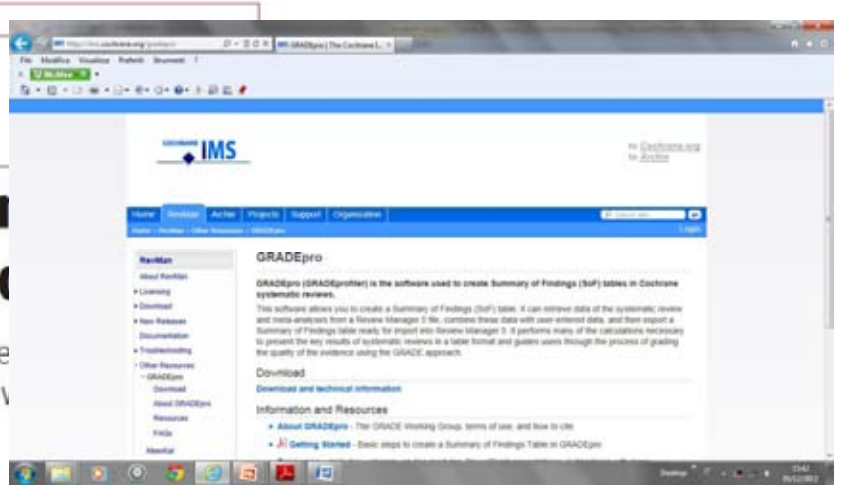
GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables

ANALYSIS

RATING QUALITY OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS

GRADE: an emerging consensus on ratin of evidence and strength of recommen

Guidelines are inconsistent in how they rate the quality of evidence and the stre recommendations. This article explores the advantages of the GRADE system, v being adopted by organisations worldwide



Clinical pathways: Result of guidelines adaptation to local situations, with their specific organizational and management characteristics.

Protocol: the detailed outline of the steps to be followed in the treatment or the diagnosis of a patient.

Guidelines for status epilepticus

Clinical question	Italian LIgue against Epilepsy 2006	EFNS 2010	National Institute for health and Care Excellence NICE, 2012	NeuroCritical Care Society 2012
Pre-hospital therapy	lorazepam, rectal diazepam, im midazolam	lorazepam, iv diazepam	rectal diazepam, oral midazolam	
Definition of “continuous”	> 20 m.	NO	> 30 min	> 5 m.
...“refractory”	>60-90 m	> 60 m or first line drug failure	first line drug failure	first line drug failure
Alternative first line drugs	phenytoin, phenobarbital, valproate, midazolam	?	valproate, levetiracetam	phenytoin, valproate, levetiracetam
Second line drugs	midazolam, tiopental, propofol, phenobarbital, lidocaine, isoflurane	midazolam, tiopental, propofol, phenobarbital	thiopental, midazolam, propofol	Continuously AED up to stop EEG or to burst suppresssion
Antiedema therapy	?	?	?	NO
Thiamine	?	YES	YES, if suggestion of alcohol abuse or impaired nutrition	?

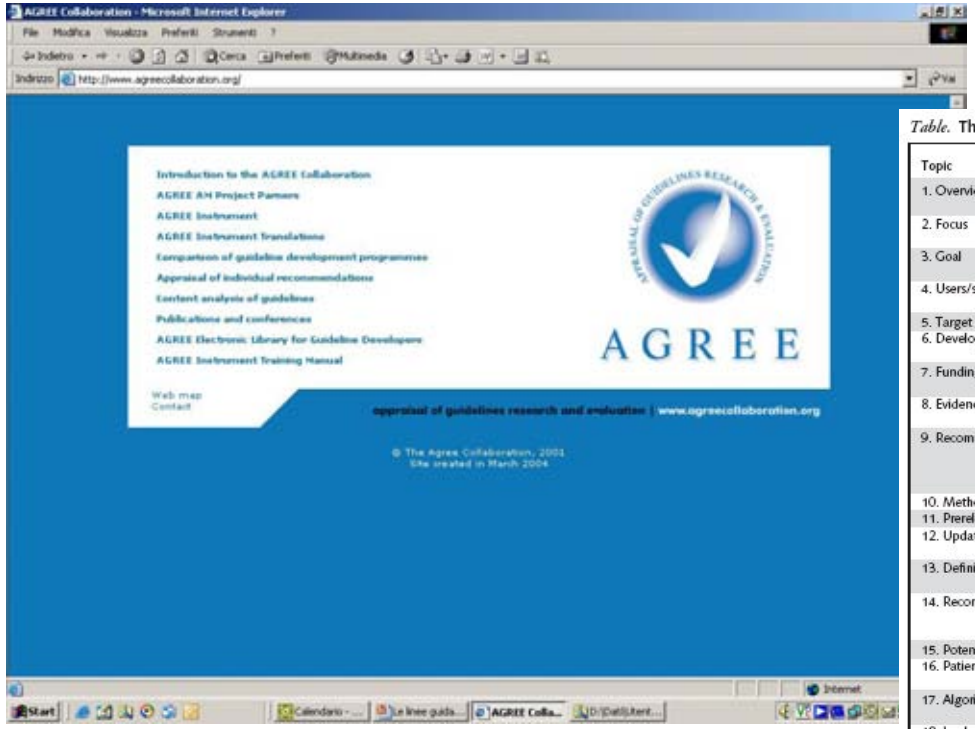


Table. The COGS Checklist for Reporting Clinical Practice Guidelines*

Topic	Description
1. Overview material	Provide a structured abstract that includes the guideline's release date, status (original, revised, updated), and print and electronic sources.
2. Focus	Describe the primary disease/condition and intervention/service/technology that the guideline addresses. Indicate any alternative preventive, diagnostic or therapeutic interventions that were considered during development.
3. Goal	Describe the goal that following the guideline is expected to achieve, including the rationale for development of a guideline on this topic.
4. Users/setting	Describe the intended users of the guideline (e.g., provider types, patients) and the settings in which the guideline is intended to be used.
5. Target population	Describe the patient population eligible for guideline recommendations and list any exclusion criteria.
6. Developer	Identify the organization(s) responsible for guideline development and the names/credentials/potential conflicts of interest of individuals involved in the guideline's development.
7. Funding source/sponsor	Identify the funding source/sponsor and describe its role in developing and/or reporting the guideline. Disclose potential conflict of interest.
8. Evidence collection	Describe the methods used to search the scientific literature, including the range of dates and databases searched, and criteria applied to filter the retrieved evidence.
9. Recommendation grading criteria	Describe the criteria used to rate the quality of evidence that supports the recommendations and the system for describing the strength of the recommendations. Recommendation strength communicates the importance of adherence to a recommendation and is based on both the quality of the evidence and the magnitude of anticipated benefits or harms.
10. Method for synthesizing evidence	Describe how evidence was used to create recommendations, e.g., evidence tables, meta-analysis, decision analysis.
11. Prerelease review	Describe how the guideline developer reviewed and/or tested the guidelines prior to release.
12. Update plan	State whether or not there is a plan to update the guideline and, if applicable, an expiration date for this version of the guideline.
13. Definitions	Define unfamiliar terms and those critical to correct application of the guideline that might be subject to misinterpretation.
14. Recommendations and rationale	State the recommended action precisely and the specific circumstances under which to perform it. Justify each recommendation by describing the linkage between the recommendation and its supporting evidence. Indicate the quality of evidence and the recommendation strength, based on the criteria described in 9.
15. Potential benefits and harms	Describe anticipated benefits and potential risks associated with implementation of guideline recommendations.
16. Patient preferences	Describe the role of patient preferences when a recommendation involves a substantial element of personal choice or values.
17. Algorithm	Provide (when appropriate) a graphical description of the stages and decisions in clinical care described by the guideline.
18. Implementation considerations	Describe anticipated barriers to application of the recommendations. Provide reference to any auxiliary documents for providers or patients that are intended to facilitate implementation. Suggest review criteria for measuring changes in care when the guideline is implemented.

* COGS = Conference on Guideline Standardization.

Basic methodological elements

- Multidisciplinarity
- Use of systematic reviews
- Explicit evaluation of quality of evidence
- Strenght of recommendations