EBM is

- "the conscientious,
- explicit and
- judicious

use of current best evidence in making decisions about the care of the individual patient.

- It means integrating individual clinical expertise with the best available external clinical evidence from systematic research (D. Sackett)
Clinical expertise refers to the clinician's cumulated experience, education and clinical skills.

The patient brings to the encounter his or her own personal and unique concerns, expectations, and values.

The best evidence is usually found in clinically relevant research that has been conducted using sound methodology.
The full integration of these three components into clinical decisions enhances the opportunity for optimal clinical outcomes and quality of life.

In other words: best possible quality of medical care.
Practice variations

- Inappropriate variations of everyday medical practice/practice patterns

- Variations which cannot be explained by:
  - Differences in natural history of the disease
  - Differences in socio-demographic or clinical characteristics of the patients
  - Differences in effectiveness of the treatment methods
  - Differences in cost-effectiveness of treatments
Practice variations

Inappropriate

appropriate
One question:

- 60 yrs old male, T2DM for 7 yrs, BP 130/80, wt: 80 kg
- Se kreat 240 microM, electrolytes OK, 24 UTP 1 g/l, se alb 41 g/l
- Eats 80 g protein/day
- What do you do?
  - Continue with 80 g protein
  - Reduce to 55 g protein
  - Reduce to 40 g protein
More questions:

- How much dialysis – how frequently?
- PD vs HD?
- HDF vs HD vs Psychosocial care
- Hb at 110 vs 120 vs 130?
- Need for SW vs psychologist vs dietician vs pharmacist vs Pt ??? in team?
- Single vs double vs triple blockade of RAAS?
- Native vs activated vitamin D?
Evidence Based Practice

- Gaps between evidence and practice
- Methods to get evidence into practice
- How to narrow the gap at the
  - Individual
  - Team, and
  - Systems levels?
- How to reduce practice variations?
- How to improve quality?
We need guidelines... (?)
Evidence based practice

Structured clinical question – based on the clinical scenario

Finding the best evidence

Critically appraising the evidence

Apply the evidence

Evaluate results
Evidence based practice

Answerable clinical question – based on the clinical scenario

Evaluate results

Find the best evidence

Apply the evidence

Critically appraising the evidence
Finding the evidence ....

- University studies
- Handbooks
- Colleagues
- Personal experience (memories)
- Literature
- Systematic reviews
- Pharmaceutical industry
- Internet
Evidence pyramid – hierarchy of evidence

- Meta-analysis of RCTs
- Randomized Controlled Double Blind Studies
- Randomized Controlled Studies
- Cohort Studies
- Case Control Studies
- Case Series
- Case Reports
- Opinions, Editorials etc.
- Animal Research
- Basic Research
Evidence based practice

Answerable clinical question – based on the clinical scenario

Finding the best evidence

Evaluate results

Apply the evidence

Critically appraising the evidence
What is clinical epidemiology?

Why is it important?
Critical appraisal

☐ Are the results valid?

☐ Are the results important?

☐ Can I apply the evidence to the specific clinical situation for the specific patient?
What is clinical epidemiology?

- Clinical epidemiology provides the methodology with which to assess the effectiveness of medical care/ specific interventions
- to improve the health of the public

- The field concerned with applying epidemiological principles in a clinical setting
- linking principles and methods of classic epidemiology, biostatistics, and clinical medicine
Selected concepts of clinical epidemiology

- study design,
- hypothesis testing,
- treatment effect,
- diagnostic performance
- outcomes assessment,
- data management
- statistical analysis.
What is epidemiology?

- **Epidemiology** is the study of
  - factors affecting the *health* and *illness* of populations,
  - Frequency of diseases in populations
  - Distribution of diseases in populations

- and serves as the foundation and *logic* for interventions made in the interest of *public health* and *preventive medicine*. 
Selected milestones in classic epidemiology - I

- **Edward Jenner** (1749-1823) – vaccine against smallpox

- **Dr. John Snow** - suppression of an 1854 outbreak of cholera in London's Soho district. He identified the cause of the outbreak as a public water pump on Broad Street and had the handle removed, thus ending the outbreak. (It has been questioned as to whether the epidemic was already in decline when Snow took action.)

- Another important pioneer was Hungarian physician **Ignac Semmelweis**, who in 1847 brought down infant mortality at a Vienna hospital by instituting a disinfection procedure. His findings were published in 1850, but his work was ill received by his colleagues.
Selected milestones in classic epidemiology - II

- **1954** - British Doctors Study (Richard Doll and Austin Bradford Hill): strong statistical support to the suspicion that tobacco smoking was linked to lung cancer Early case-control study. Smoking and carcinoma of the lung: Preliminary report. [Br. Med. J. 2:739, 1950]

- **Cohort study**: longitudinal study in a population (cohort): Framingham study. 10,000 inhabitant of the town have been enrolled at baseline. F/U cca 50 yrs. [Annals New York Academy of Sciences 107:539;1963]
Basic principles of clinical studies - I

1. Research question – we do need one

About natural history, etiology, prognosis or treatment of diseases (population level).
Basic principles of clinical studies - II

2. Design

Dependent variable (outcome)
Independent variable(s) (exposure)
Population studied
Temporality; directionality
Prospective, Retrospective, cross-sectional

- case definition/event definition
- collection/documentation of „caseness”/ events
- planning/timing the study; selecting the setting;
designing the population (inclusion/exclusion/sample size)
Ethical considerations (confidentiality; appropriateness; consent)
3. **Realization of the study**

Proper representation of the target population; selection process; non-response.

Observation/data collection; availability, reliability, validity, consistency, standardized protocol, coding manual & training of quality control data management.
Basic principles of clinical studies - IV

4. **Analysis**
   Quality of data – data capture, data entry, quality assessment; cleaning;

   Descriptive statistics
   - frequency, association

   Hypothesis testing
   - statistics
5. **INTERPRETATION**
bias, validity, generalizability, consequences, importance, strengths and limitations – new and additional questions, hypotheses
- Formulate a concise clinical question
- Identify the best type of study to answer clinical questions;
- Identify major sources of bias and their likely effects on results;
- Understand and interpret: 95% confidence intervals; p values; and power estimates;
- Understand and interpret: prevalence; incidence; relative risk; risk ratio; odds ratio; risk difference;
Types of clinical studies
### TYPES OF CLINICAL QUESTIONS

<table>
<thead>
<tr>
<th>Types</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>What is the likelihood for a patient having a specific symptom or yielding „positive” on a specific test to have the disease?</td>
</tr>
<tr>
<td>Therapy</td>
<td>Is the therapy in question more effective in achieving a particular outcome than an alternative therapy (including no therapy)?</td>
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<td>What is the cause of the disease? OR: how likely is a particular intervention to cause a specific side effect?)</td>
</tr>
</tbody>
</table>
## TYPES OF CLINICAL QUESTIONS

<table>
<thead>
<tr>
<th>Minority</th>
<th>„Exposure”</th>
<th>„effect”</th>
</tr>
</thead>
<tbody>
<tr>
<td>diagnosis</td>
<td>result of a test</td>
<td>disease</td>
</tr>
<tr>
<td>therapy</td>
<td>medication, surgery</td>
<td>recovery side effect</td>
</tr>
<tr>
<td>prevention</td>
<td>e.g. pt. information, medication</td>
<td>no disease</td>
</tr>
<tr>
<td>prognosis</td>
<td>risk factor</td>
<td>eg. morbidity</td>
</tr>
</tbody>
</table>
Types of clinical studies - I

- In *observational studies* researchers observe patient groups without allocation of the intervention, whereas in *experimental studies* researchers allocate the treatment.
Types of clinical studies - II

- Studies may be
  - retrospective, meaning that the direction of inquiry is backward from the cases and that the events of interest transpired before the onset of the study.
  - prospective, meaning that the direction of inquiry is forward from the cohort inception and that the events of interest transpire after the onset of the study.
Types of clinical studies - III

**Retrospective**
- Exposure
- Outcome
- Cases

**Prospective**
- Cohort
- Exposure
- Outcome

*study onset

Direction Of Inquiry
Cross-sectional studies are used to survey one point in time.

Longitudinal studies follow the same patients over multiple points in time.
GENERAL STRUCTURE OF A CLINICAL STUDY

<table>
<thead>
<tr>
<th>„Exposure“ (eg. risk factor, medication)</th>
<th>yes</th>
<th>no</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>no</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

„effect“ (eg. disease, recovery)

Measures of the effect: eg. Relative risk \[\frac{a}{(a+b)/c/(c+d)}\]
CROSS SECTIONAL STUDY

- Advantages
  - cheap, simple, fast
  - No ethical problem

- disadvantages
  - It may suggest association but not causality
  - Bias
  - Distribution of confoundings may be unequal
  - Group size may be different
  - Neyman bias
CASE-CONTROL STUDIES

- After selecting „cases” and „controls” one compares the presence or absence of a hypothetical „cause” or exposure in the past in the two groups.

- It is important to make the „controls” as similar to „cases” as possible (except the presence of the symptom or disease).
CASE-CONTROL STUDIES

Risk factor present?  

<table>
<thead>
<tr>
<th>yes</th>
<th>disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>no</td>
<td></td>
</tr>
</tbody>
</table>

Sample of "cases"

population

Sample of "controls"

Direction of the study

<table>
<thead>
<tr>
<th>risk factor</th>
<th>disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>a</td>
</tr>
<tr>
<td>yes</td>
<td>b</td>
</tr>
<tr>
<td>no</td>
<td>c</td>
</tr>
<tr>
<td>no</td>
<td>d</td>
</tr>
</tbody>
</table>
**CASE-CONTROL STUDIES**

Diuretics, beta-blockers, and the risk for sudden cardiac death in hypertensive patients  
Ghoes AW. et al. NEJM 1995;123:481-7

- **Question:** Is there a correlation between the use of K-sparing diuretics and sudden death?
- **Method:** review of charts of 257 pts with HTN who died of sudden death vs 257 alive pts with HTN („controls”) (usage of diuretics)

<table>
<thead>
<tr>
<th></th>
<th>case</th>
<th>controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>33</td>
<td>23</td>
</tr>
<tr>
<td>no</td>
<td>224</td>
<td>234</td>
</tr>
</tbody>
</table>

**Diuretics**

**OR** = 1.50
CASE-CONTROL STUDIES

- advantages:
  - effective, cheap, fast – there is no F6u
  - Usually less patients are needed than for a cross-sectional study
  - The only feasible design for very rare disorders or for ones with very long latency period;

- disadvantage:
  - Potential for bias (selection bias, recall bias – problems with documentation, etc.)
  - Confoundings;
  - selection of control groups is difficult
  - Temporality may be questionable
COHORT STUDY
COHORT STUDY

- F/u of groups („cohorts”) of pts exposed versus not exposed to a given factor (risk factor) than a comparison of a pre-specified outcome (e.g. appearance of a disease) between the two groups.

- To make the two groups as similar as possible

- At the beginning no one shows the symptoms
COHORT STUDY


- **Question:** Is salt sensitivity a risk factor for cardiovascular events?
- **Method:** 62 salt-sensitive (proposed “cause”) and 94 salt-resistant pts, 7.3 yrs f/u, outcome (“effect”) CV events

<table>
<thead>
<tr>
<th>CV event</th>
<th>yes</th>
<th>no</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SS</strong></td>
<td>17</td>
<td>45</td>
<td>1.87</td>
</tr>
<tr>
<td><strong>SR</strong></td>
<td>14</td>
<td>80</td>
<td></td>
</tr>
</tbody>
</table>

RR= 1.87
COHORT STUDY

- **advantages**
  - No ethical problems
  - It can determine temporality and directionality
  - The only way to establish the role real risk factors in humans
  - Exclusion and inclusion criteria can be standardized
  - One can look at several outcomes
  - Cheaper and more simple than RCT

- **Disadvantages**
  - Effect of a confounding can not be ruled out
  - Still expensive, takes time,
  - It is difficult and not feasible for rare disorders or for ones with long latency-periods
  - Groups may not be comparable
Randomized Controlled Trial

- Randomized (by chance) allocation of patients into experimental (e.g., new medication) or control (e.g., placebo or conventional therapy) group than patients are followed prospectively and outcomes are compared between the two groups.

- A special "cohort" study

- Randomization renders the two groups comparable.
Randomized Controlled Trial

Patients

sample

New therapy
(random allocation)

yes

yes

Follow up

Better outcome?

yes

no

no

(控制 group)

New therapy

outcome

<table>
<thead>
<tr>
<th>good</th>
<th>bad</th>
</tr>
</thead>
<tbody>
<tr>
<td>New therapy</td>
<td>a</td>
</tr>
<tr>
<td>Control</td>
<td>c</td>
</tr>
</tbody>
</table>
Randomized Controlled Trial

Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study


- Qestion: Is intensive risk factor management more effective to prevent nephropathy than standard therapy?
- Method: randomization- 80 pts intensive therapy, 80 pts standard therapy, 3,8 yrs f/u, outcome - diabetic nephropathy

<table>
<thead>
<tr>
<th>nephropathy</th>
<th>yes</th>
<th>no</th>
<th>RR= 0.42</th>
</tr>
</thead>
<tbody>
<tr>
<td>intenztive</td>
<td>8</td>
<td>72</td>
<td>80</td>
</tr>
<tr>
<td>standard</td>
<td>19</td>
<td>61</td>
<td>80</td>
</tr>
</tbody>
</table>
RANDOMIZED CONTROLLED TRIAL

- advantage
  - Equal distribution of potential confoundings
  - „blinding” is possible
  - Randomization facilitates statistical comparison
  - Secondary analyses

- disadvantage
  - Ethical difficulties
  - expensive, complicated
  - volunteer bias
<table>
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<th>What is the likelihood for a patient having a specific symptom or yielding „positive” on a specific test to have the disease??</th>
<th>Cross sectional study</th>
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<tbody>
<tr>
<td>Therapy</td>
<td>Is the therapy in question more effective in achieving a particular outcome than an alternative therapy (including no therapy)?</td>
<td>Prospective, randomized, controlled study</td>
</tr>
<tr>
<td>Prognosis</td>
<td>What is the likelihood of a particular outcome in this patient?</td>
<td>Longitudinal cohort-study</td>
</tr>
<tr>
<td>Etiology</td>
<td>What is the cause of the disease? OR: how likely is a particular intervention to cause a specific side effect?)</td>
<td>Studies comparing “cases” and “controls” (RCT, case-control or cohort- study)</td>
</tr>
</tbody>
</table>
LEVELS OF EVIDENCE  (therapy)

- Ia: Systematic review of RCTs SR (with homogeneity) of RCTs
- Ib: At least one good RCT (with narrow Confidence Interval)
- II.a: SR (with homogeneity) of cohort studies
- II.b: Individual cohort study (including low quality RCT; e.g., <80% follow-up)
- III.a: SR (with homogeneity) of case-control studies
- III.b: Individual Case-Control Study
- IV. Case-series (and poor quality cohort and case-control studies)
- V. Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"
## Grades of Recommendation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>consistent level 1 studies</td>
</tr>
<tr>
<td>B</td>
<td>consistent level 2 or 3 studies or extrapolations from level 1 studies</td>
</tr>
<tr>
<td>C</td>
<td>level 4 studies or extrapolations from level 2 or 3 studies</td>
</tr>
<tr>
<td>D</td>
<td>level 5 evidence or troublingly inconsistent or inconclusive studies of any level</td>
</tr>
<tr>
<td>Grade of Recommendation*</td>
<td>Benefit vs Risk and Burdens</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Strong recommendation, high-quality evidence, Grade 1A</td>
<td>Desirable effects clearly outweigh undesirable effects, or vice versa</td>
</tr>
<tr>
<td>Strong recommendation, moderate-quality evidence, Grade 1B</td>
<td>Desirable effects clearly outweigh undesirable effects, or vice versa</td>
</tr>
<tr>
<td>Strong recommendation, low or very low-quality evidence, Grade 1C</td>
<td>Desirable effects clearly outweigh undesirable effects, or vice versa</td>
</tr>
<tr>
<td>Weak recommendation, high-quality evidence, Grade 2A</td>
<td>Desirable effects closely balanced with undesirable effects</td>
</tr>
<tr>
<td>Weak recommendation, moderate-quality evidence, Grade 2B</td>
<td>Desirable effects closely balanced with undesirable effects</td>
</tr>
<tr>
<td>Weak recommendation, low or very low-quality evidence, Grade 2C</td>
<td>Desirable effects closely balanced with undesirable effects</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Numbers</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------</td>
</tr>
<tr>
<td>High</td>
<td>1</td>
</tr>
<tr>
<td>Moderate</td>
<td>2</td>
</tr>
<tr>
<td>Low</td>
<td>3</td>
</tr>
<tr>
<td>Very low</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Action based on balance between benefit and harm</th>
<th>Numbers</th>
<th>Letters</th>
<th>Traffic lights</th>
<th>Thumbs</th>
<th>Arrows</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do</td>
<td>1</td>
<td>A</td>
<td>°</td>
<td>✓✓✓✓✓</td>
<td>↑↑</td>
</tr>
<tr>
<td>Probably do</td>
<td>2</td>
<td>B</td>
<td>°</td>
<td>✓✓✓✓</td>
<td>↑↓</td>
</tr>
<tr>
<td>Probably don't do</td>
<td>3</td>
<td>C</td>
<td>°</td>
<td>✓✓✓✓</td>
<td>↓↓</td>
</tr>
<tr>
<td>Don't do</td>
<td>4</td>
<td>D</td>
<td>°</td>
<td>✓✓✓✓</td>
<td>↓↓</td>
</tr>
</tbody>
</table>
RCT? Vs observational data

Decisions for an individual based on data from populations - Typical? If not then what?

MDRD, HEMO, DECOR, etc – $$$$$$$$$$$$

Observational – hypothesis: what happens to the hypotheses?

What happens meanwhile or at all?