Antimicrobial stewardship approach to the treatment of community-acquired respiratory tract infections

Bojana Beović

Univerza v Ljubljani
Medicinska fakulteta

univerzitetni klinični center ljubljana
University Medical Centre Ljubljana

- Acute non-specified respiratory tract infection
- Sore throat
- Acute rhinosinusitis
- Laryngitis, bronchiolitis, bronchitis
- Community-acquired pneumonia (CAP)
- Acute exacerbation of COPD

- **Acute non-specified respiratory tract infection**
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Indications for antibiotic treatment in outpatients

(1691 patients in Ljubljana region)

Type of infection	% of antibiotic treatments
Upper respiratory tract	53.5
Lower respiratory tract	14.0
Skin/skin structure	12.7
Urinary tract	21.2
Other	9.3

Lovšin B, Beović B. Infektološki simpozij 2003.

Antibiotic treatment for pneumonia, lower and upper respiratory tract infections: Global PPS, Europe

Respiratory tract infections are the most common indications for antibiotics in hospitals!

- Pneumonia and lower respiratory tract infections: 14.3 – 28.2%
- Upper respiratory tract infections, bronchitis and acute exacerbations of chronic bronchitis: 3.5 – 5.6%
- Community vs hospital-acquired infections: 36.7- 56.7%

*% of all antibiotic treatments
PPS: point-prevalence survey

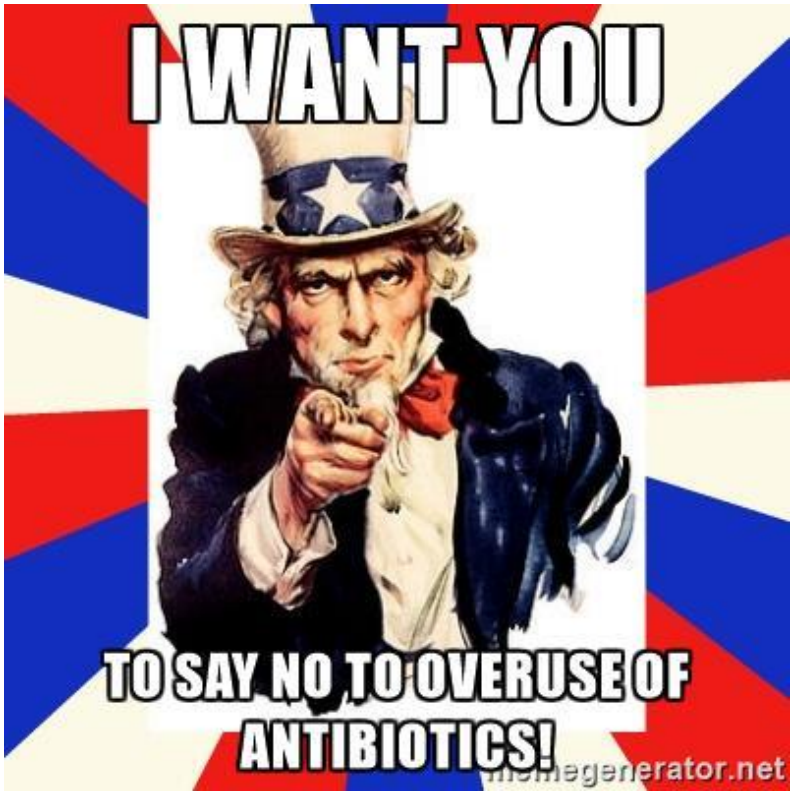
Versporten A, et al. *Lancet Glob Health* 2018; 6: e619–29

Antimicrobial Stewardship in Community-acquired Respiratory Tract Infections: points for interventions

- **Indications for antibiotic treatment**
- **Choice of antibiotics**
- **Streamlining of antibiotic treatment**
- **Duration of antibiotic treatment**

Antibiotics:

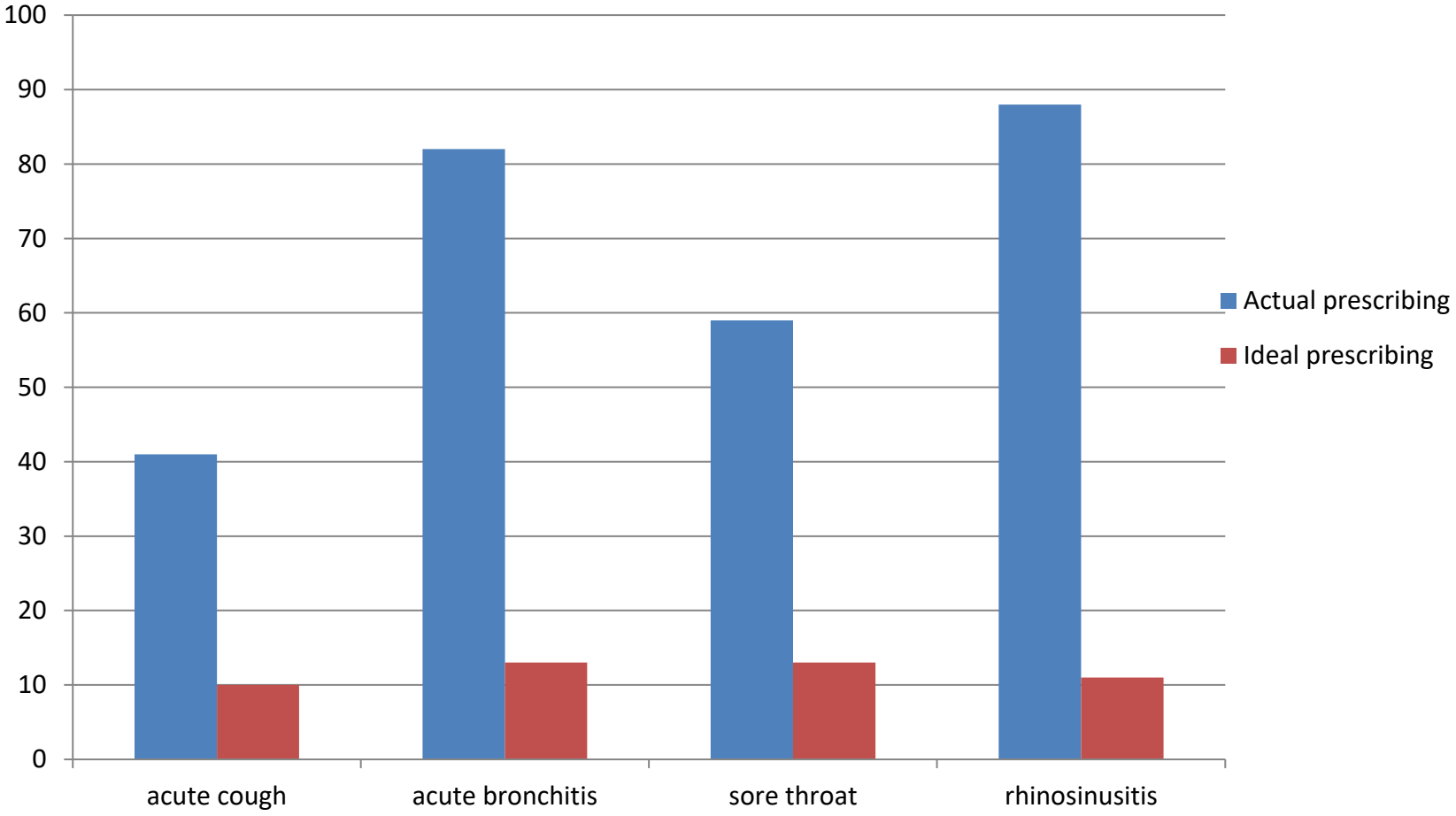
Acute Nonspecific Respiratory Tract Infections



Viral diseases!
Talk to the patient!

https://memegenerator.net/instance/65024089/uncle-sam-i-want-you-i-want-you-to-say-no-to-overuse-of-antibiotics

Proportion of visits with antibiotic prescription in primary care, %



Pouwels K, et al. J Antimicrob Chemother 2018;73(Suppl 2):19–26

Antibiotics or Not for ARI?

1,531,019 visits with ARI in primary care, 65% received antibiotics

	Serious adverse events*	Minor adverse events	Pneumonia*
	per 100,000 patients		
Antibiotic therapy	8.48	83.18**	17.96**
No antibiotic therapy	7.75	28.00**	21.93**

*not adjusted, **significant

Number needed to be treated to avoid 1 pneumonia: 12,255
The difference in pneumonia rate was non-significant when they excluded pneumonias diagnosed on index day.

Antibiotics are most effective against rapidly evolving pneumonia?
The difference is caused by miss-diagnosis of pneumonia on index day?

Meropol SB, et al. Ann Fam Med 2013;11:165-72.

Antibiotics or Not in ARI: are All Syndromes the Same?

Table 4 | Protective effect of antibiotics for common respiratory tract infections and number needed to treat to prevent one complication

Infection/adverse outcome (age group)	Adjusted odds ratio* (95% CI)	Number needed to treat (95% CI)	P value
URTI/pneumonia (all ages)	0.68 (0.58 to 0.79)	4407 (2905 to 9126)	<0.001
Otitis media/mastoiditis (all ages)	0.56 (0.37 to 0.86)	4064 (2393 to 13 456)	0.008
Sore throat/quinsy (all ages)	0.84 (0.73 to 0.97)	4300 (2522 to 14 586)	0.021
Chest infection/pneumonia (significant interaction between prescribing and age):			
0-4 years	0.22 (0.17 to 0.27)	101 (85 to 125)	<0.001
5-15 years	0.18 (0.13 to 0.24)	96 (73 to 137)	<0.001
16-64 years	0.27 (0.23 to 0.32)	119 (105 to 136)	<0.001
≥65 years	0.35 (0.33 to 0.38)	39 (36 to 42)	<0.001

URTI=upper respiratory tract infection.
*Adjusted for age, sex, and social deprivation.

Petersen I, et al. BMJ 2007; 335: 982.

ESCMID & ERS Guidelines 2011

A patient with lower respiratory tract infection should be suspected of having pneumonia if one of the following SIGNS/SYMPTOMS is present:

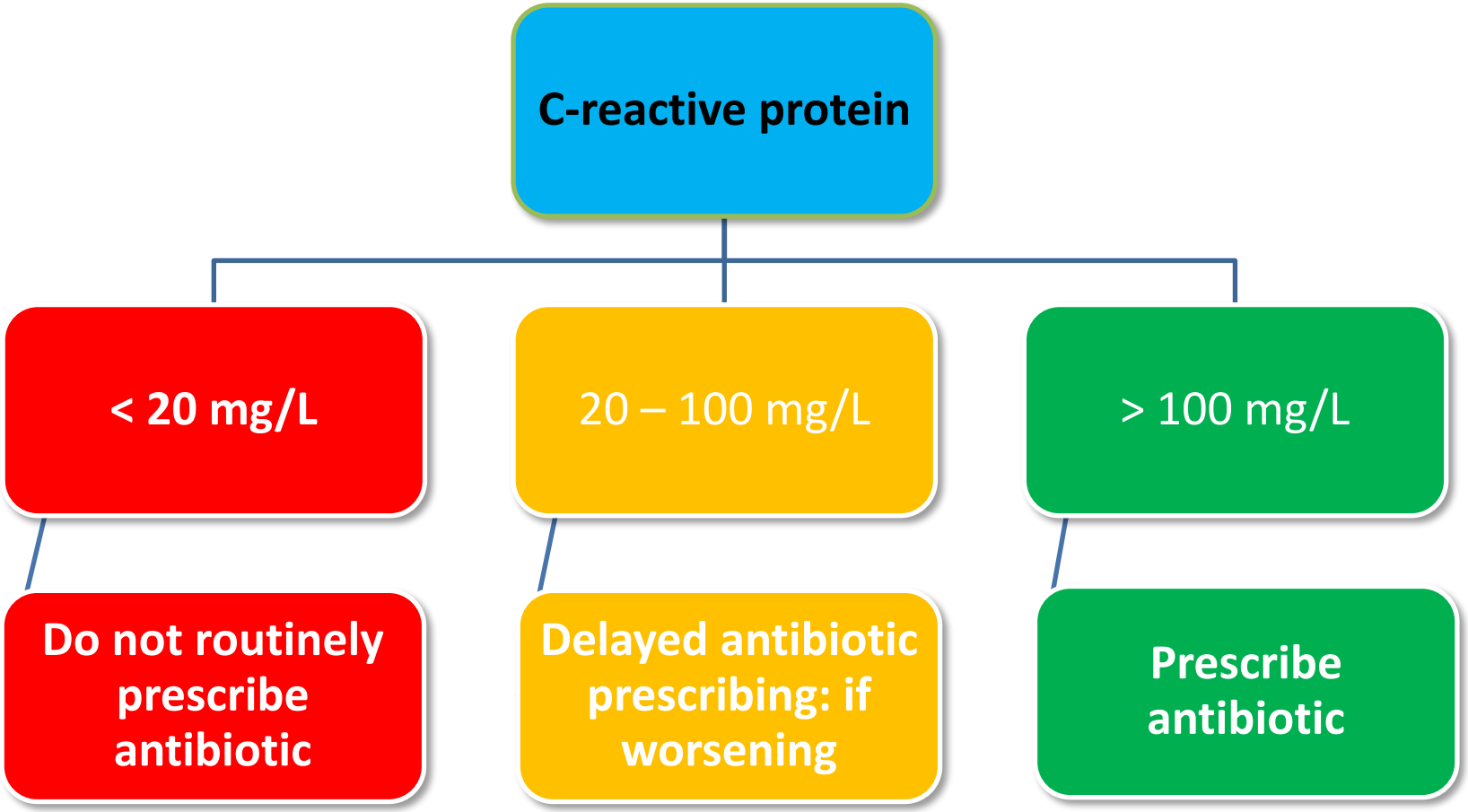
- new focal chest signs,
- dyspnoea/tachypnoea
- pulse rate >100
- fever >4 days

Antibiotics should be considered in patients with lower respiratory chest infections and serious COMORBIDITIES:

- cardiac failure;
- insulin-dependent diabetes mellitus;
- a serious neurological disorder (stroke etc.)

Woodhead W, et al. Clin Microbiol Infect 2017; (Suppl. 6): 17: 1–24.

National Institute for Health and Clinical Excellence (NICE): C-reactive protein as a diagnostic tool for patients with community-acquired pneumonia



https://www.nice.org.uk/guidance/cg191

Choice of Antibiotic

Etiology of CAP

- *S. pneumoniae* is the most frequent causative agent, but the frequency of its isolation is not high.
- *H. influenzae* and *Enterobacteriaceae* may colonizer respiratory tract and may contaminate the samples
- *C. pneumoniae* serology might be false positive.
- No major change in the last years.
- Similar results of other European studies.

Wiersinga WJ, et al. Neth J Med. 2018 Jan;76(1):4-13.

Severity assessment

Pneumonia Severity Index:

- widely studied, but complex

C(U)RB65

- **C**onfusion
- **U**rea >7 mmol/l
- **R**espiratory rate ≥30/min
- low systolic (<90 mm Hg) or diastolic (≤60 mm Hg) **B**lood pressure
- age ≥**65** years

Mortality (CURB65)
score 0, 0.7%
score 1, 2.1%
score 2, 9.2%
scores 3–5, 15–40%

https://www.brit-thoracic.org.uk/standards-of-care/guidelines/bts-guidelines-for-the-management-of-community-acquired-pneumonia-in-adults-update

Comparison of recent community-acquired pneumonia treatment guidelines: outpatients

ESCMID 2011	**amoxicillin**, doxycycline alternative: azithromycin, clarithromycin, erythromycin
Sweden 2017	**amoxicillin** alternative doxycycline or erythromycin
NICE 2014, 2019	**amoxicillin** alternative: doxycycline (clarithromycin, erythromycin)
BTS 2015	**amoxicillin** alternative: claritromycin, doxycycline
The Netherlands 2016	**amoxicillin** alternative: doxycycline
USA 2019	**amoxicilin or doxycycline or macrolide** comorbidities: co-amoxiclav + macrolide or fluoroquinolone monotherapy

Woodhead M, et al. Clin Microbiol Infect 2011. Athlin S, et al. Infect Dis 2017;1-26., Wiersinga WJ et al. Concept Update 2016 SWAB/NVALT. Lim WS, et al. Thorax 2015., https://www.nice.org.uk/guidance/cg191, Metlay JP, AJRCCM 2019;200:e45-e67.

Comparison of recent community-acquired pneumonia treatment guidelines: inpatients

	CURB65 0-1	CURB65 2	CURB65 3-5
NICE 2014, 2019	amoxicillin	amoxicillin (higher dose) + clarithromycin or erythromycin	amoxicillin/clavulanic acid + clarithromycin or erythromycin
BTS 2015	Mild pneumonia: Oral: amoxicillin Parenteral : amoxicillin, penicillin G, clarithromycin Moderately severe pneumonia: Oral: amoxicillin + macrolide Parenteral: amoxicillin or penicillin G + clarithromycin		Severe pneumonia: amoxicillin/clavulanic acid + macrolide

Woodhead M, et al. Clin Microbiol Infect 2011. Spindler C, et al. Scand J Infect Dis 2012., Wiersinga WJ et al. Concept Update 2016 SWAB/NVALT. Lim WS, et al. Thorax 2015., https://www.nice.org.uk/guidance/cg191

Comparison of recent community-acquired pneumonia treatment guidelines: inpatients (con‘t)

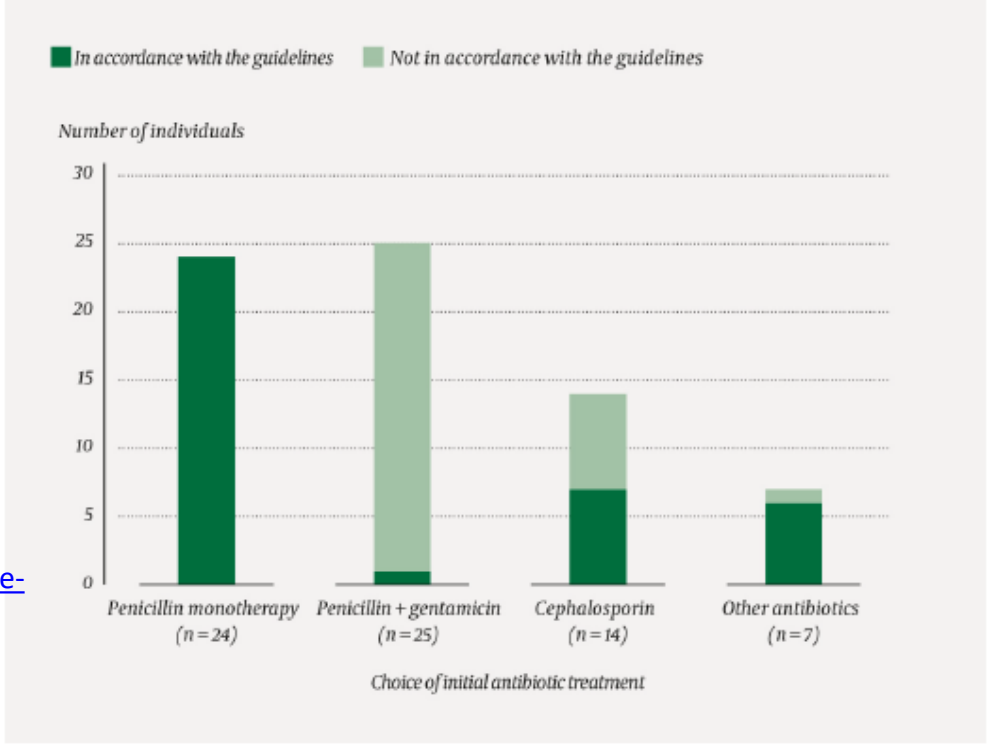
	CURB65 0-1	CURB65 2	CURB65 3-5	ICU
The Netherlands 2016		penicillin G or amoxicillin	cephalosporins 2nd or 3rd generation	moxifloxacin or cephalosporins 2nd or 3rd generation + ciprofloxacin
Sweden 2017	penicillin G (modification according to clinical presentation and risk factors, severe lung disease…)		cephalosporins 3rd generation + macrolide or penicillin G + fluoroquinolone	
ESCMID/ERS 2011	aminopenicillin +/- macrolide aminopenicillin/inhibitor β-laktamaze +/- macrolide cefalosporin w/o activity against *Pseudomonas aeruginosa* cephalosporins 3rd generation +/- macrolide levofloxacin moxifloxacin penicillin G +/- macrolide			cephalosporins 3rd generation + macrolide or moxifloxacin or levofloxacin +/- cephalosporins 3rd generation
USA 2019	Beta-lactam (3rd generation cephalosporins, ceftaroline, ampi/sulbactam…) + macrolide/fluoroquinolone with various modification for MRSA, Pseudomonas aeruginosa, other risk factors…			

Woodhead M, et al. Clin Microbiol Infect 2011., Athlin S, et al. Infect Dis 2017,1-26., Wiersinga WJ et al. Concept Update 2016 SWAB/NVALT. Lim WS, et al. Thorax 2015., https://www.nice.org.uk/guidance/cg191, Metlay JP, AJRCCM 2019;200:e45-e67.

Norway: CAP guidelines and compliance with guidelines

Variable	Result (N = 70)
Sex	
Men	49
Women	51
Age in years, median (interquartile range)	68 (47–82)
Multiple diagnoses in medical records	57
CRB-65 score	
0	37
1	31
2	20
3	7
4	0
Incomplete[1]	4
Culture results	
S. pneumoniae	57
H. influenzae	43
Duration of hospitalisation in days, median (interquartile range)	10 (8–11)

Therapy of choice: penicillin 3 g/6h IV or amoxicillin PO
For CRB65 3-4: addition of gentamicin or cefotaxim
Addition of erythromycin, if legionella or mycoplasma suspected



www.helsedirektoratet.no/retningslinjer/antibiotika-i-sykehus/nedre-luftveier#samfunnservervet-pneumoni, 09. mai 2019
Berild AG, et al. Tidsskr Nor Laegeforen. 2018 Nov 26;138(19).

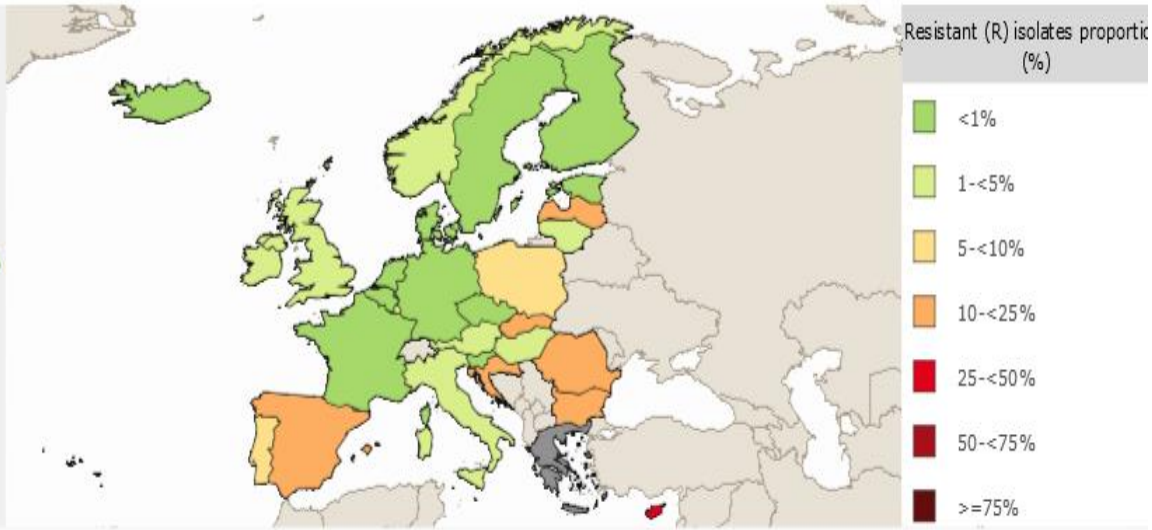
General principles of antibiotic treatment of CAP

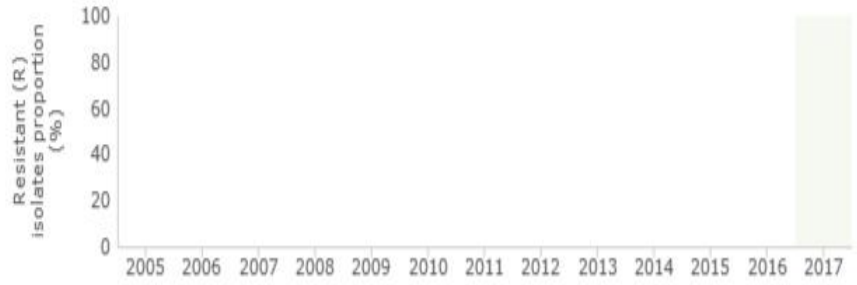
- never forget *S. pneumoniae*!
- selection of empirical antibiotic therapy should be guided by the severity of disease at presentation!

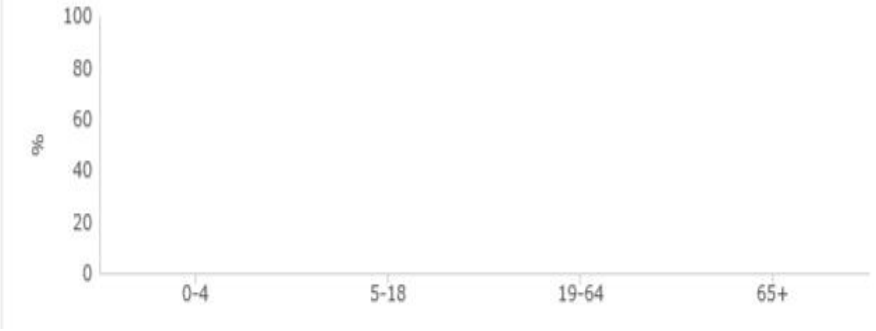
Surveillance Atlas of Infectious Diseases

Antimicrobial resistance | Streptococcus pneumoniae | Penicillins | Resistant (R) isolates proportion | 2017

Region	Resistant (R) isolates proportion (%)
Austria	2.6
Belgium	0.2
Bulgaria	17.2
Croatia	22.5
Cyprus	45.5
Czech Republic	0.5
Denmark	0.0
Estonia	0.0
Finland	0.6







https://atlas.ecdc.europa.eu/public/index.aspx?Dataset=27&HealthTopic=4

The relationship of dose and MIC for clinical efficacy of beta-lactams

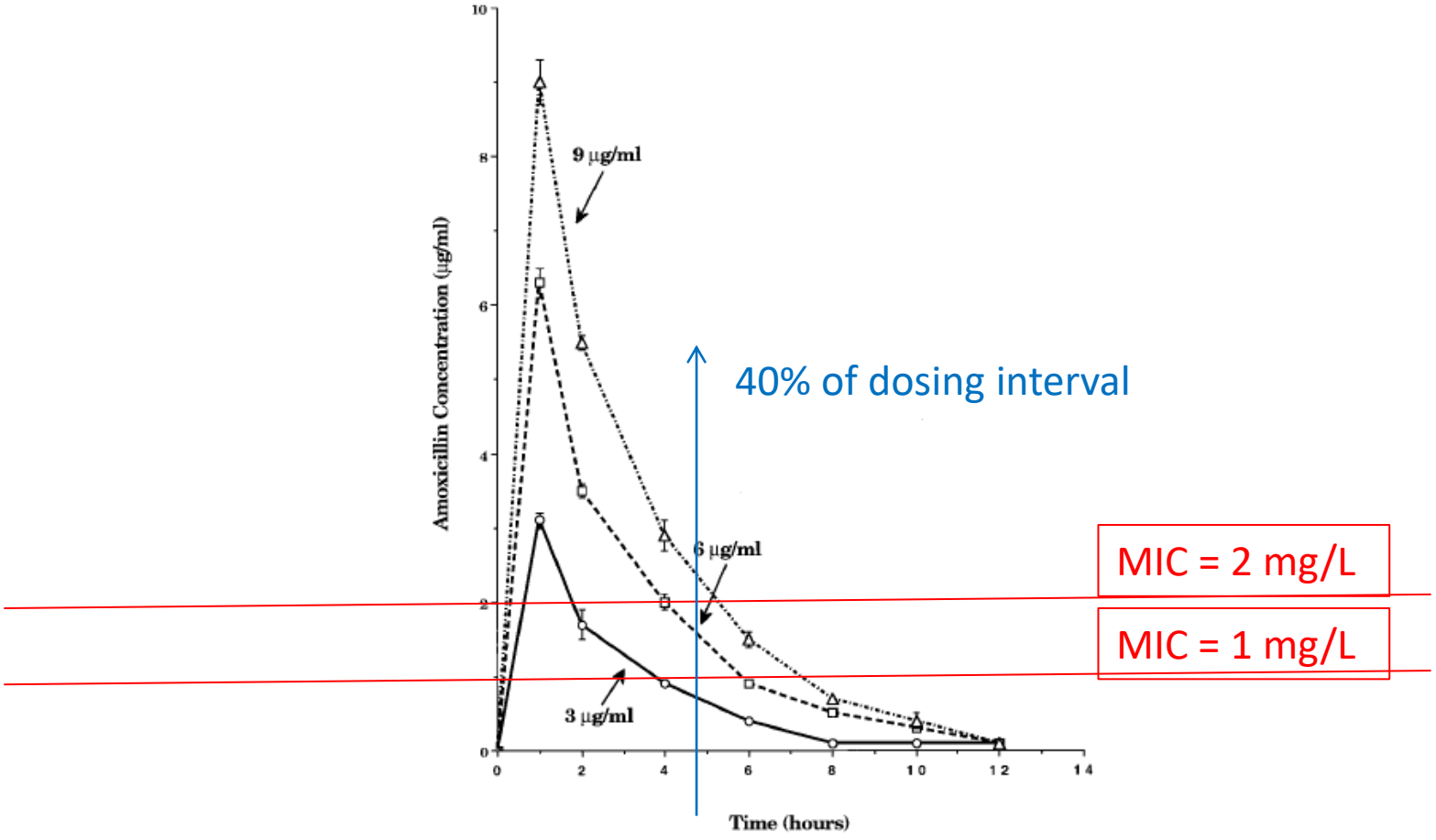


FIG. 2. Single-dose pharmacokinetic profiles of 3-, 6-, and 9-μg/ml peak amoxicillin doses in the peripheral compartment of the IVPM after introduction into the central reservoir. Drug levels were measured by bioassay. Each datum point represents the mean drug level in the peripheral compartment (in micrograms per milliliter) for three experimental runs. Error bars show the SEM.

Lister PD, et al. Antimicrob Agents Chemother 1997; 41:1926-32.
Craig WA. Diagn Microbiol Infect Dis 1996;25(4):213-7.

Susceptibility of *S. pneumoniae* in Slovenia and its impact on penicillin dosing for the treatment of CAP (2017) (1538 isolates)

Občutljivost / odpornost pri različnih odmerkih penicilina [Op. 1]	Delež izolatov
Občutljivost za oralni penicilin ali i.v. penicilin v odmerku 1 milijon IE x 4 (MIK ≤ 0,06 mg / L)	84,8
Občutljivost za i.v. penicilin v odmerku 2 milijona IE x 4 (MIK ≤ 0,5 mg / L)	95,2
Občutljivost za i.v. penicilin v odmerku 4 milijone IE x 4 ali 2 milijona IE x 6 (MIK ≤ 1 mg / L)	98,2
Občutljivost za i.v. penicilin v odmerku 4 milijone IE x 6 (MIK ≤ 2 mg / L)	99,6
Odpornost proti i.v. penicilinu ne glede na odmerek. (MIK >2 mg / L)	0,4

[Op. 1] Rezultati v tabeli veljajo za zdravljenje pljučnice. Delež občutljivih izolatov je odvisen od maksimalne MIK v populaciji izolatov in od odmerka penicilina, ki je v tabeli izražen v mednarodnih enotah [21].
V oklepaju je naveden največji MIK penicilina, ki opredeljuje potrebni i.v. odmerek penicilina [21].

Štrumbelj I, Pirš M, Berce I, Bombek Ihan M, Fišer J, Golle A, Grmek Košnik I, Harlander T, Jeverica S, Kavčič M, Matos T, Mioč V, Mueller - Premru M, Paragi M, Piltaver Vajdec I, Ribič H, Seme K, Štorman A,Tomič V, Zdolšek B, Žolnir - Dovč M. *Pregled občutljivosti bakterij za antibiotike - Slovenija 2017*. Ljubljana: Slovenska komisija za ugotavljanje občutljivosti za protimikrobna zdravila (SKUOPZ); 2018. 1. izdaja. Dosegljivo na: http://www.imi.si/strokovna-zdruzenja/skuopz

Combination empirical antibiotic treatment of CAP

Combination vs monotherapy

- CH 2014 (prospective randomized) : comparable efficacy of monotherapy and betalactam+macrolide combination, trend toward better efficacy of combination in severely ill.
- NL 2015 (prospective randomized) : the same efficacy in patients who do not need ICU
- Meta-analysis I 2016: better efficacy of combination, but poor quality of the studies
- Meta analysis II 2016: advantage of the combination in more severely ill (CURB65 ≥2, PSI 4,5)
- Comparison of beta-lactam+macrolide combination with fluoroquinolones: longer hospital stay and higher mortality in patents treated with fluoroquinolones.

Garin N, et al. JAMA Intern Med. 2014; 174: 1894., Postma DF, et al. N Engl J Med. 2015; 372: 1312–23., Lee JS, et al. JAMA. 2016; 315: 593–602., Horita N, et al. Respirology. 2016; 21: 1193–200., Vardakas KZ, et al. Clin Microbiol Infect 2017; 23: 234–41.

„Directed empirical“ antibiotic treatment of CAP

- Effective treatment of CAP with high dose of penicillin based on pneumococcal urinary antigen test.
- Effective treatment of CAP with high dose of penicillin based on sputum smear.
- Effective treatment of CAP based on clinical assessment, sputum smear and pneumococcal urinary antigen testing.

Falguera M, et al. Thorax 2010;65:101e106.
Fukuyama H, et al. BMC Infectious Diseases 2014, 14:534.
Komagamine J. BMC Res Notes (2018) 11:399.

Urinary antigen testing in CAP

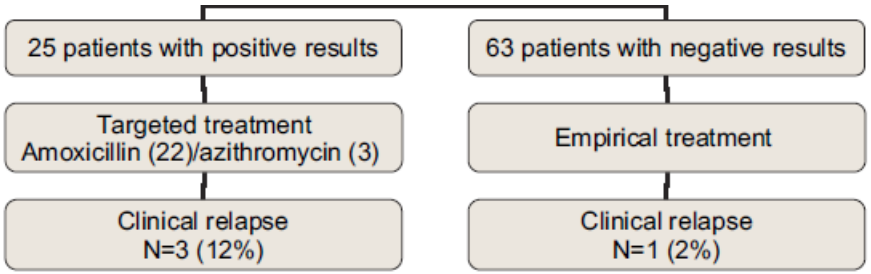
- **pneumococcal antigen** (C-polysaccharide antigen)
- specificity: 95 – 97.5%
- sensitivity: 74 – 75%
- Pre-test probability, not in children!

- **Legionella antigen** (*Legionella pneumophila* serogroup 1)
- specificity ~ 100%
- sensitivity 75-80%
- may miss other serogroups and species!

Viasus D, et al. Expert Rev Anti-infect Ther 2019. DOI: 10.1080/14787210.2019.1565994.

De-escalation in Patients with Pneumococcal Pneumonia: the Role of Urinary Pneumococcal Antigen

Spanish randomized controlled study (de-escalation and switch to oral)



P=0.04
One of 3 pts with „relapse“ had *E. coli* bacteremia.

Practice in the Dpt. of Infectious Diseases, UMC Ljubljana

May 2015 – April 2016

315 pts with CAP: 115 microbiologically confirmed

52 pneumococcal pneumonia, 17 confirmed only by urinary antigen
De-escalation performed in 13/17: pleural drainage in one patient, no other complications.

Falguera M, et al. Thorax 2010;65:101-6.
Pečavar B, personal communication.

Duration of Antibiotic Treatment in Community-acquired Pneumonia

IDSA Guidelines 2007

5 days *(strong recommendation, high evel of evidence)*, patients should be afebrile for 48–72 hours and should have no more than one CAP-associated sign of clinical instability prior to therapy discontinuation *(moderate recommendation, level II evidence)*

IDSA, Infectious Diseases Society of America

Mandell LA, et al. Clin Infect Dis 2007;44: suppl2: S27–S72.

ERS & ESCMID 2011

Treatment duration should be based on response to biomarkers such as procalcitonin; in any case, the duration of antimicrobial therapy should not exceed **8 days** in responding patients.

ERS, European Respiratory Society
ESCMID, European Society of Clinical Microbiology and Infectious Diseases

Woodhead M, et al. Clin Microbiol Infect 2011.

NICE (update 2019):

Choice of antibiotic: adults aged 18 years and over

Antibiotic[1]	Dosage and course length[2]
First choice oral antibiotic if low severity (based on clinical judgement and guided by CRB65 score 0 or CURB65 score 0 or 1)[3]	
Amoxicillin	500 mg three times a day (higher doses can be used - see BNF) for 5 days[4]
Alternative oral antibiotics if low severity, for penicillin allergy or if amoxicillin unsuitable (for example, atypical pathogens suspected[5])[3]	
Doxycycline	200 mg on first day, then 100 mg once a day for 4 days (5-day course in total)[4]
Clarithromycin	500 mg twice a day for 5 days[4]
Erythromycin (in pregnancy)	500 mg four times a day for 5 days[4]
First choice oral antibiotics if moderate severity (based on clinical judgement and guided by CRB65 score 1 or 2, or CURB65 score 2); guided by microbiological results when available[3]	
Amoxicillin ***with (if atypical pathogens suspected[5]):***	500 mg three times a day (higher doses can be used – see BNF) for 5 days[4]
Clarithromycin[6] *or*	500 mg twice a day for 5 days[4]
Erythromycin[6] (in pregnancy)	500 mg four times a day for 5 days[4]
Alternative oral antibiotics if moderate severity, for penicillin allergy; guided by microbiological results when available[3]	
Doxycycline	200 mg on first day, then 100 mg once a day for 4 days (5-day course in total)[4]
Clarithromycin	500 mg twice a day for 5 days[4]
First choice antibiotics if high severity (based on clinical judgement and guided by CRB65 score 3 or 4, or CURB65 score 3 to 5); guided by microbiological results when available[3]	
Co amoxiclav ***with:***	500/125 mg three times a day orally or 1.2 g three times a day IV[7] for 5 days[4]
Clarithromycin *or*	500 mg twice a day orally or IV[7] for 5 days[4]
Erythromycin (in pregnancy)	500 mg four times a day orally for 5 days[4]
Alternative antibiotic if high severity, for penicillin allergy; guided by microbiological results when available[3]	
Levofloxacin[8] (consider safety issues)	500 mg twice a day orally or IV[7] for 5 days[4]
Consult local microbiologist if fluoroquinolone not appropriate	

Stop antibiotic treatment after **5 days** unless microbiological results suggest a longer course is needed or the person is not clinically stable!

www.nice.org.uk/guidance/cg191

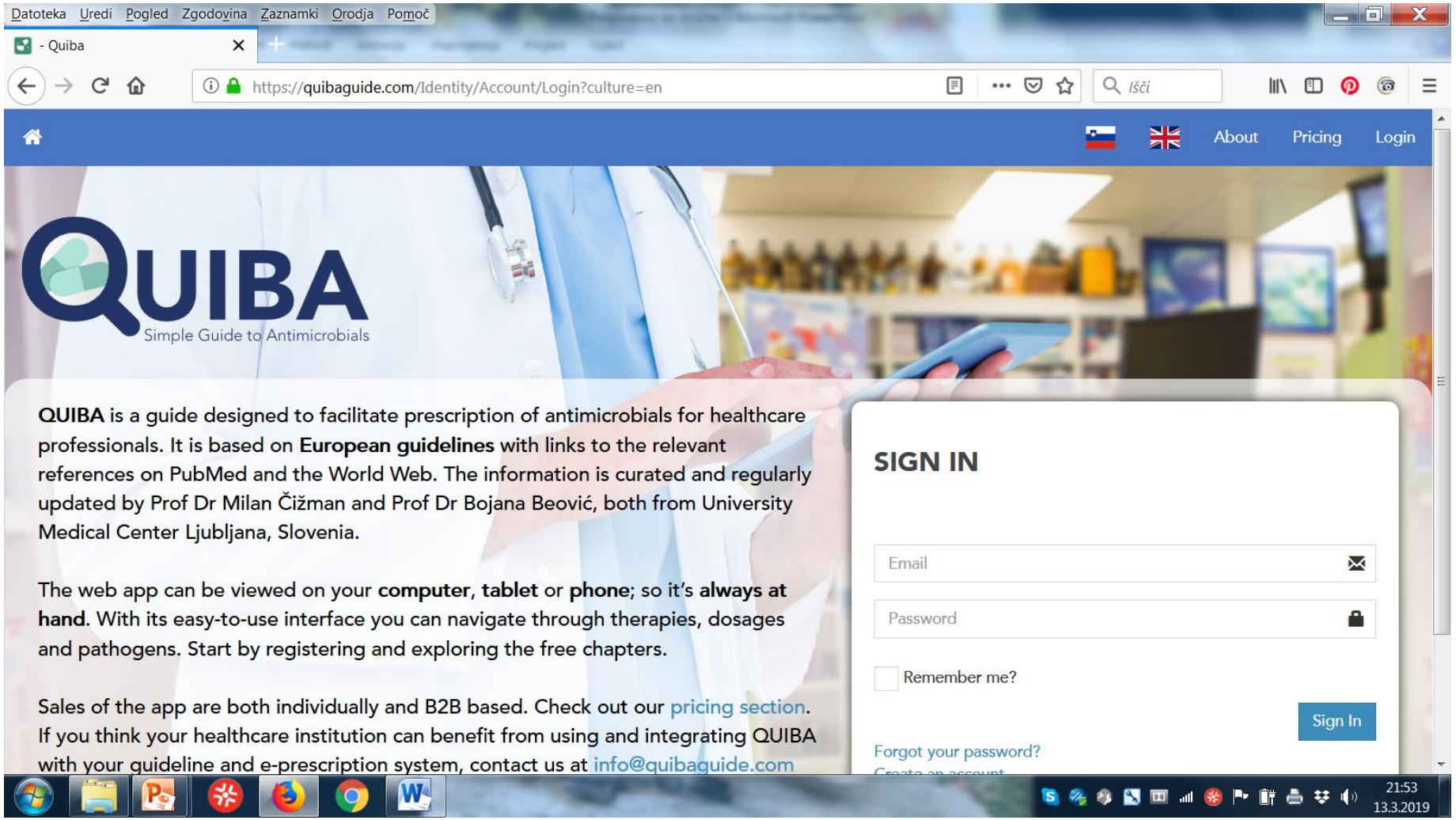
8 days of antibiotics vs 5 days

=

+ 60% !!!!

Conclusion

- **Clinical assessment (presentation + underlying diseases) + CRP for the decision on antibiotic treatment!**
- **Local susceptibility data!**
- **Clinical assessment, rapid microbiology testing (sputum smear, urinary antigens) for the choice of antibiotics!**
- **De-escalation (?)**
- **5 days of treatment in most patients without complications!**



www.quibaguide.com