Evidence-Based Guidelines for the Hospital Use of Antibiotics


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- Presentation of the guideline
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**

**National**

- Quinolones 3° génération oraux
- + quinolones 3° génération IV
- Pénicillar large spectre
  - avec inhib. bêta-lact. oraux + IV
  - Quinolones 3°
  - génération IV
  - Pénicillar large spectre
  - avec inhib. bêta-lact. IV
  - Quinolones 3°
  - génération oraux
  - Céphalosporines 2° génération
  - (exc. Anaérobies) IV
  - Pénicillar large spectre
  - avec inhib. bêta-lact. oraux + IV + aminos IV
  - Pénicillar large spectre
  - avec inhib. bêta-lact. IV + aminos IV
  - Autres
Good clinical practice guidelines, can help the clinician in making the most appropriate choice of antibiotics to provide the best quality of care.
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).
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

- Meta analyses, systematic reviews
- Randomised controlled trials
- *Observational studies
- "Non-analytic studies"
- Expert opinion

Quality rating

Evidence table

Considered Judgement

Graded Recommendation
Subject

Search for the evidence & existing guidelines
Appraisal & Summary

Search for the evidence & existing guidelines
Appraisal & Summary

Selection of board of experts

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
<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1++</td>
<td>High quality meta analyses, systematic reviews of RCT's, or RCT's with a very low risk of bias</td>
</tr>
<tr>
<td>1+</td>
<td>Well conducted meta analyses, systematic reviews, or RCT's with a low risk of bias</td>
</tr>
<tr>
<td>1-</td>
<td>Meta analyses, systematic reviews, or RCT's with a high risk of bias</td>
</tr>
<tr>
<td>2++</td>
<td>High quality systematic reviews of case-control or cohort studies</td>
</tr>
<tr>
<td>2+</td>
<td>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</td>
</tr>
<tr>
<td>2-</td>
<td>Well conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal</td>
</tr>
<tr>
<td>2-</td>
<td>Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal</td>
</tr>
<tr>
<td>3</td>
<td>Non-analytic studies, e.g., case reports, case series</td>
</tr>
<tr>
<td>4</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>
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+.
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.
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
Boelaert J. (nephrology, AZ St. Jan Brugge): no
De Groote P. (urology, Clin. Europe, Brussels): no
De Ridder D. (urology, UZ Leuven): no
Donders G. (obstetrics & gynecology, H.H. Tienen & UZ Leuven): no
D’Orio V. (emergency medicine, CHU Liège): no
Firre E. (internal medicine and nephrology, CHR Citadelle Liège): no
Hubinont C. (gynéco-obstétrique, UCL): no
Jadoul M. (Cliniques Universitaires Saint-Luc, nephrology, Bruxelles): no
Machiels P. (Notre-Dame, Gosselies): no
Peetermans W. (infectiology, UZ Leuven): no
Struelens M. (Erasme, ULB, Bruxelles): no
Van Wijngaerden E. (infectiology, UZ Leuven): no
Vandercam B. (Cliniques Universitaires Saint-Luc – Infectiology - Bruxelles): no
Verschraegen G. (Laboratorium voor bacteriologie en virologie, UZ Gent): no

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.
A guideline development group is multidisciplinary including experts from the clinical specialities involved in the subject and uses a explicitly structured & rigourous methodology.
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
A guideline should always be quality appraised using a validated instrument and should be externally reviewed before dissemination.
Systematic review pyelonephritis

- **Existing guidelines:**
  Searching all available Internet guideline clearinghouses and Medline:
  - John Hopkins University ([http://www.hopkins-id.edu](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 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

- CHU Liège
- Erasmus Brussel
- CH Mouscron
- CH Nivelles
- JOL La Louvière
- Som Heist o/d berg
- Mont Godinne
- CHUVésalius
- St Pierre Brussel
- UCL St Luc
- St Pierre Ottignies
- St Elisabeth Ukkel
- OLVMechelen
- MCHLeuven
- ZOL Genk
- UZA Antwerpen
- CHUVésalius

Number of urine cultures - outpatients
Distribution of pathogens

- Pseudomonas
- Klebsiella
- Proteus
- Enterococ
- E. Coli

% of pathogens in urinary cultures

N =

- E. Coli: 19
- Enterococ: 7
- Proteus: 18
- Klebsiella: 16
- Pseudomonas: 18
Sensitivity - E. coli

The sensitivity of E. coli to various antibiotics is shown in the diagram. The antibiotics include ampicillin, cefuroxim, amox/clav, cotrimoxazol, temocillin, and FQ2. The sensitivity levels are indicated with box plots, showing the distribution of sensitivity values for each antibiotic.
Sensitivity - Enterococcus

- Enterococcus

Sensitivity results for various antibiotics:
- FQ2 (oflox, cipro)
- Cotrimoxazol
- Ampicillin
- Aminosides

Box plot showing the distribution of sensitivity levels for different antibiotics.

N = 1, 10, 1, 00, 0, 90, 0, 80, 0, 70, 0, 60, 0, 50, 0, 40, 0, 30, 0, 20, 0, 10, 0, 00

Antibiotics:
- Aminosides
- Ampicillin
- Cotrimoxazol
- FQ2 (oflox, cipro)
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
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 (FQ₁), such as norfloxacin, 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.
**MILD PYELONEPHRITIS - empirical therapy**

<table>
<thead>
<tr>
<th></th>
<th>For non-pregnant women with mild pyelonephritis (no clinical signs of severe sepsis, patient can take oral medication):</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Empiric therapy with oral fluoroquinolone</td>
</tr>
<tr>
<td>B</td>
<td>without the association of an aminoglycoside</td>
</tr>
<tr>
<td></td>
<td>(If fluoroquinolones are contra-indicated, switch to the alternatives in the next guideline)</td>
</tr>
</tbody>
</table>
**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).
### SEVERE PYELONEPHRITIS - empirical therapy

<table>
<thead>
<tr>
<th></th>
<th>For more severe cases (vomiting, dehydration, severe sepsis; failure to improve during outpatient treatment; or inability to take oral medication), requiring hospitalisation:</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>- Empiric therapy with parenteral fluoroquinolone.</td>
</tr>
<tr>
<td></td>
<td>- Alternatives:</td>
</tr>
<tr>
<td>D</td>
<td></td>
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</tbody>
</table>
Directed therapy and Duration

- Always perform 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 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).
**Directed therapy and Duration**

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<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>- for a total duration of antibiotic treatment of at least 7 to a maximum of 14 days for fluoroquinolones in non-diabetic female patients;</td>
</tr>
<tr>
<td>A</td>
<td>- for 14 days for all other oral antibiotics.</td>
</tr>
</tbody>
</table>
Literature - men

- data from controlled studies are lacking
- low number of included men in mixed trials
- Mombelli, Johnson: eradication & recurrence FQ > β-lactams
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.
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).
For **pregnant women**, cefuroxime or ceftriaxone is recommended as initial parenteral empirical therapy.

**Alternatives:**

- amoxicillin-clavulanic acid
- aztreonam in case of penicillin allergy

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 cephalosporin), for a total duration of 14 days.

Suppressive therapy with nitrofurantoin to prevent recurrent disease is not indicated.
www.health.fgov.be/antibiotics