Coördinatiecommissie Antibioticabeleid / Commission de coordination de la politique antibiotique

Evidence-Based Guidelines for the Hospital Use of Antibiotics

Antibiotic treatment of **acute community-acquired pyelonephritis** in immunocompetent adults. A national clinical guideline.

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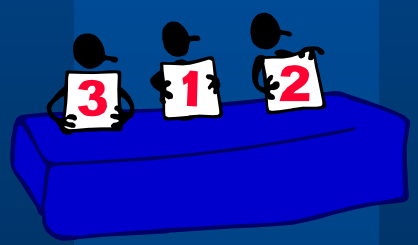


1	2	3	4	5
strongly disagree	disagree	no opinion	agree	strongly agree

Mission of the project

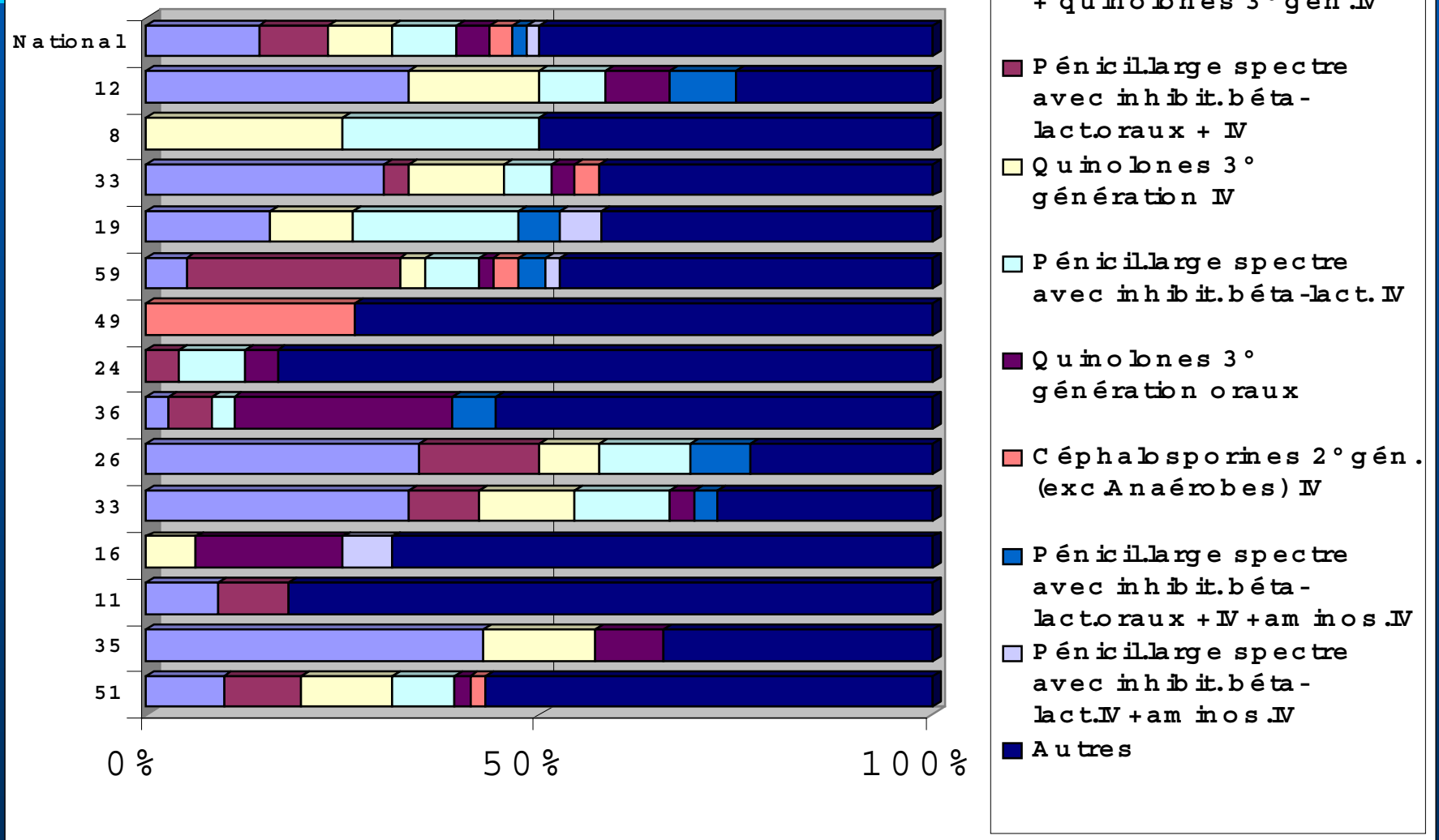
- **To promote the appropriate use of antibiotics:**
  - **to reduce overuse and inappropriate use of antibiotics**
  - **to reduce the use of newer antibiotics when existing antibiotics are effective**
  - **to avoid or limit the development of antibiotic resistance**

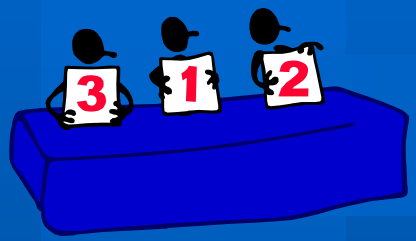
➔best medical practice, quality of care

Clinical Practice Guidelines

- *"systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances"*
- They are designed *to help* practitioners assimilate, evaluate and implement the ever-increasing amount of evidence and opinion on best current practice
- Clinical guidelines are intended as neither cookbook nor textbook but, where there is evidence of *variation in practice* and a strong research base providing evidence of effective practice, guidelines can assist health care professionals in making decisions about appropriate and effective care for their patients

Minimal Data Analysis





Opinion 1

- **Good clinical practice guidelines, can help the clinician in making the most appropriate choice of antibiotics to provide the best quality of care**

1	2	3	4	5
strongly disagree	disagree	no opinion	agree	strongly agree

What is Evidence-Based Medicine?

- The conscientious,explicit and judicious use of current best evidence in making decisions about the care of individual patients
- The integration of individual clinical expertise with the best available external evidence and patient's values and expectations
- Can provide the best and most cost-effective care for every patient (e.g. via E-B guidelines)

What EBM is not!

- EBM is not cook-book medicine
  - evidence needs extrapolation to the patient's unique biology and values
- EBM is not cost-cutting medicine
  - when efficacy for my patient is paramount, costs may even rise
- EBM is not restricted to randomised trials and meta-analyses

EBM in 5 steps...

1. Translation of the **subject** to an answerable question
2. Efficient **search** for the best evidence
   - primary literature
   - secondary (pre-appraised) sources e.g., Cochrane; E-B Journals
3. Critical **appraisal** of the evidence for its validity and clinical applicability ➡ generation of a summary and categorisation (level of evidence 1 → 5).

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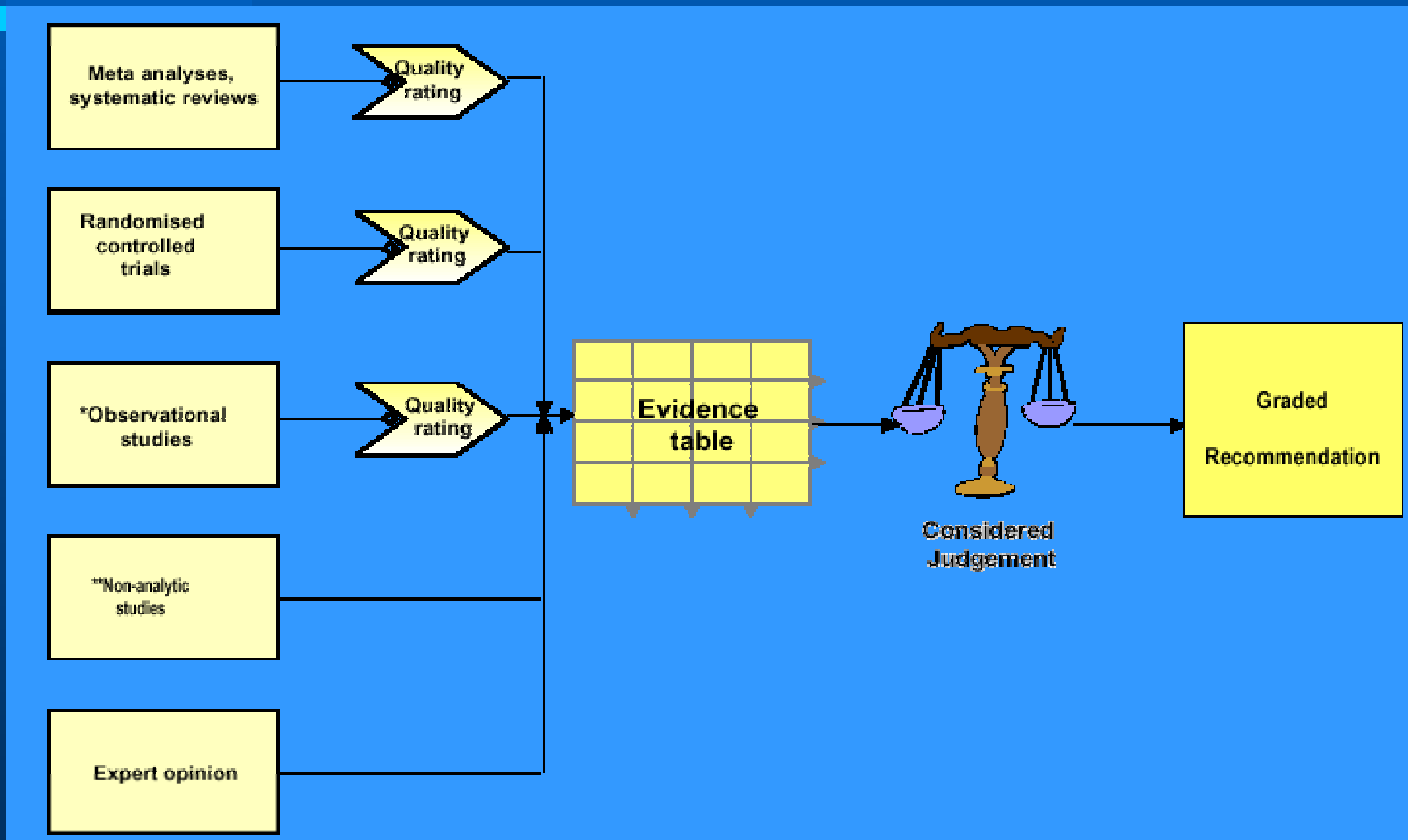
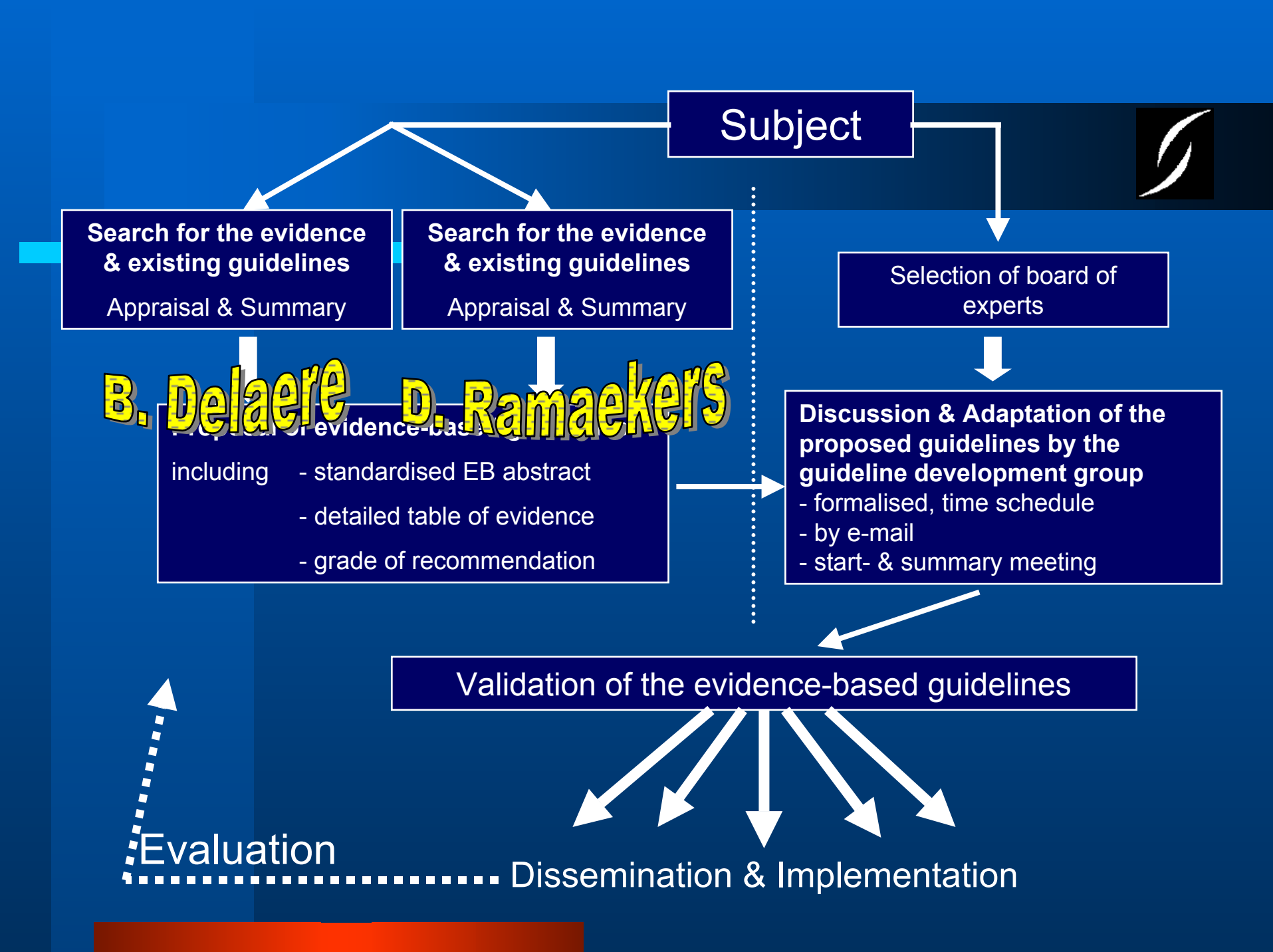
4. Integration of that critical appraisal with clinical expertise and patient's unique biology and beliefs ➡ action
5. Evaluation of performance

Why *Evidence-Based* guidelines?

- **consensus opinion of experts based on**
  - systematic review of the scientific literature &
  - microbiological survey
- **potential sources of bias are minimised & likely validity of the recommendations is maximised**
- **conclusions from the external evidence are as paramount as the microbiology**
  - e.g. relapse rate
  - e.g. ceftriax versus cefotax
- **‘No evidence to support…’**

Development of E-B guidelines



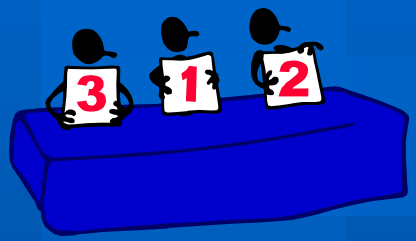

Subject
Search for the evidence & existing guidelines
Appraisal & Summary
Search for the evidence & existing guidelines
Appraisal & Summary
Selection of board of experts
B. Delaere
D. Ramaekers
including - standardised EB abstract
- detailed table of evidence
- grade of recommendation
Discussion & Adaptation of the proposed guidelines by the guideline development group
- formalised, time schedule
- by e-mail
- start- & summary meeting
Validation of the evidence-based guidelines
Evaluation
Dissemination & Implementation

Levels of evidence (www.sign.ac.uk)

1++	High quality meta analyses, sytematic reviews of RCT's, or RCT's with a very low risk of bias
1+	Well conducted meta analyses, systematic reviews, or RCT's with a low risk of bias
1-	Meta analyses, systematic reviews, or RCT's with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies High quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e;g. case reports, case series
4	Expert opinion

Grades of recommendations

A	A least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; *or* A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; *or* Extrapolated evidence from studies rated as 2+



Opinion 2

- **Clinical practice guidelines should take into account the results of a systematic review of the literature (& local microbiology) and the recommendations should be graded according to the level of evidence, explicitly defining expert opinion as such**

1	2	3	4	5
strongly disagree	disagree	no opinion	agree	strongly agree

guideline development group

multidisciplinary group!

- ✓ minimum 6, maximum 12-15 members
- ✓ team manager (B. Delaere, D. Ramaekers)
- ✓ at least one infectiologist and one microbiologist
- ✓ several clinical experts in the area covered by the guideline
- ✓ experts from the (scientific) association(s)

microbiological survey resistance patterns

GDG acute pyelonephritis

Ameye F. (urology, St. Lucas Gent): no conflict of interest
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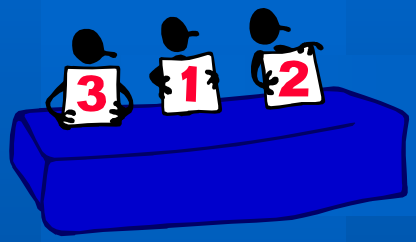
- Supervised by the Coördinatiecommissie Antibioticabeleid / Commission de coordination de la politique antibiotique. However, neither this commission nor the Government has influenced the contents of these recommendations.



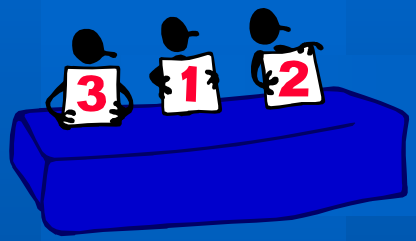
Opinion 3

- **A guideline development group is multidisciplinary including experts from the clinical specialities involved in the subject and uses a explicitly structured & rigourous methodology**

1	2	3	4	5
strongly disagree	disagree	no opinion	agree	strongly agree

Validation of the EBG

- Quality appraisal of the guideline
  - formalised checklist: >90%
  - http://www.agreecollaboration.org/
- External review
  - expert(s) in systematic reviews and guideline development
  - expert(s) with clinical expertise, potential user(s) of the EBG
  - www.cebam.be



Opinion 4

- **A guideline should always be quality appraised using a validated instrument and should be externally reviewed before dissemination**

1	2	3	4	5
strongly disagree	disagree	no opinion	agree	strongly agree

Systematic review pyelonephritis

- **Existing guidelines:**

  Searching all available Internet guideline clearinghouses and Medline:
  - IDSA (on-line: http://www.idsociety.org/pg/toc.htm issue practice guidelines)
  - John Hopkins University (http://www.hopkins-id.edu/)
  - French consensus on antibiotherapy of urinary tract infections.
  - Nederlands Kwaliteitsinstituut voor de gezondheidszorg CBO.

- **PubMed search (Medline) / Grateful Med (Medline, Healthstar):**

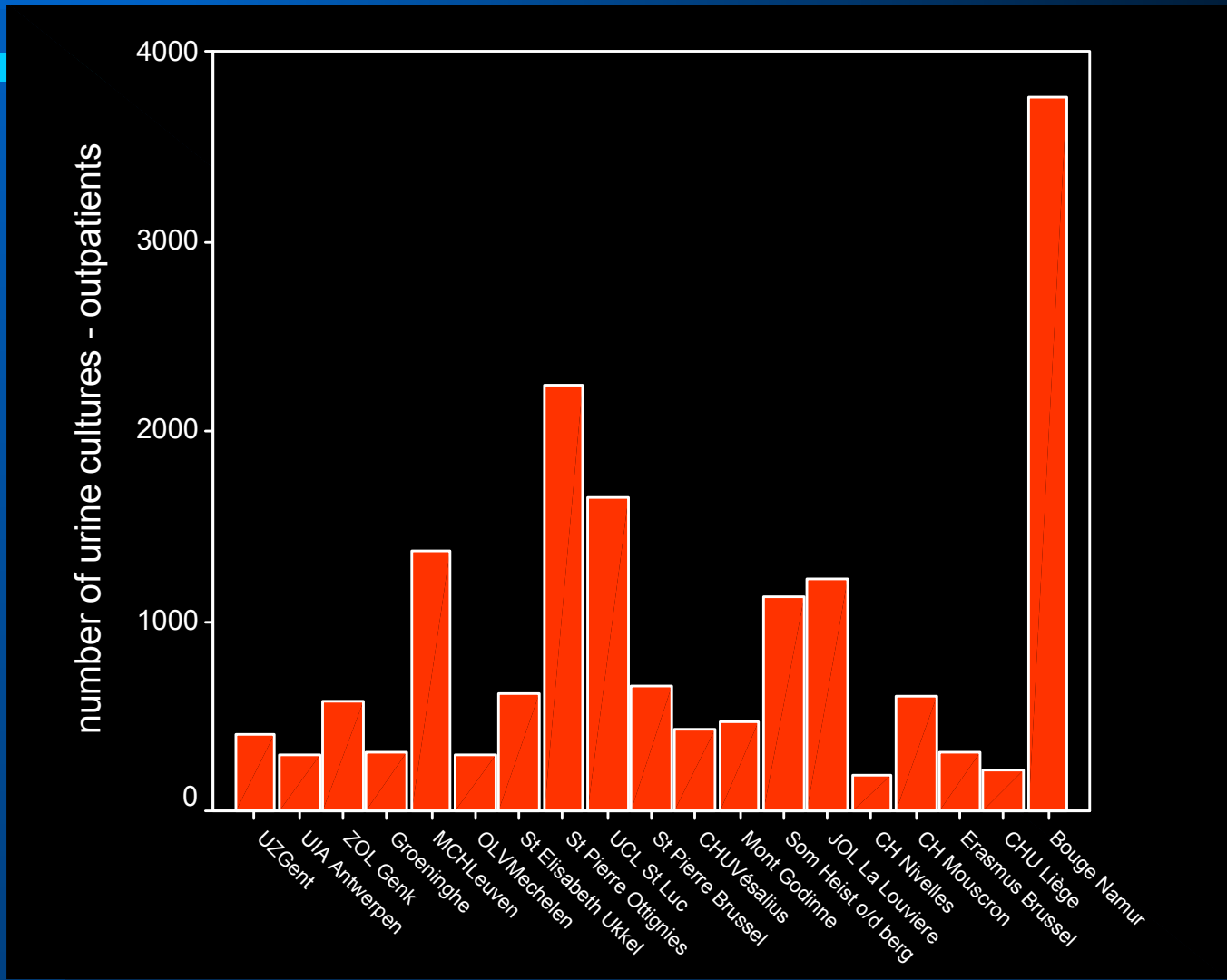
  Both the primary terms and the related MeSH's (Medical Subject Headings)
  - For Women: pyelonephritis/therapy[MESH]; 1980 to 2000; female.
  - For Men: pyelonephritis/therapy[MESH]; 1980 to 2000; male.
  - For Pregnancy: pregnancy[MESH] AND pyelonephritis/therapy[MESH], 1980 to 2000.

  For all these subjects, a separate search was performed for the different types of publication: *meta-analysis; randomised controlled trial*; *clinical trial*; *review*; *practice guideline*.

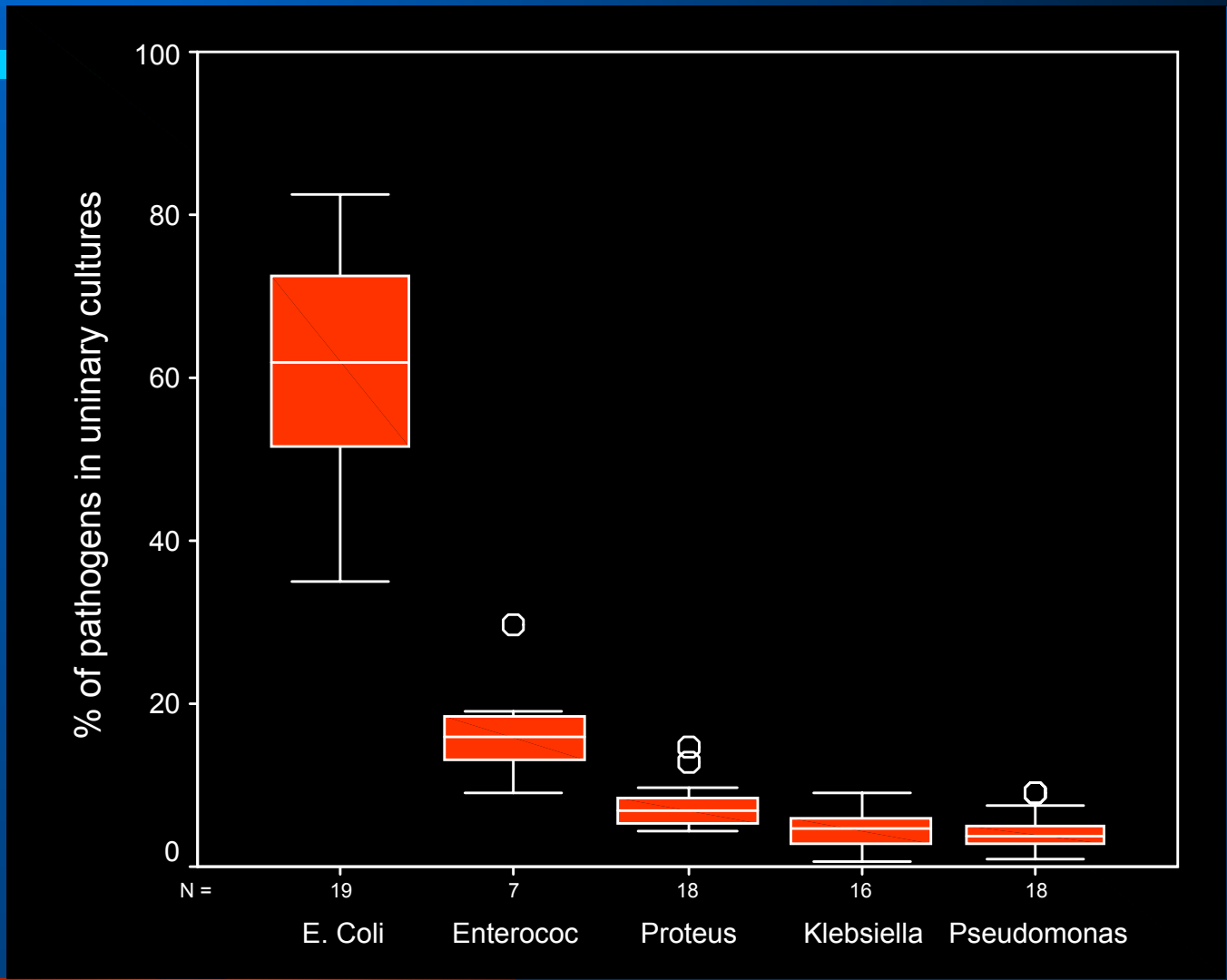
- **Cochrane Library / DARE / CCT**

  All these databases were searched with the primary term: *pyelonephritis*.

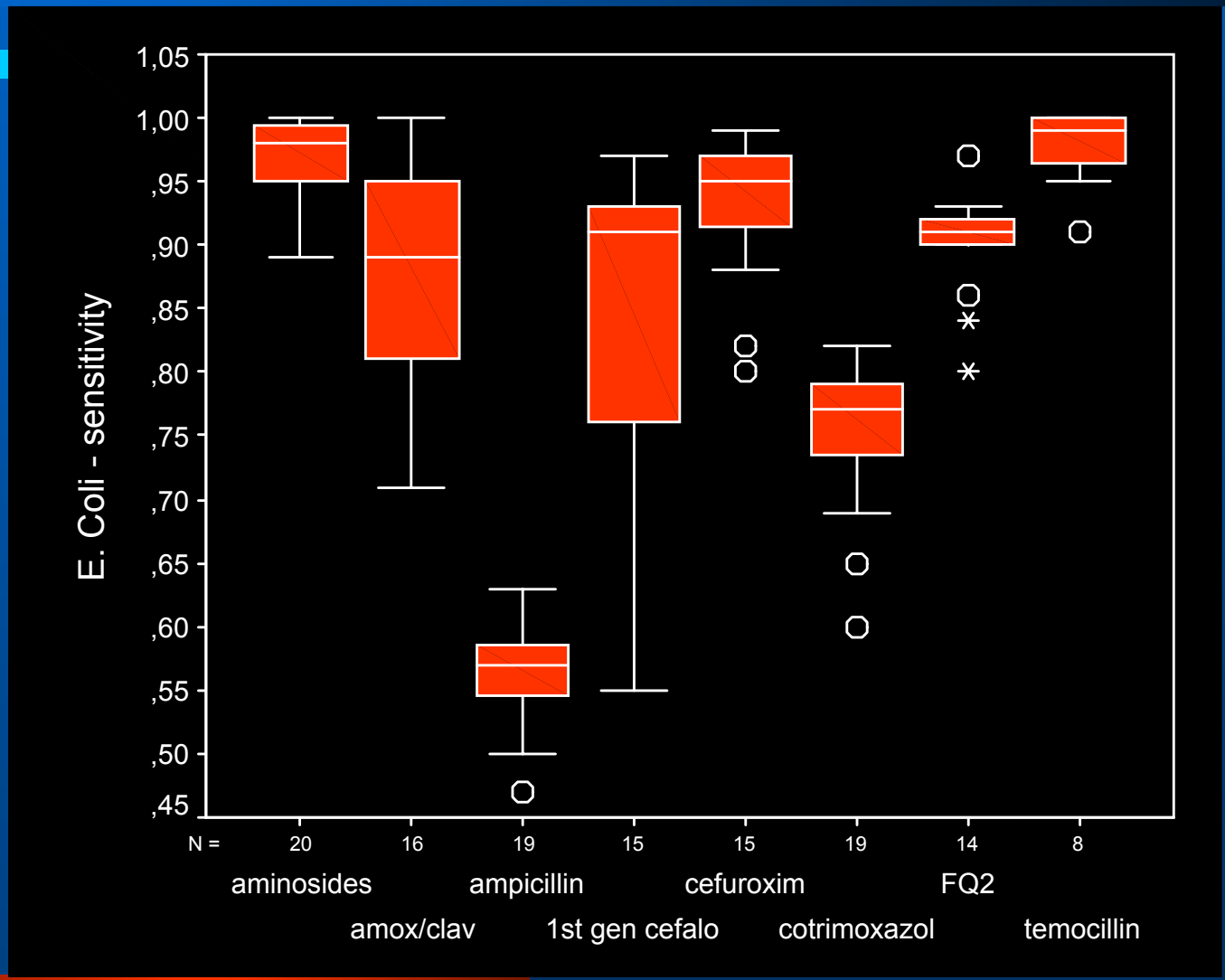
Results of the microbiological survey



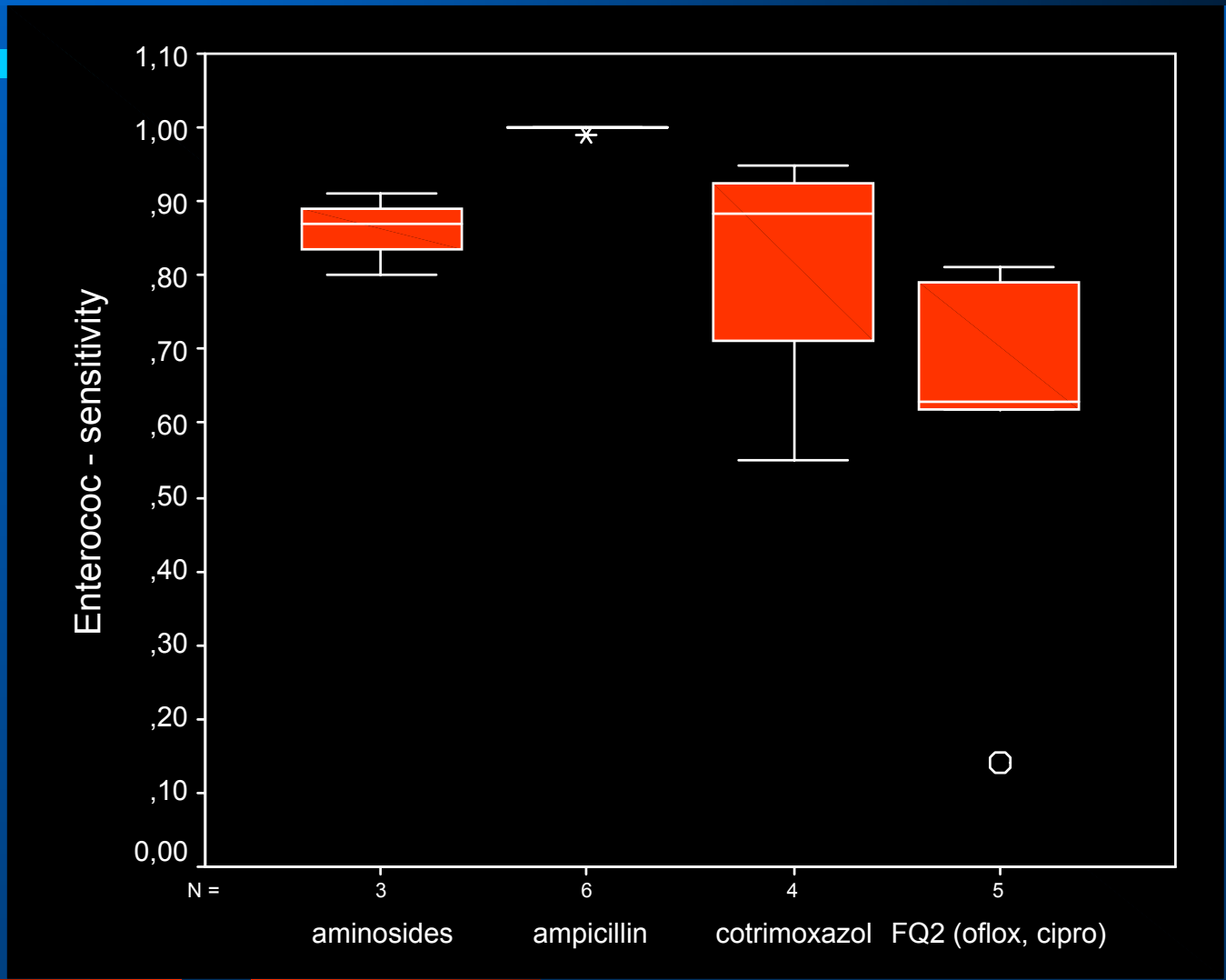
Distribution of pathogens



Sensitivity - E. coli



Sensitivity - Enterococcus



Literature - non-pregnant women

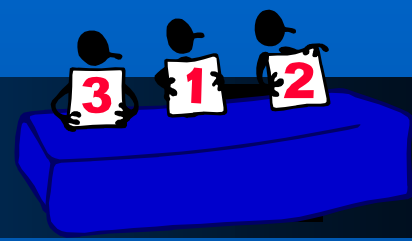
- meta-analysis IDSA 4 RCT's (Jernelius, Johnson, Stamm, Ode): FQ or CTX > ampi; 14 days
- Talan: cipro 7d > CTX 14 d
- Mombelli: cipro iv = cipro oral
- Richard: levo = cipro
- Sandberg: FQ > β-lactams
- (Sandberg - Le Conte: addition tobramycin not superior)
- (8 studies excluded)
- Hooton, Israel: outpatient switch therapy safe & effective
- Limited or no clinical studies amox/clav, cephalo 1 & 2, temo
- Few reports on cephalo 3

Recommendations non-pregnant women (1)

MILD PYELONEPHRITIS - empirical therapy

- The efficacy of fluoroquinolones for empiric therapy has been established (1++, A).
- Oral therapy is proposed for patients without clinical signs of severe sepsis (1++, A). Outpatient treatment with oral fluoroquinolones is safe in absence of severe sepsis and renal insufficiency, and with the ability to take oral medication (1+, B).
- First generation fluoroquinolones (FQ_1), such as norfloxacine, are not recommended because of their low serum concentration (4, D).
- Association of an aminoglycoside is not recommended in absence of severe sepsis (1+, B).
- Co-trimoxazole, ampicillin and first generation cephalosporins cannot be recommended as empiric therapy due to the high level of resistance in many regions of Belgium.

Guideline - non-pregnant women (1)



MILD PYELONEPHRITIS - empirical therapy

	For **non-pregnant women with mild pyelonephritis** (no clinical signs of severe sepsis, patient can take oral medication):
A	Empiric therapy with oral fluoroquinolone
B	without the association of an aminoglycoside
	(If fluoroquinolones are contra-indicated, switch to the alternatives in the next guideline)

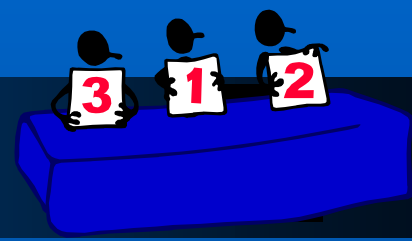
1	2	3	4	5
strongly disagree	disagree	no opinion	agree	strongly agree

Recommendations non-pregnant women (2)

SEVERE PYELONEPHRITIS - empirical therapy

- The efficacy of FQ for empirical therapy has been established (1++, A).
- Temocillin, amox/clav and 2nd gen. cephalo's are a valuable alternative in patient needing initial iv therapy (3, D).
  This is also supported by the current resistance figures of the Belgian microbiological survey.
- The utility of an aminoglycoside in association with amox/clav or 2nd gen. cephalo's is not supported by the literature. The association of an aminoglycoside should be reserved to patients with septic shock (3,D).
- In patients that fail to improve during outpatient treatment after 48-72 hours, treatment should be changed to a parenteral FQ or one of the alternatives depending on the choice of the initial oral antibiotic and the result of the urinary culture (4,D).

Guideline - non-pregnant women (2)



SEVERE PYELONEPHRITIS - empirical therapy

	For more severe cases (vomiting, dehydration, severe sepsis; failure to improve during outpatient treatment; or inability to take oral medication), requiring hospitalisation:
A	- Empiric therapy with parenteral fluoroquinolone.
	- Alternatives:
D	• temocillin, second generation cephalosporin or amoxicillin-clavulanic acid
D	• only in cases of septic shock, an aminoglycoside can be associated to the second generation cephalosporin or amoxicillin-clavulanic acid.

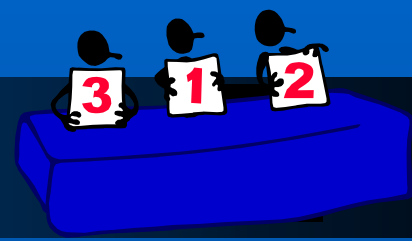
1	2	3	4	5
strongly disagree	disagree	no opinion	agree	strongly agree

Recommendations non-pregnant women (3)

Directed therapy and Duration

- Always perfrom a urine culture including antibiogram.
- The clinical and bacteriological efficacy of fluoroquinolones (1+, A) and co-trimoxazole (1+, A) is significantly better than that of β-lactams (recurrence).
- If enterococcus sp. is isolated, ampicillin is the recommended directed therapy (3,D), alone or in association with an aminoglycoside (3,D).
- Outpatient treatment is safe in absence of severe sepsis and renal insufficiency, and with the ability to take oral medication (1+, B).
  In more severe cases requiring initial iv therapy, a switch to oral therapy is proposed after 24-48h, once symptoms and fever have disappeared (2++, B).
- In with uncomplicated pyelonephritis, without severe sepsis and without diabetes, at least 7 days of fluoroquinolones (1+, B).
  In other cases (severe sepsis, diabetes or treatment with another antibiotic) a duration of treatment of 14 days, but not longer, is warranted (1++, A).

Guideline - non-pregnant women (3)



Directed therapy and Duration

B	Upon clinical improvement (resolution of fever), switch of intravenous therapy, based on the antibiogram of the urinary pathogen cultured, to an oral antibiotic (preferentially a fluoroquinolone or co-trimoxazole and for enterococci amoxicillin)
B	- for a total duration of antibiotic treatment of at least 7 to a maximum of 14 days for fluoroquinolones in non-diabetic female patients;
A	- for 14 days for all other oral antibiotics.

1	2	3	4	5
strongly disagree	disagree	no opinion	agree	strongly agree

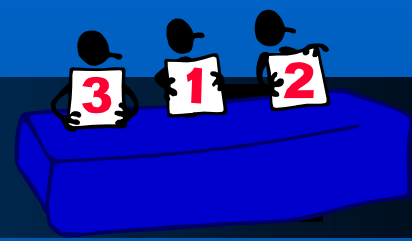
Literature - men

- data from controlled studies are lacking
- low number of included men in mixed trials
- Mombelli, Johnson: eradication & recurrence FQ > β-lactams

Recommendations men

- The same antibiotic regimens are recommended in men (3, D).
- Note the high rate of relapse with beta-lactams in studies were both sexes were included and where men could be isolated with, however, mostly a minority of men.
- Standard duration of therapy is 2 weeks since no studies are available to determine the most appropriate duration in men (4, D).

Guideline - men



D	For **men**, the same antibiotic regimens are recommended, for 14 days.

1	2	3	4	5
strongly disagree	disagree	no opinion	agree	strongly agree

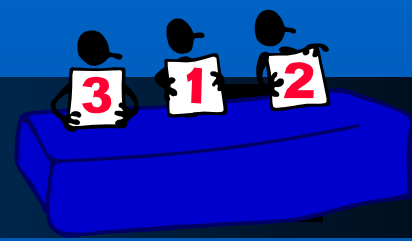
Literature - pregnant women

- Cochrane review Vacquez
- Wing: cefazol = ceftriax = ampi/genta
- Sanchez-Ramos: ceftriax = cefazolin
- (Angel: cephalo 1 iv = oral)
- Millar, Wing: outpatient treatment safe & effective in selected pts.
- Lenke, Van Dorsten: doubt on suppressive therapy nitrofurantoin
- Cochrane review Smaill: asymptomatic bacteriuria

Recommendations pregnant women

- Fluoroquinolones are not indicated for the treatment of acute pyelonephritis in pregnant women (FDA safety categories).
- Parenteral cefazolin (resistance) and ceftriaxone are the most evaluated as empirical therapy (1+, B). Several experts consider parenteral cefuroxime or amoxicillin/clavulanic acid as valuable and safe alternatives (4, D).
- Directed therapy depends on the antibiogram and on the safety for pregnancy.
- In patients without severe sepsis, concurrent medical conditions or pre-term labour, a brief hospital stay followed by oral outpatient therapy is suggested (2+, C). Oral cefuroxime (2+, C) is recommended as outpatient therapy for a total duration of antibiotic treatment of 10-14 days (2+, C). In later pregnancy, few women will be candidate for outpatient management.
- There is no conclusive evidence for the use of suppressive therapy with nitrofurantoin (1+, B). However, close surveillance for and prompt treatment of recurrent or persistent even asymptomatic urinary tract infection is recommended (2+, C).

1	2	3	4	5
strongly disagree	disagree	no opinion	agree	strongly agree



Guideline - pregnant women

C, B	For **pregnant women**, cefuroxime or ceftriaxone is recommended as initial parenteral empirical therapy. Alternatives:
D	• amoxicillin-clavulanic acid
D	• aztreonam in case of penicillin allergy
C	A brief hospital stay is recommended. Upon clinical improvement (48 hours resolution of fever) and without severe sepsis, concurrent medical conditions or pre-term labor, the patient can be discharged on an oral antibiotic depending on the antibiogram of the urinary pathogen cultured and the safety profile of the antibiotic (preferentially a first generation cefalosporin), for a total duration of 14 days.
B	Suppressive therapy with nitrofurantoin to prevent recurrent disease is not indicated.

www.health.fgov.be/antibiotics