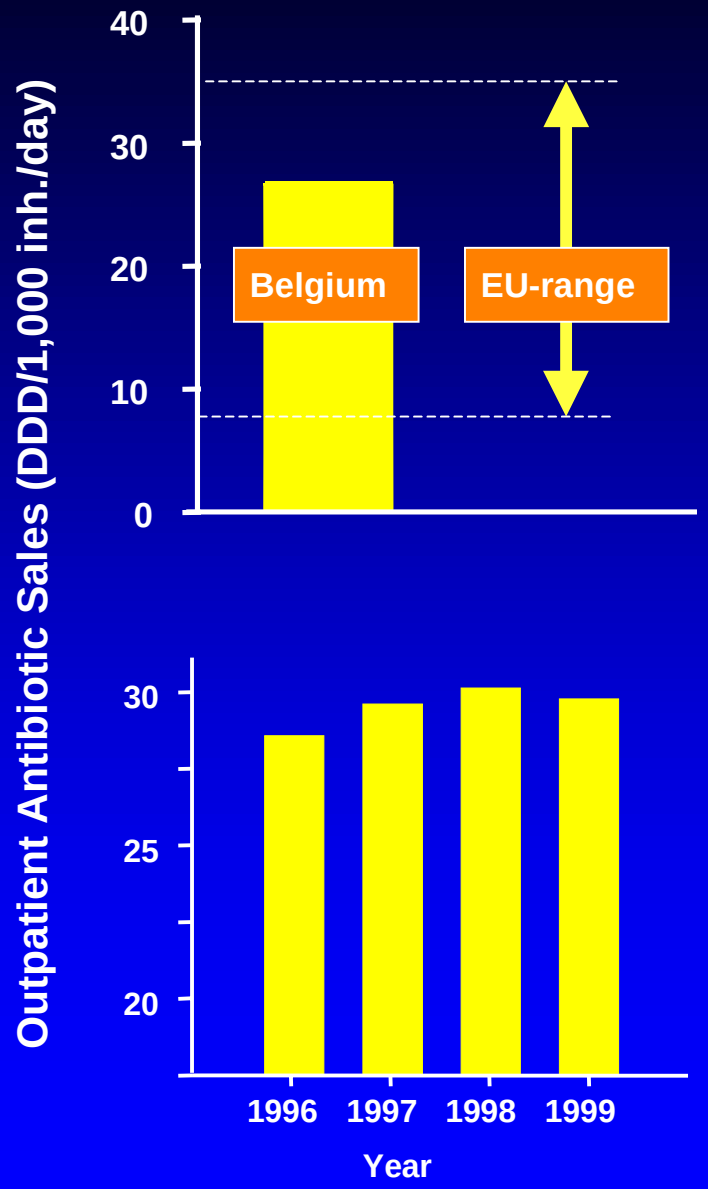
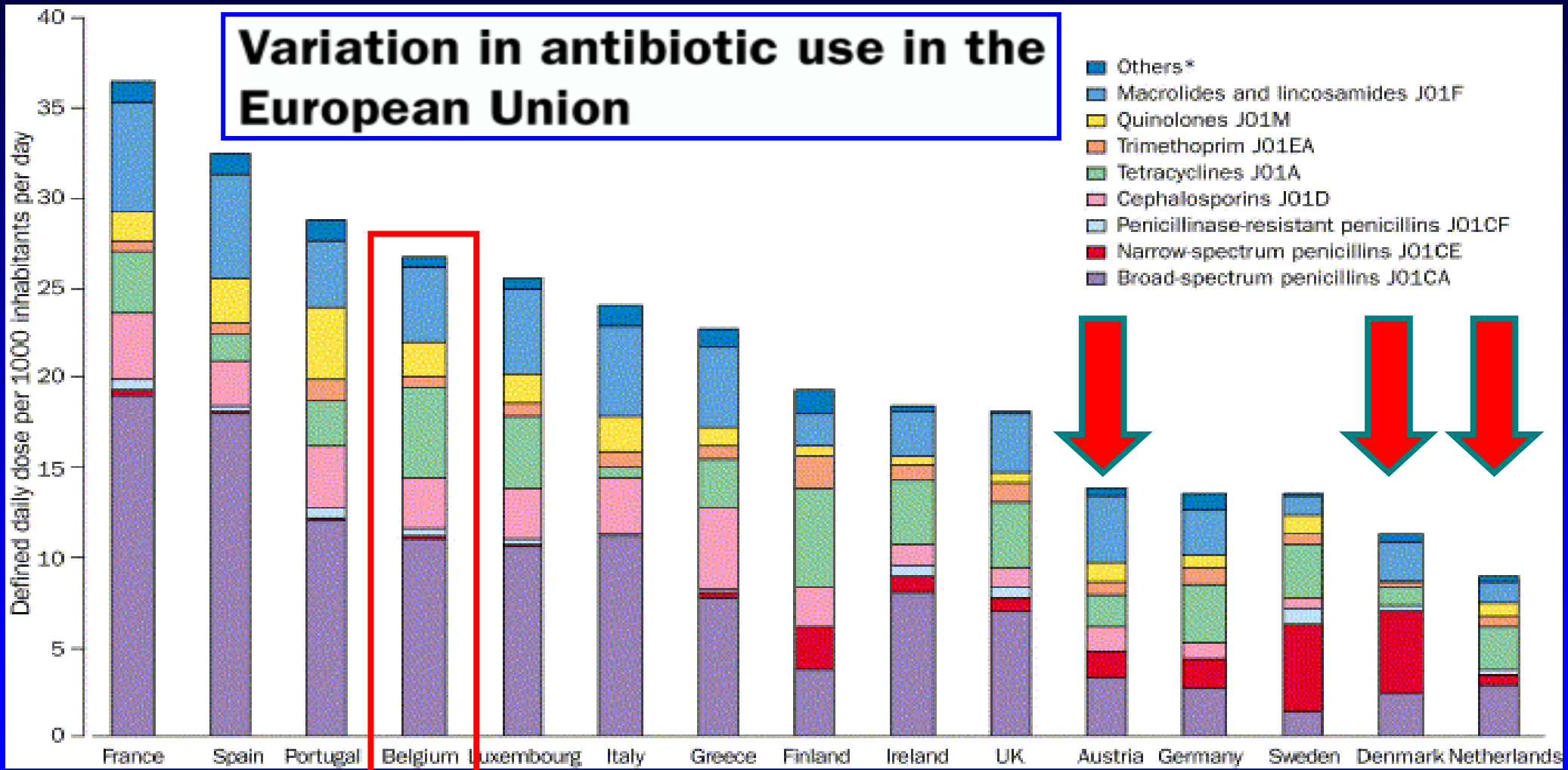
Belgian use of antibiotics



- Belgium (10 mill. inhab.) has a larger AB consumption than most EU countries
  (data of 1997 according to Cars et al., Lancet 357:1851, 2001);

- this consumption has remained constantly high over the 1996 - 1999 period
  (data from the Belgian Institute of Pharmacoepidemilogy [IPhEB-IFEB])

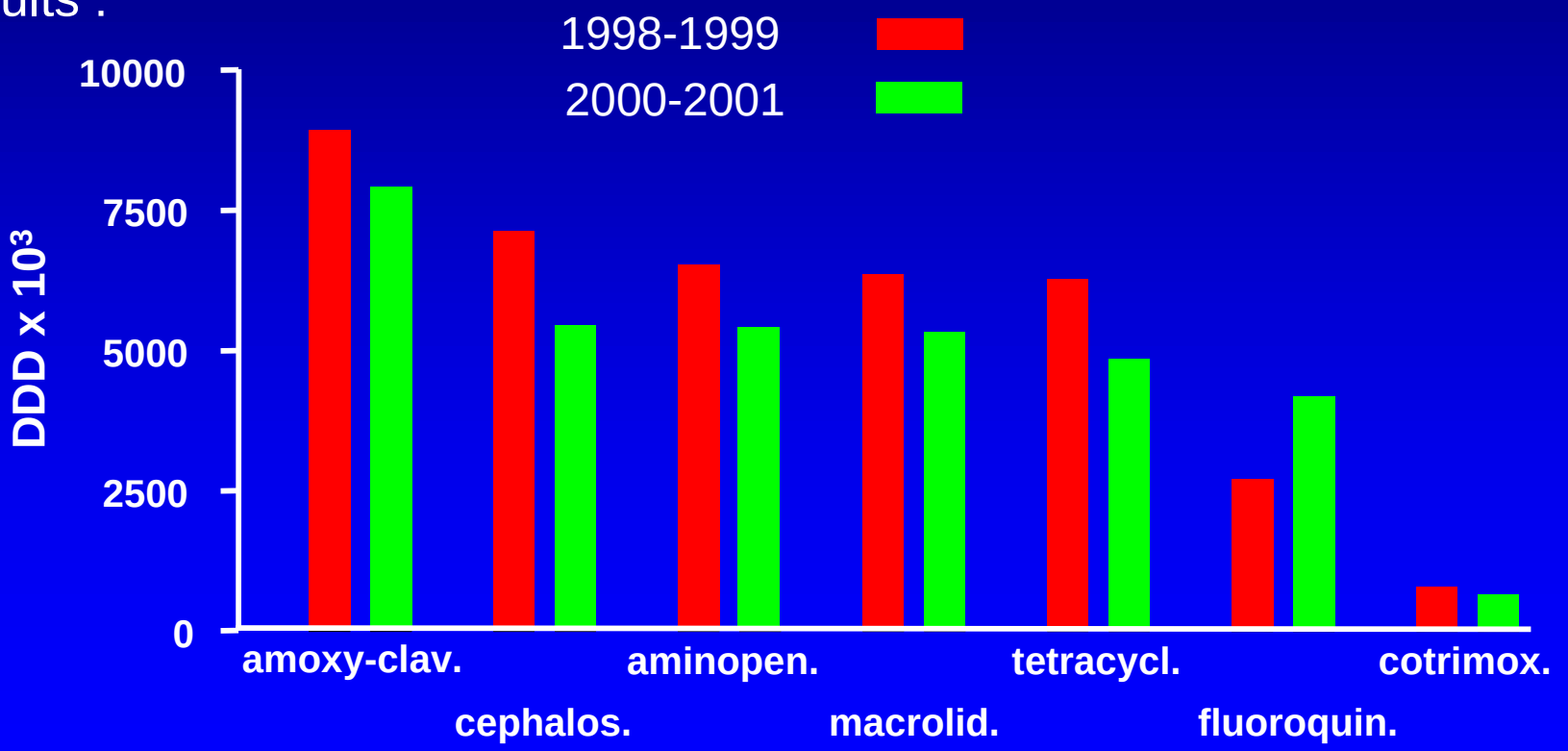
Know who you are ...



Cars & Mölstad, Lancet, 357, 2001

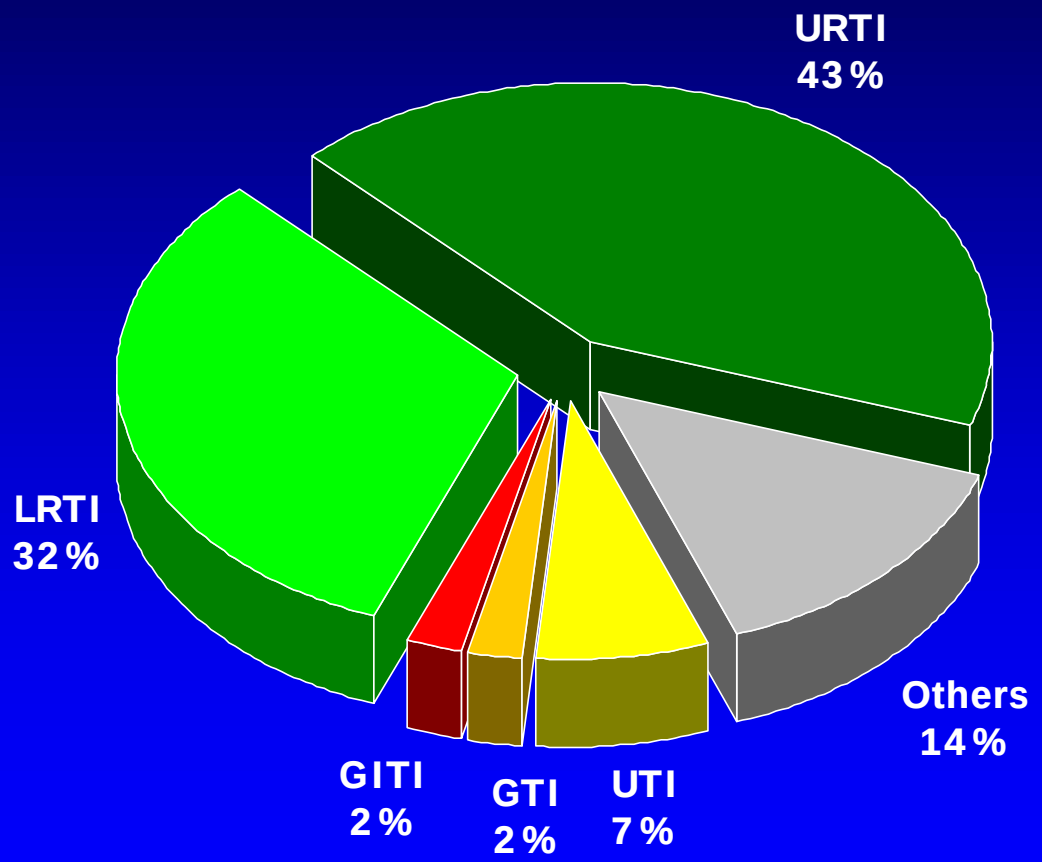
Distribution of antibiotic consumption in the community in Belgium

Results :

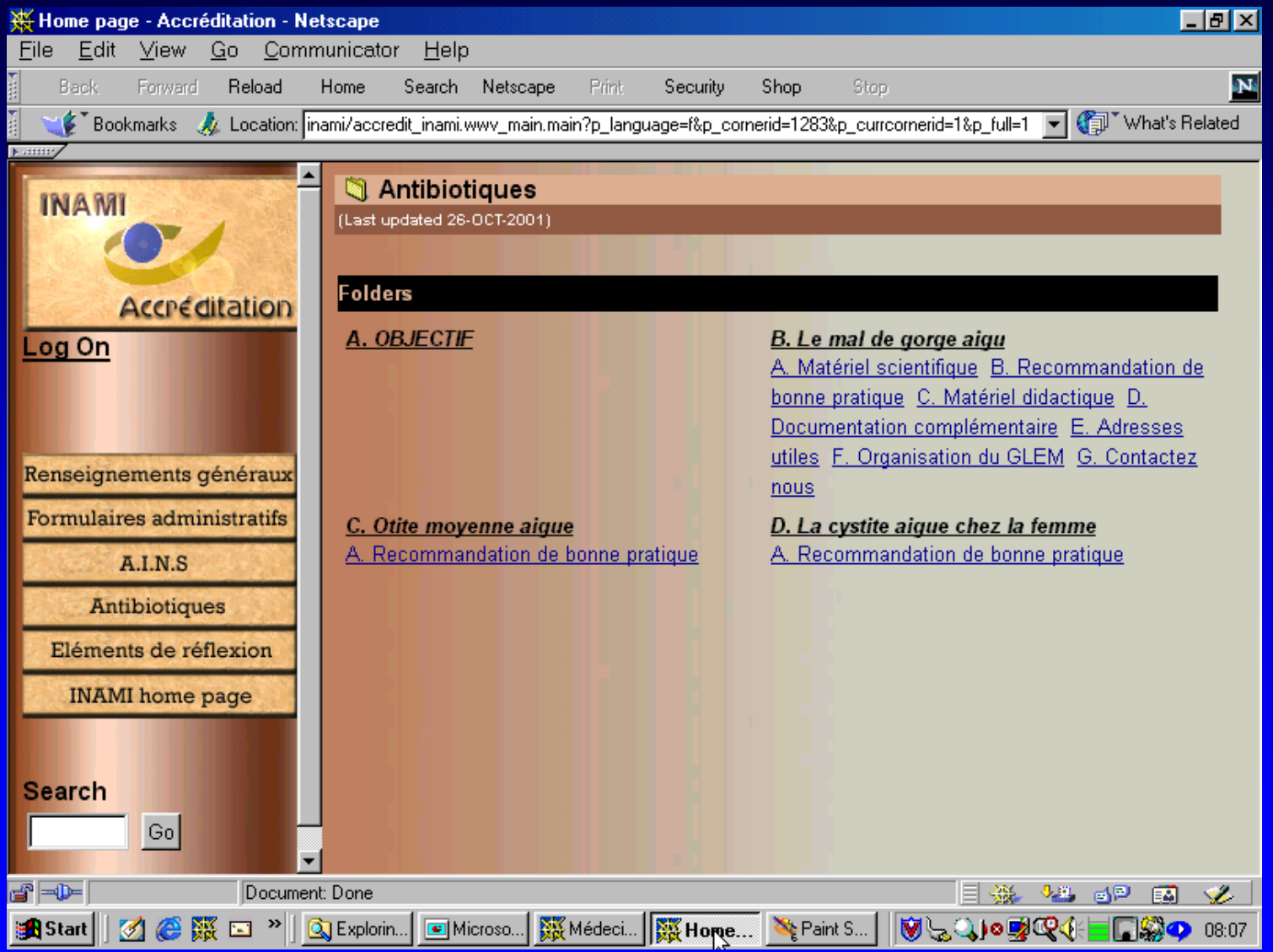


* accounting for 97.7 % of total antibiotic outpatient sales

Antibiotic prescriptions in Belgium outpatients (Q4/99)



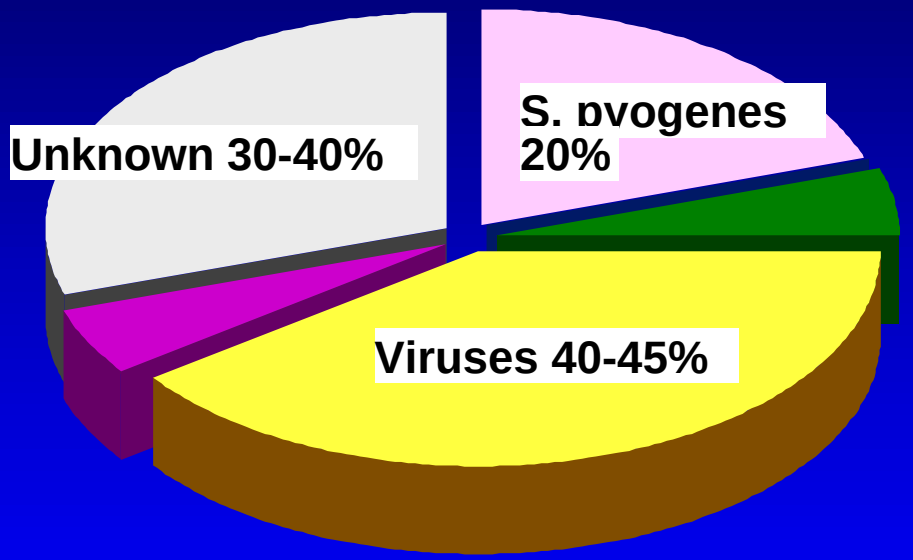
➔ fournir des “guidelines”



➔ fournir des “guidelines”

- Pharyngite
- Otite
- Sinusite
- Bronchite
- Pneumonie communautaire

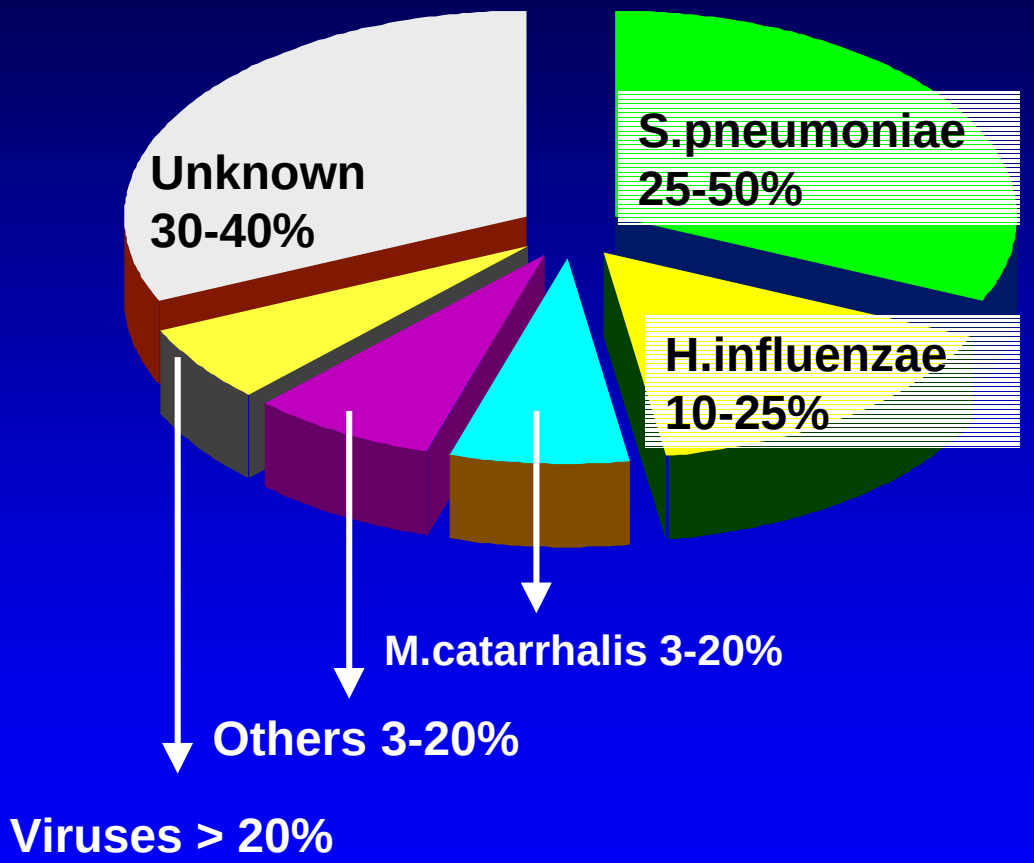
Pharyngite



Sources: “Infection 2000”, Genval, 1998; Sanford belge, 1999; Van Bambeke & Tulkens, 1999; Mandell 2000.

- <u>diagnostic :</u>
  test antigénique rapide; culture
- <u>traitement</u>
  - pénicilline V (pénicilline orale) / clométocilline
  - alternative : érythromycine ou néomacrolide (16 atomes actifs sur *S. pyogenes* résistant par efflux)

Otite moyenne



Sources: “Infection 2000”, Genval, 1998;
Sanford belge, 1999; Van Bambeke & Tulkens, 1999;
Mandell 2000.

- traitement

  - traitement symptomatique: analgésique, antipyrétique

  - Traitement empirique:
    - beta-lactame (ampi) + inhibiteur de β-lactamase
    - céphalo II (céfuroxime axétil)
  - Si *S. pneumoniae*:
    - ampicilline / amoxicilline seule mais dose ↗

Bonchite aiguë

- le plus souvent virale
- rarement :
  - *Mycoplasma pneumoniae* *
  - *Chlamydia pneumoniae* *
  - *Bordetella pertussis*

- <u>Traitement de la Br. aiguë</u> :

  avant tout symptomatique !

  - Analgésique-antipyrétique (aspirine -ibuprofen)
  - Antitussifs

- Si persistance des signes > 6 jours : antibiotique
  - amoxycilline
  - macrolide *

Sources: “Infection 2000”, Genval, 1998;
Sanford belge, 1999; Van Bambeke & Tulkens, 1999;
Mandell 2000.

Pneumonie communautaire

- pneumonie typique
  - patient âgé
  - expectoration purulente
  - température élevée, frissons
  - dyspnée
  - douleur pleurale
  - extrathoraciques

→ *S. pneumoniae*
H. influenzae

- pneumonie atypique
  - patient jeune
  - toux non productive
  - température variable
  - prodrome grippal et sujet très abattu pour son âge
  - symptomes extrathoraciques

→ *Mycoplasma*
Chlamydia p.
Legionella p.

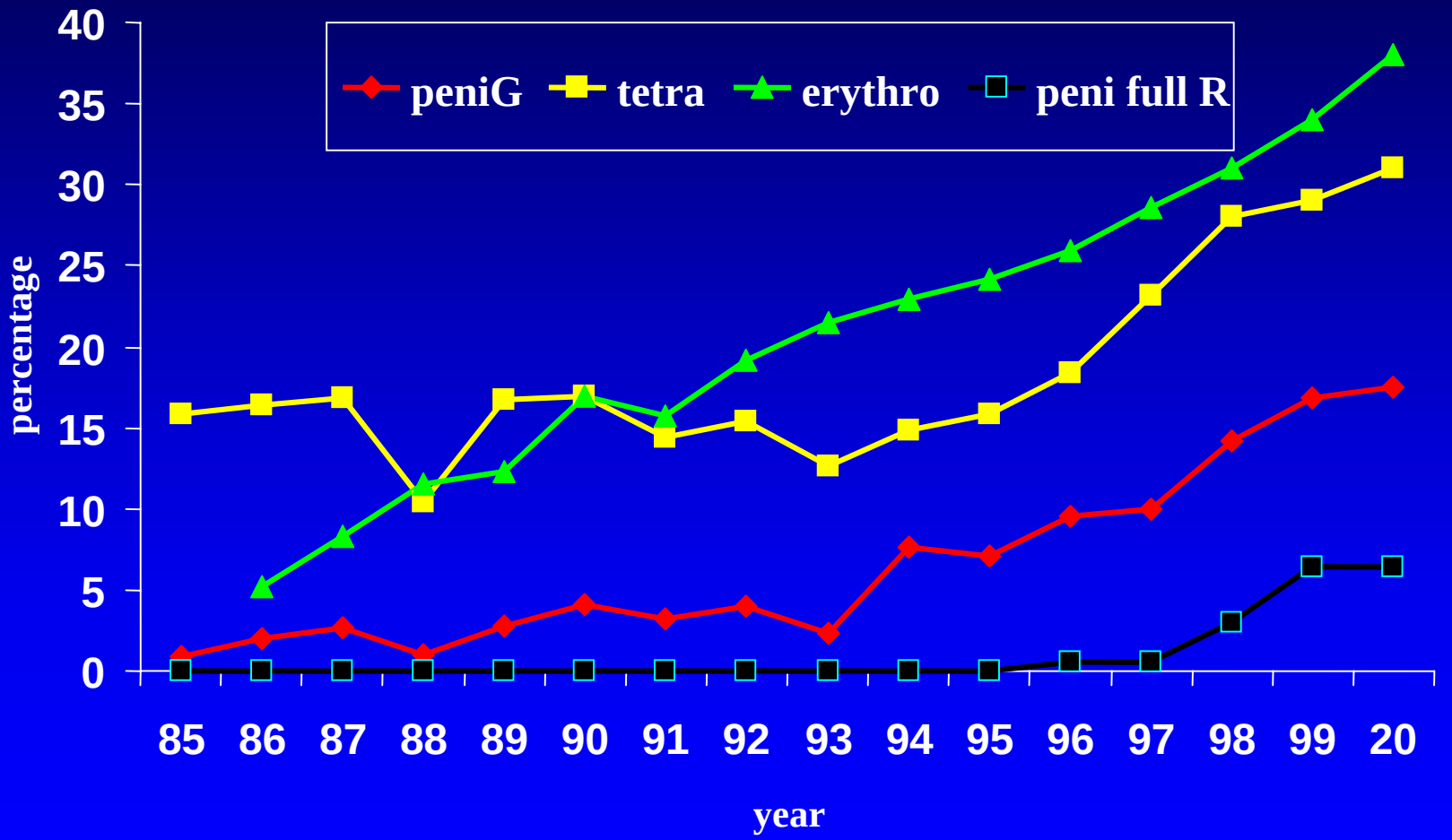
Pneumonie communautaire

4 classes de patients

- ambulant de < 60 ans, sans facteur de risque
  - ➔ principalement *Str. pneumoniae* (sauf signes cliniques clairs d'atypique)
- patient ambulant avec co-morbidité ou > 60 ans
  - ➔ risque réel de co-contamination par *H. influenzae*
- nécessitant une hospitalisation
- hospitalisation aux soins intensifs (fréquence respiratoire > 30/min; insuff. respir. sévère, anomalies radiologiques profondes, choc

Risque de *S. aureus* et/ou de Gram (-)

Evolution of *S. pneumoniae* resistance in Belgium



Referentielabo pneumokokken, Leuven, 2000

Belgian antimicrobial resistance patterns of respiratory pathogens

- *S. pneumoniae* :
  - tetracycline resistance : 31.7 %
  - erythromycin resistance : 36.5 %
    - complete cross-resistance between all (neo-) macrolides/azalides (including miocamycin) in 90% of erythromycin-resistant strains
    - No cross resistance with telithromycin (ketolide)

- *Clin Microbiol Infect 2000; 6: 661-669*
- *Pneumokokkeninfecties België, 2000*

Macrolide-resistant S. pneumoniae

RESISTANCE MECHANISMS

- **BELGIUM**

  methylation of ribosomal RNA (erm B gene): 92 %

  efflux (mef E gene): 3 %

  both (erm B gene + mef E gene): 5 %

  J Antimicrob Chemother 2000; 45: 119-121.

- **USA**

  mostly efflux mechanism

MIC efflux << MIC ribosomal :
In Belgium: macrolide resistance = treatment failure

Belgian antibiotic resistance :

Haemophilus influenzae

- M. Delmée et al. Acta clin Belg 1996; 51: 237-243.
  - beta-lactamase-positive: 16,7 %
  - bla-neg ampi R: 1,1 %
- P. De Mol unpublished results 2000 (n=474)
  - beta-lactamase-positive: 16,0 %
  - bla-neg amp R: 3,0 %

Belgian antibiotic resistance:

Moraxella catarrhalis

- P. De Mol. unpublished data 2000 (n=164 clinically significant isolates)

  beta-lactamase positive: 75 %

- remain susceptible to amoxi-clav, cephalo 2, macrolides and fluoroquinolones

Antimicrobial resistance patterns of respiratory pathogens : conclusions

- Very high resistance rates for all (neo-) macrolides, azalides and tetracyclines make them contra-indicated in monotherapy if *S. pneumoniae* is a possible cause of CAP

- *S. pneumoniae* increasingly penicillin-resistant but (increased dosages of) b-lactams still first choice for *S. pneumoniae* CAP

- Production of b-lactamase in *H. influenzae* stable around 17%

Belgian guidelines on the initial diagnostic and therapeutic approach of Community Acquired Pneumonia

(CAP)

BELGIAN CAP - GUIDELINES
Premises (1)

1. **No demonstrated need for systematic coverage of atypicals in subgroups 1, 2 and 3**

atypicals in subgroups 1, 2 and 3 should be covered <u>only</u> when suspected on clinical or epidemiological grounds

2. **In Belgium, presently available macrolides, azalides and older quinolones offer inadequate coverage of *S. pneumoniae***

BELGIAN CAP - GUIDELINES
Premises (2)

3. High β lactam dosages are preferred :
   - ↓ resistance selection
   - adequate time > MIC for Peni I / Peni R | *S. pneumoniae*

4. First generation cephalosporins (also cefaclor) are less active than amoxicillin or cefuroxime against Peni I / R S. pneumoniae

BELGIAN CAP - GUIDELINES
Premises (3)

5. Parenteral 3rd generation cephalosporins are only first choice in subgroup 4, especially when :
   - previous b-lactam treatment (within last 15 days ?)
   - previously hospitalized patients
   - proven/potential simultaneous CNS spread

Belgian guidelines on the initial diagnostic and therapeutic approach of CAP in the immunocompetent patient

Update of the CAP consensus text of the IDAB 2002

Brussels -- 20/9/2002 -- Presented by Yvan Valcke MD, PhD

Adaptation pour les étudiants FARM21 - 21-1-2003

CAP Guidelines available in other parts of the world (references)

- **CDC :** **Arch Intern Med 160, 2000**
- **IDSA :** **Clin Infect Dis 31, 2000**
- **CIDS/CTS :** **Clin Inf Dis 31, 2000**
- **ATS :** **Am J Respir Crit Care Med 163, 2001**
- **BTS :** **Thorax 56, 2001**
- **ERS :** **Eur Resp J, 1998**

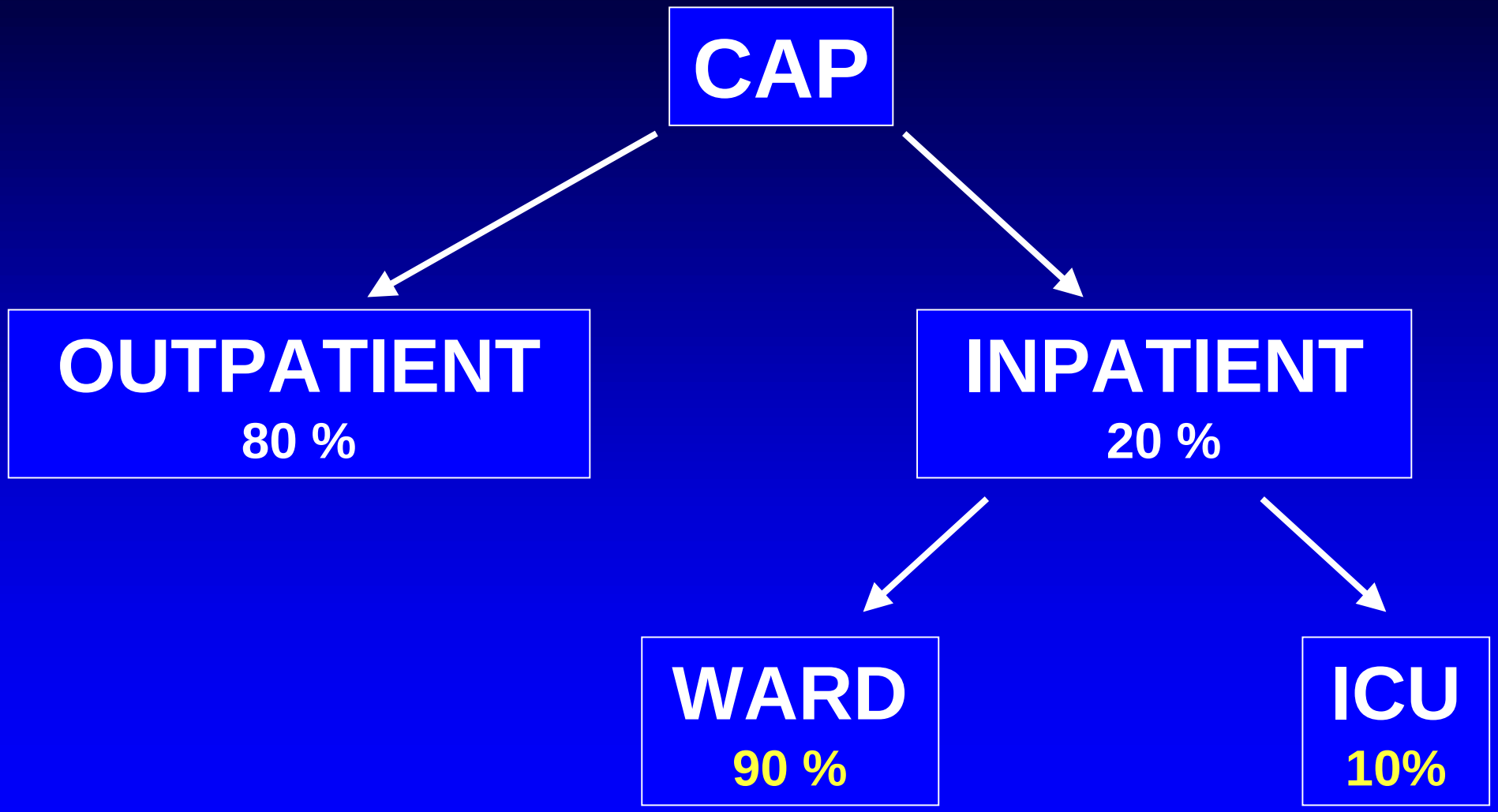
CDC: Center for Disease Control (USA); IDSA: Infectious Diseases Society of America
CIDS: Clinical Infectious Diseases Society; ATS: American Thoracic Society
BTS: Britisch Thoracic Society;;ERS: European Respiratory diseases Society

Microbial aetiology (%) of adult CAP in the UK

Pathogen	Community[a] (n=236)	Hospital[b] (n=1137)	Intensive care[b] (n=185)
S. pneumoniae	**36.0**	**39.0**	**21.6**
H. influenzae	**10.2**	**5.2**	**3.8**
S. aureus	**0.8**	**1.9**	**8.7**
***Legionella* spp.**	**0.4**	**3.6**	**17.8**
M. pneumoniae	**1.3**	**10.8**	**2.7**
C. pneumoniae	**?**	**13.1**	**?**
C. psittaci	**1.3**	**2.6**	**2.2**
C. burnetii	**0.0**	**1.2**	**0.0**
Viral	**13.1**	**12.8**	**9.7**
Mixed	**11.0**	**14.2**	**6.0**
Other	**1.7**	**2.0**	**6.5**
Not established	**45.3**	**30.8**	**32.4**

[a]1 study; [b]4 studies

CAP - Classification



IDSA and CIDS-CTS, 2000

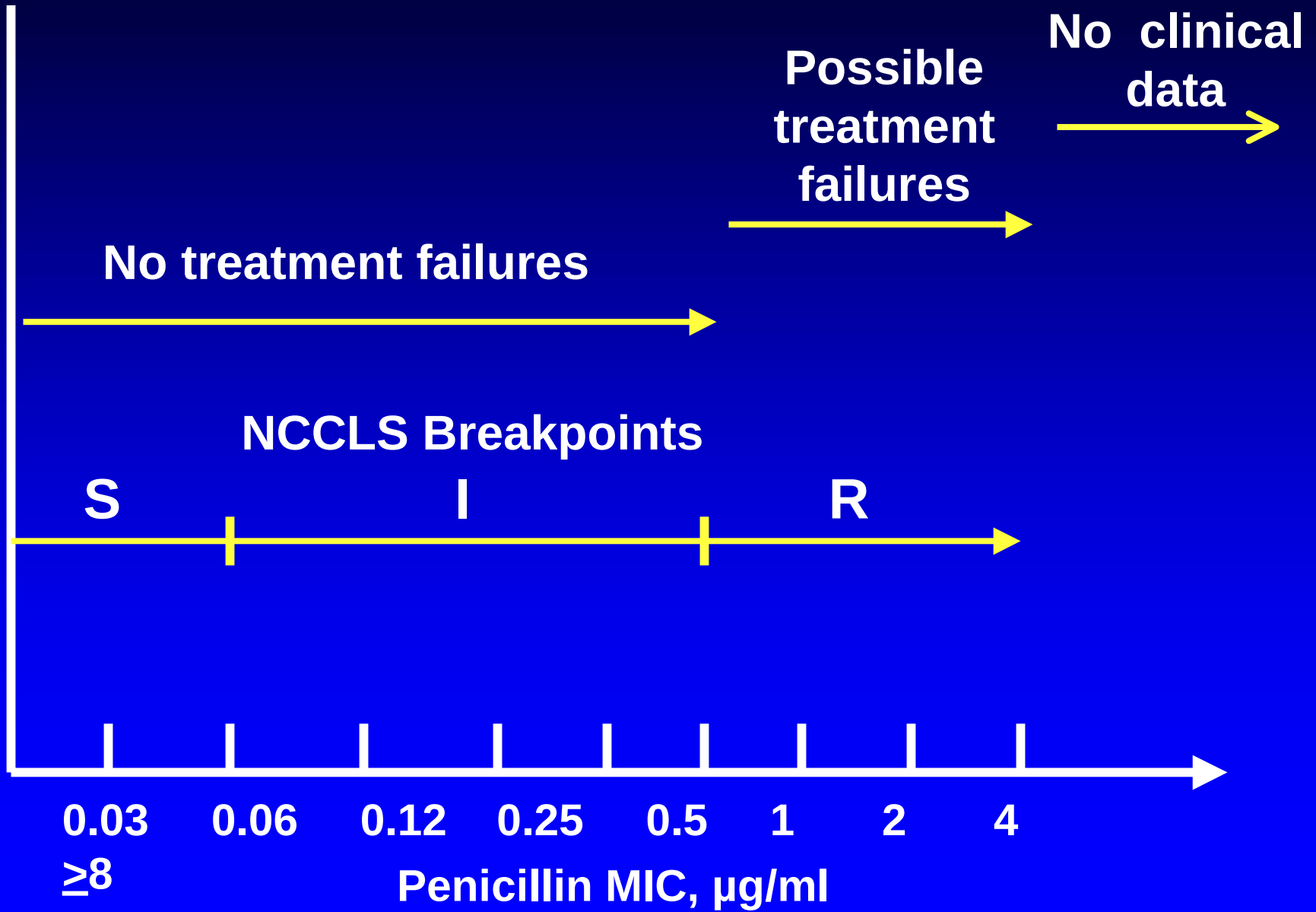
CAP - Classification

SUBGROUPS

1. Outpatient without comorbidity
2. Outpatient with comorbidity
3. CAP requiring hospitalization
4. CAP requiring ICU-hospitalization

ICU: Intensive Care Units

Pneumococcal CAP : Peni-Resistance *vs.* Clinical Outcomes



Clinical re-definition of Peni-Resistance of *S. pneumoniae* in RTI

- **NCCLS (1) :**

  Sensitive : MIC ≤ 0.06 mcg/ml
  /ntermediate: MIC 0.1 – 1.0 mcg/ml
  Resistant: MIC ≥ 2.0 mcg/ml

- **Suggested clinical re-definition (2) :**

  Sensitive : MIC ≤ 1.0 mcg/ml
  /ntermediate: MIC 2.0 mcg/ml
  Resistant: MIC ≥ 4.0 mcg/ml

(1) NCCLS, 1998
(2) Arch Intern Med 2000;160:1399

Clinical significance of Peni-Resistance in Pneumococcal CAP

- **Beta-lactams :**

  - still do the job in pneumococcal CAP (MIC ≤ 2mcg/ml)

  - should be adequately dosed :
  to obtain T>MIC: > 40% of dosing interval
  to prevent further emergence of resistance

- **New « respiratory » antimicrobials : not needed in first choice**

Arch Intern Med 2000;160:1399

Oral *vs.* IV therapy in CAP

CAP 3: +/- same causative organisms as CAP 2, but :

- **More co-morbidities**
- **Higher mortality / morbidity**
- **More frequent extra-pulmonary spread**
- **More frequent prior AB use**
- **More frequent resistant strains**

High AB tissue- and serum- concentrations needed

➔ intravenous therapy

Oral *vs.* IV therapy in CAP 3

High AB tissue- and serum- concentrations needed :

- **Betalactams : initial IV therapy needed; sequential to oral ASAP**

- **fluoroquinolones (pharmacokinetic bioequivalency IV/PO) :**

- **clinical success rates: sequential IV/PO = PO (1)**
- **if adequate absorption : initial oral therapy possible**

- **Mortality decreases significantly when 1st AB dose given < 8h after hospitalization (2)**

(1) ICAAC 2001; P854
(2) JAMA 1997;278:2080

FQ with antipneumococcal activity available in Belgium

Name	Use	Dose
Levofloxacin	PO IV	500 mg OD/BID
Moxifloxacin	PO	400 mg OD

Concentration dependent, rapidly bactericidal

PO: per os (oral)
IV: intravcenous

OD: once daily
BID: twice daily ("bis in die")

Levofloxacin and moxifloxacin in CAP

PRO'S

Anti-bacterial activity and clinical efficiency

- Respiratory bacteria and atypicals
- Not related to peni- and macrolide-resistance

Pharmacokinetic advantages

- Bio-equivalency po - iv
- Quick sequential therapy
- OD - BID
- High tissue disposition

FQ: Antibacterial activity
MIC_{90} (mcg/ml)

Organism	OFL	CIP	LFX	MOX
S. pneumoniae	4	2	1-2	0.06-0.25
H. influenzae Bla + en -	0.05	0.03	0.03-0.47	0.03-0.06
M. catarrhalis Bla + en -	0.12	0.06	0.06-0.094	0.012-0.06

OFL: ofloxacin; CI: ciprofloxacin; LFX: levofloxacin, MOX: moxifloxacin
Bla + : beta-lactamase producer

JAC 1999;43SB:1
Sem Resp Inf 2001;16:155

MIC_{90} (mcg/ml) of levofloxacin and moxifloxacin against S. *pneumoniae* (n=1385)

Organism	Range	LFX	MOX
Penicillin-susceptible *(n=1317)*	< 0.1	1-2	0.06-0.25
Penicillin-intermediate *(n=40)*	0.1-1	1-2	0.12-0.25
Penicillin-resistant *(n=28)*	> 2	1-2	0.12-0.25

JAC 1999;43SB:13
Sem Resp Inf 2001;16:155

Fluoroquinolones: activity *vs.* « atypicals »
MIC_{90} (mcg/ml)

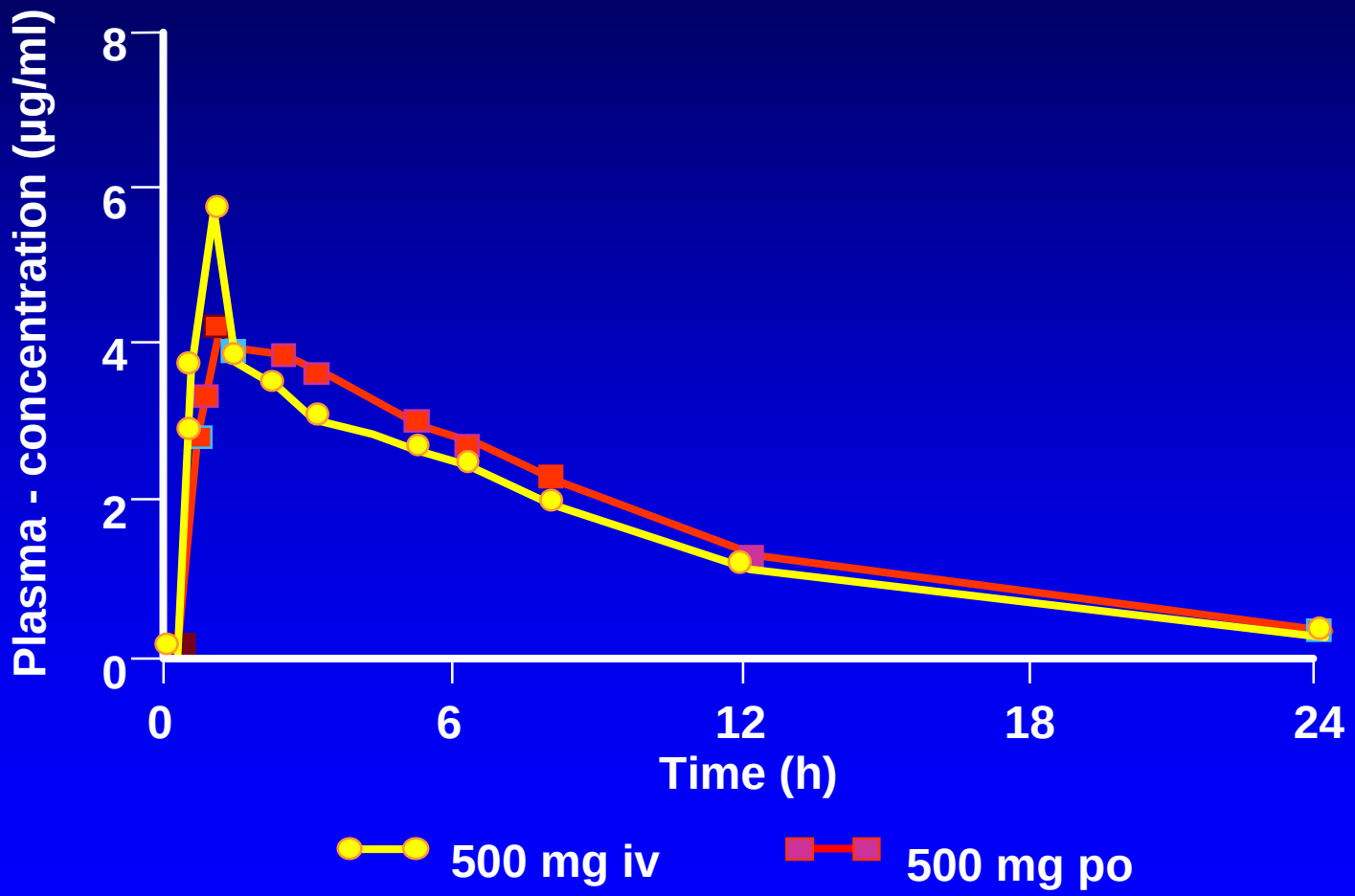
Organism	OFL	CIP	LFX	MOX
Myc. pneumoniae	**1**	**1**	**0.5**	**0.25**
Chl. pneumoniae	**2**	**1**	**0.12**	**0.12**
Leg. pneumophila	**0.03**	**0.12**	**0.015**	**0.06**

OFL: ofloxacin; CI: ciprofloxacin; LFX: levofloxacin, MOX: moxifloxacin

Sem Resp Inf 2001;16:155-168

Levofloxacin

Bio-equivalence oral ↔ iv



PK/PD of levofloxacin and moxifloxacin *vs. S. pneumoniae*

	DOSE (mg)	MIC_{90} (mcg/ml)	Peak/MIC	AUC/MIC
LFX	500	1-2	3-6	24-48
MOX	400	0.125-0.25	9-18	96-192

AUIC (AUC/MIC) minimal for successful outcome = 35 - 40 (minimal)

High Peak/MIC: also important for prevention of resistance selection

JAC 2000;46:669

Fluoroquinolones

Problems

- **Safety / Unexpected toxicity (PMS)**
- **Commercial benefits =**
  flu-like syndroms, URTI, AECB
- **Massive use = resistance**
  among respiratory pathogens
  among commensal gut-flora

Fluoroquinolone resistance in *S. pneumoniae*

"The incidence of pneumococci highly resistant to quinolones (ciprofloxacin MIC ≥8 mg/L) is currently very low, but this may change with selective pressure due to widespread use of new broad spectrum agents against community-acquired respiratory tract infections."

PC Appelbaum

Invited presentation at the 38th ICAAC, September 1998

Fluoroquinolone resistance

- Anti-pneumococcal in vitro activity and AUIC: moxifloxacin > levofloxacin
- Weaker fluoroquinolones may lead to more rapid emergence of resistance
- Reports of treatment failure and resistance development with levofloxacin (NEJM 2002;346:747)
- When a fluoroquinolone is indicated: use the most potent agent

Fluoroquinolones in CAP

New fluoroquinolones: Reserved for selected patients with CAP

1. **Failure of first-line regimens**

2. **Allergy to first-line agents**

- **Documented infection with highly resistant *S. pneumoniae***

- **As first choice in subgroup 3 when oral therapy is possible (?)**

KETOLIDES

Name	Use	Dose
Telithromycin	PO	800 mg OD (= 2x400 mg tabl.)

Concentration and time (AUC) - dependent bactericidal activity

MIC_{90} (mcg/ml) of telithromycin against *S. pneumoniae*

Organism	CLA	AZI	TEL
Penicillin-susceptible *(n = 21)*	**0.015**	**0.06**	**0.015**
Penicillin-intermediate *(n=20)*	**0.015**	**0.06**	**0.015**
Penicillin-resistant *(n=20)*	**0.015**	**0.06**	**0.008**

CLA: clarithromycin
AZI: azithromycin
TEL: telithromycin

Abstract F166 ICAAC, 1997
JAC 1999;44:445

Resistance to macrolide antimicrobials

- **Target modification (MLS_B resistance):**
  - methylation of rRNA blocks drug binding
  - methylase encoded for by plasmid-borne *erm* genes
  - confers resistance to all macrolides, streptogramins and lincosamides
  - inducible or constitutive
- **Efflux (M-resistance):**
  - confers resistance to other macrolides but not other members of MLS group

Resistance to erythromycin confers cross-resistance to all other macrolides except telithromycin

AAC 1995;39:577–85
AAC 1997;41:2251–5

MIC_{90} (mcg/ml) of telithromycin against *S. pneumoniae*

Organism	ERY	CLD	TEL
Erythromycin-resistant *(n = 30)*	> 512	256	0.5

ERY: erythromycin
TEL: telithromycin
CLD: clindamycin

JAC 2000;45:167

MIC_{90} (mcg/ml) of telithromycin against CAP pathogens

Organism	CLA	AZI	TEL
S. pneumoniae	0.015	0.06	0.015
H. influenzae Bla + en -	8	1	2
M. catarrhalis Bla + en -	0 .06	0.03	0.06

Abstract F166 ICAAC, 1997

MIC_{90} (mcg/ml) of telithromycin against CAP pathogens

Organism	CLA	TEL	LFX	MOX
Myc. pneumoniae	0.015	0.004	0.5	0.25
Chl. pneumoniae	0.25	0.25	0.12	0.12
Leg. pneumophila	0.004	0.03	0.015	0.06

Abstract F166 ICAAC, 1997

TELITHROMYCIN in CAP

PRO'S

Anti-bacterial activity and clinical efficiency

- ***S. pneumoniae*** **and atypicals**
- **Not related to peni- and macrolide-resistance**

Pharmacokinetic advantages

- **OD**
- **High tissue disposition**

TELITHROMYCIN in CAP

CON'S

- **Weak anti – *H. influenzae* activity**
- **Only orally**
- **Commercial benefits =**
  flu-like syndroms, URTI, AECB: resistance
- **Studies in peni- and erythro-R CAPs needed**
- **Further data on cardiotoxicity (QTc) needed**

2002 Belgian guidelines on the initial diagnostic and therapeutic approach of CAP in the immunocompetent patient

Working group CAP of IDAB 2002

- Herman Goossens
- Paul Jordens
- Willy Peetermans
- Yves Sibille
- Yvan Valcke (chairman)
- Johan Van Eldere
- Yves Van Laethem
- Walter Vincken

Subgroup 1 : Outpatient without comorbidity

PREFERRED TREATMENT :

amoxicilline 1g q8h PO

Subgroup 1

SPECIFIC INDICATIONS (1) :

Non – IgE - mediated beta-lactam allergy.

cefuroxime - axetil 500 mg q8h PO

Subgroup 1

SPECIFIC INDICATIONS (2) :

IgE-mediated beta-lactam allergy or major beta-lactam intolerance.

1. **moxifloxacin 400 mg q24h PO**
   or levofloxacin 500 mg q12h PO
2. **telithromycin 800 mg (= 2 tablets) q24h PO**

Subgroup 1

SPECIFIC INDICATIONS (3) :

Clinical failure after 3 days of beta-lactams (cover atypicals).

1. moxifloxacin 400 mg q24h PO
   or levofloxacin 500 mg q12h PO
2. telithromycin 800 mg (= 2 tablets) q24h PO
3. association with neomacrolide or azalide PO

Subgroup 2 : Outpatient with comorbidity

PREFERRED TREATMENT :

1. amoxi/clav 875/125 mg q8h PO
2. cefuroxime-axetil 500 mg q8h PO

Subgroup 2

SPECIFIC INDICATIONS (1) :

IgE-mediated beta-lactam allergy or major beta-lactam intolerance.

moxifloxacin 400 mg q24h PO

or

levofloxacin 500 mg q12h PO

Subgroup 2

SPECIFIC INDICATIONS (2) :

Clinical failure after 3 days of beta-lactams (cover atypicals).

1. moxifloxacin 400 mg q24h PO
   or levofloxacin 500 mg q12h PO
2. association with neomacrolide or azalide PO

Subgroup 3 : Hospitalized

IV treatment needed !!

- **Predominant Gram+ diplococci on representative sputum sample :**

  penicillin G 2 MIU q4h IV

- **Sputum sample inconclusive/unavailable :**

  amoxi/clav 1 g q6h IV
  or
  cefuroxime 0.75-1.50 g q8h IV

Subgroup 3

SPECIFIC INDICATIONS (1) :

IgE-mediated beta-lactam allergy or major beta-lactam intolerance.

levofloxacin 500 mg q12h IV

Subgroup 3

SPECIFIC INDICATIONS (2) :

Clinical failure after 3 days of beta-lactams (cover atypicals).

1. **levofloxacin 500 mg q12h IV**
2. **association with neomacrolide IV**

Non - ICU - hospitalized CAP

- Treat orally whenever possible

- When IV needed : sequential to oral asap :

  afebrile for 48 h
  declining inflammatory parameters
  favourable clinical evolution

Subgroup 3 : Hospitalized

When oral treatment is possible

moxifloxacin 400 mg q24h PO

or

levofloxacin 500 mg q12h PO

Subgroup 4 : ICU - hospitalized

amoxi/clav 1g q6h IV *or* cefuroxime 1.5 g q8h IV *or* cefotaxime 2g q8h IV (*) *or* ceftriaxone 2g q24h IV (*)

with

clarithromycin 500 mg q12h IV
***or* fluoroquinolone IV**

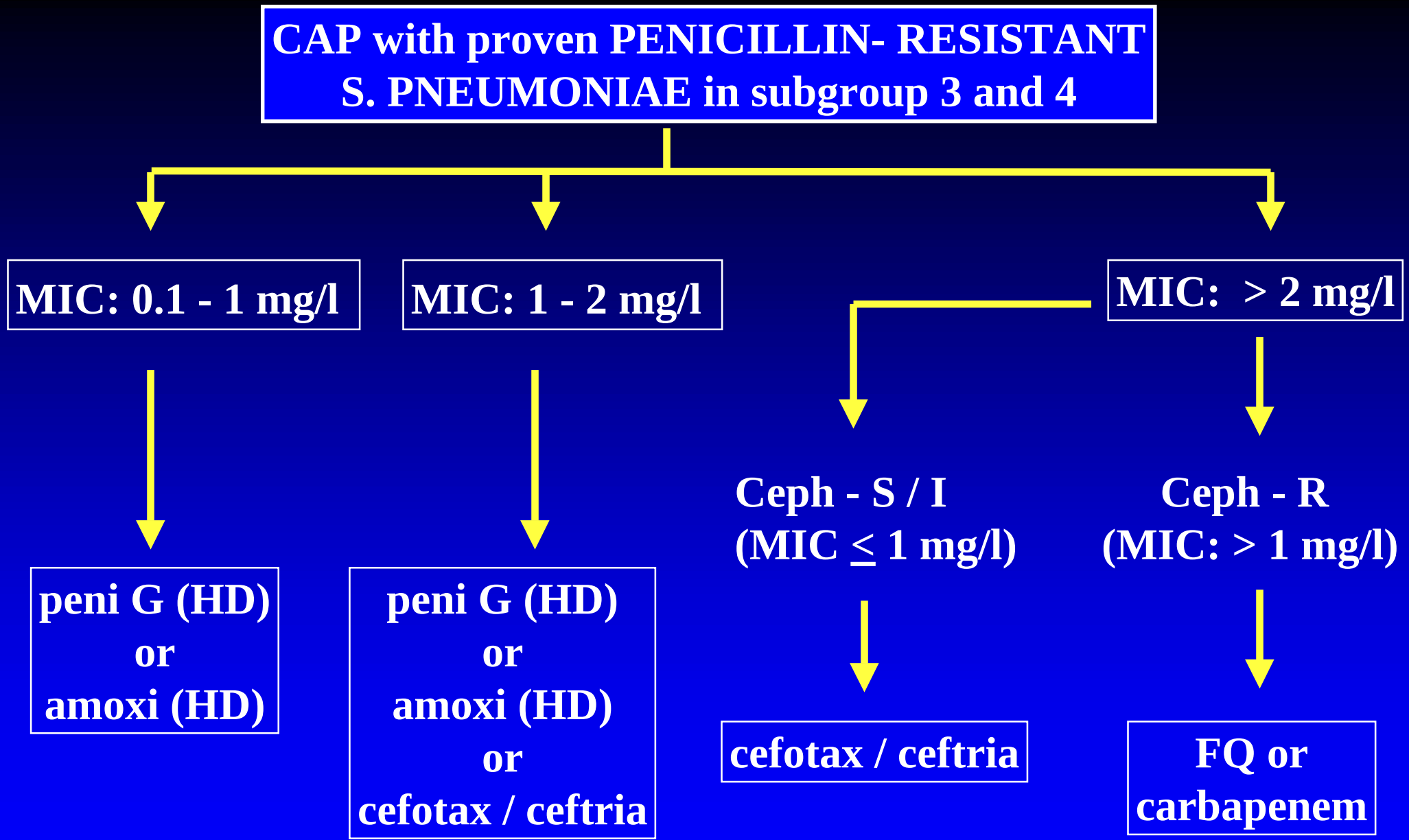
(*) indicated when suspicion of invasive CNS pneumococcal infection, recent hospitalization, or recent broad spectrum antibiotics

Pseudomonas risk :
structural lung disease (bronchiectasis)

carbapenem or cefepime
with
ciprofloxacin 400 mg q8h IV

OR

carbapenem or cefepime
with
amikacin or isepamicin q24h IV
with
clarithromycin 500 mg q12h IV
or fluoroquinolone IV


CAP with proven PENICILLIN- RESISTANT S. PNEUMONIAE in subgroup 3 and 4
MIC: 0.1 - 1 mg/l
MIC: 1 - 2 mg/l
MIC: > 2 mg/l
Ceph - S / I (MIC ≤ 1 mg/l)
Ceph - R (MIC: > 1 mg/l)
peni G (HD) or amoxi (HD)
peni G (HD) or amoxi (HD) or cefotax / ceftria
cefotax / ceftria
FQ or carbapenem