Infectious Disease
Otitis media, Bronchitis, Strep throat, Sinusitis, CAP, Influenza, SSTI, UTI's,

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Pharmacology 101

Inhibit synthesis of or activate enzymes to disrupt the bacterial cell wall

- penicillins, cephalosporins, vancomycin, imidazole antifungals

Act directly on cell wall

- polymyxin, amphotericin,

Affect function of bacterial ribosomes and create a reversible inhibition of protein synthesis

- chloramphenicol, tetracyclines, macrolides, and clindamycin

Bind to 30 S ribosomal subunits and alter protein synthesis

- aminoglycosides

Antimetabolites that block essential metabolic steps

- sulfonamides, trimethoprim

Prevent supercoiling of DNA

- quinolones

ORAL Antibiotic Susceptibility Chart

	Streptococcos pneumoniae/ S. vlridans/S. faecalis (Enterococcos faecalis)	*Staphylococcus aureus* or *S. epldermidis* (Non-Penlcllinease Producing/ Penicillinase Producing/ Methicillln Resistant)	*Escherichia coli or Proteus mlrabilis*	*Klebsiella pneumoniae*	*Haemophilus Influenzae* (Ampicillin Sensitive/ Ampicillin Resistant)	*Neisseria gonorrhoeae* (Non-Penlcillinase Producing/ Penicillinase Producing)/*Neisseria meningitidis*	*Chlamydia spp/ Mycoplasma/ Legionella*	*Pseudomonas aeruginosa* or *Acinetobacter calcoacetlcus*	Anaerobes Above the Diaphragm (Anaerobic Cocci)	Anaerobes Below the Diaphragm (*Bacteroldes fragilis)*
penicillin V or G	yes/yes/var	yes/no/no	no	no	no/no	yes/no/yes	no	no	yes	no
amoxicillin, ampicillin	yes/yes/var	yes/no/no	yes	no	yes/no	yes/no/yes	yes/no/no	no	yes	no
amoxicillin-clavulanate	yes/yes/yes	yes/yes/no	yes	yes	yes/yes	yes/yes/yes	yes/no/no	no	yes	yes
cloxacillin	yes/yes/no	yes/yes/no	no	no	no/no	no/no/no	no	no	yes	no
cephalexin	yes/yes/no	yes/yes/no	yes	yes	no/no	no/no/no	no	no	yes	no
cefuroxime, cefuroxime axetil. cefaclor	yes/yes/no	yes/yes/no	yes	yes	yes/yes	yes/yes/yes	no	no	yes	no
cefixime	yes/yes/no	no/no/no	yes	yes	yes/yes	yes/yes/yes	no	no	yes	no
chloramphenicol	yes/yes/no	yes/yes/var	yes	yes	yes/yes	yes/no/yes	yes/yes/yes	no	yes	yes
ciprofloxacin, norfloxacin(bladder)	no/no/yes	yes/yes/no	yes	yes	yes/yes	yes/yes/yes	yes/yes/yes	yes	no	no
levofloxacin, moxifloxacin -resp	yes/no/yes	yes/yes/no	yes	yes	yes/yes	yes/yes/yes	yes/yes/yes	yes	no	no
clindamycin	yes/yes/no	yes/yes/no	no	no	no/no	no/no/no	yes/no/no	no	yes	yes
trimethoprim-sulfamethoxazole	yes/yes/yes	yes/yes/var	yes	yes	yes/yes	no/no/yes	var/var/var	no	var	no
erythromycin	yes/yes/no	yes/yes/no	no	no	yes/var	yes/no/no	yes/yes/yes	no	yes	no
clarithromycin, azithromycin	yes/yes/no	yes/yes/no	no	no	yes/var	yes/no/no	yes/yes/yes	no	yes	no
metronidazole	no/no/no	no/no/no	no	no	no/no	no/no/no	yes/no/no	no	yes	yes
tetracycline, doxycycline	yes/yes/no	no/no/no	var	no	yes/yes	var/var/yes	yes/yes/yes	no	yes	yes (doxycycline) var (tetracycline)

yes = clinically useful: no = not clinically useful: var = variable depends on local sensitivities

The only oral antibiotics you really need to use

Penicillin V

Amoxicillin

Cloxacillin

Cephalexin

Macrolide - erythromycin/clarithromycin

Cotrimoxazole (trimethoprim/sulfamethoxazole)

Doxycycline

Ciprofloxacin/levofloxacin - maybe

Clindamycin

Metronidazole

Nitrofurantoin

Evidence

OTITIS MEDIA	ABX (%)	PLACEBO (%)
Pain at 24 hours	NSS	
Pain at 2-7 days	16	22
Vomiting, diarrhea, skin rash	16	10
Contralateral otitis	NSS	
Recurrences	NSS	
Tympanometry	NSS	
Deafness	NSS	
Perforation	NSS	
Mastoiditis	NSS	

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ACUTE BRONCHITIS	ABX (%)	PLACEBO (%)
Limitation in work, productive cough at follow up, adverse effects	NSS	
Cough at follow-up	33	51
Night cough at follow-up	30	45
Days of cough, feeling ill	0.6 less	
Not improved at follow-up MD's global assessment	8	18

productive cough and sometimes LRTI ruled out by x-ray Cochrane

STREP THROAT	ABX (%)	PLACEBO (%)
Otitis media at 14 days	0.5	1.9
Quinsy	0.1	2.3
Rheumatic fever	0.7	1.7
Symptoms of sore throat at 3 days	49	66
Mean reduction in Sx	16 hours	
Fever day 3	12	18
Headache day 3	22	41
Sinusitis	NSS	
Glomerulonephritis	NSS	

Cochrane

most studies in 50s

Steroids for pain relief in patients with a sore throat

Complete pain relief at 24 hours
39% (steroid)
12% (placebo)

BMJ 2009;339:b2976

ACUTE SINUSITIS	ABX (%)	PLACEBO (%)
Cure or improvement at 7-15 days	90	83
Improvement at 16-60 days	NSS	

Cochrane

Empiric recommendations for CAP

British Guidelines

1st - Amoxicillin - if pen allergic erytho/clarith

Amoxicillin plus macrolide if hospitalised

Cefuroxime plus macrolide if severe

Canadian Guidelines

1st -Erythromycin, azithromycin, clarithromycin or doxycycline

COLD – newer macrolide or doxycycline

COLD + recent abx – respiratory flouroquinolone or amox-clav or 2nd gen ceph plus macrolide

American Guidelines

1st - Erythromycin, azithromycin, clarithromycin or doxycycline

Recent abx - A respiratory fluoroquinolone alone, an advanced macrolide plus high-dose amoxicillin, or an advanced macrolide plus high-dose amoxicillin-clavulanate

ß-lactam versus antibiotics with activity against atypical organisms

(Mycoplasma, Chlamydia, Legionella)

18 studies - 6,749 subjects

4 unpublished

meta-analysis to compare the efficacy of beta lactam antibiotics with antibiotics active against atypical pathogens in adults with community acquired pneumonia

BMJ (published 31 January 2005)

ß-lactam versus antibiotics with activity against atypical organisms (2% overall mortality)

	% failing to achieve clinical cure or improvement
Macrolide	17
ß-lactam	20
Quinolone	18
ß-lactam	18
Total	18
ß-lactam	18

All results NSS

BMJ (published 31 January 2005)

ß-lactam versus antibiotics with activity against atypical organisms (found in 7-8% of patients)

	# failing to achieve clinical cure or improvement		
	Mycoplasma	Chlamydia	Legionella
Macrolide/ Quinolone	11/152	8/63	4/38
ß-lactam	20/159	2/52	15/38
	NSS	NSS	SS

BMJ (published 31 January 2005)

"No benefit of survival or clinical efficacy was shown to empirical atypical coverage in hospitalized patients with CAP. This conclusion relates mostly to the comparison of quinolone monotherapy to beta-lactams (BL) or cephalosporins. Further trials, comparing BL or cephalosporins therapy to BL or cephalosporins combined with a macrolide in this population, using mortality as its primary outcome, should be performed."

Atypicals better with Legionella
No difference in overall adverse effects - more GI (1% higher) in beta-lactam group

Cochrane Library CD004418

Ambulatory community-acquired pneumonia Choice of Drug

"Currently available evidence from RCTs is insufficient to make evidence-based recommendations for the choice of antibiotic to be used for the treatment of CAP in ambulatory patients"

Cochrane CD002109

Duration of treatment

There is lots of evidence that treatment for longer than 5 days for AECB, otitis media, and GABHS tonsillopharyngitis is unnecessary and increases the chance of adverse effects.

Drugs 2003;63:2169-84

"Three to six days of oral antibiotics had comparable efficacy compared to the standard duration 10 day oral penicillin in treating children with acute GABHS pharyngitis. In countries with low rates of rheumatic fever, it appears safe and efficacious to treat children with acute GABHS pharyngitis with short duration antibiotics"

Cochrane Library
CD004872

"There are no controlled trials that have specifically assessed the optimum duration of antimicrobial treatment in CAP"

"Until further data are available, it seems reasonable to treat bacterial infections such as those caused by S. pneumoniae until a patient is afebrile for 72 h"

Lancet 2003;362:1991–2001

very good review - suggests 5 days and afebrile for 2-3 days"

Curr Opin Infect Dis 2007; 20:177–81

Three versus eight days of antibiotics for pneumonia

Patients

119 adults with pneumonia (mild to moderate-severe) who had substantially improved after 3 days of IV therapy - median age 57, approx 60% male,

Treatment

3 days IV amoxicillin followed by placebo or oral amoxicillin for 5 days

Duration

8 days

Results

Cure rates - 3 day (90%), 8 days (88%)

Mild adverse events 3 day (11%), 8 days (21%)

BMJ 2006;332:1355-61

Non-severe community-acquired pneumonia - duration

"The evidence of this review suggests that a short course (three days) of antibiotic therapy is as effective as a longer treatment (five days) for non-severe CAP in children under five years of age. However, there is a need for more well-designed RCTs to support our review findings"

Cochrane CD 005976

Three days of i.v. benzylpenicillin for the treatment of adults with meningococcal disease is effective

Internal Medicine Journal 2004;34:383–387

BUT - short duration not for all infections - osteomyelitis, endocarditis, prostatitis etc

BMJ

EDITORIALS

A prescription for improving antibiotic prescribing in primary care

Comprehensive education programmes can reduce antibiotic prescriptions, but the impact on clinical outcomes is unclear

James McCormack *professor*[1], G Michael Allan *associate professor*[2]

"the admonition to make sure [patients] finish the whole antibiotic course is not evidence-based"

In view of this, use of the prescription label "Finish all this medication unless otherwise directed by prescriber" should be discouraged

"a reasonable approach for most primary care infections would be to tell the patient to continue the antibiotic until they have been asymptomatic or afebrile for 72 hours and then to stop"

BMJ 2012;344:d7955 doi: 10.1136/bmj.d7955 (Published 2 February 2012)

BMJ

EDITORIALS

A prescription for improving antibiotic prescribing in primary care

Comprehensive education programmes can reduce antibiotic prescriptions, but the impact on clinical outcomes is unclear

James McCormack *professor*[1], G Michael Allan *associate professor*[2]

"Delayed prescriptions can reduce the proportion of people who receive antibiotics for upper respiratory tract infections from 93% to 32%"

"Patients who are not given a prescription initially will still ultimately get an antibiotic 14% of the time"

"Most community acquired infections still respond to the same antibiotics that have been used for decades and many guidelines still support their use"

Neuroaminidase inhibitors (oseltamivir, zanamivir)

25 studies - primarily adults during influenza season

Time to first alleviation of symptoms - 160 hours (placebo) - 139 hours (oseltamivir) - no effect on hospitalization

Nausea - 10% (drug) vs 6% (placebo)

Vomiting - 9% vs 4%

Diarrhea 6% vs 7% Cochrane CD008965

6 studies children - oseltamivir and zanamivir reduced illness by ~ 36 hours and otitis media from 19% to 9% in those with confirmed influenza - vomiting increased from 12% to 19% with oseltamivir

Influenza vaccine

28 children over the age of 6 need to be vaccinated to prevent one case of laboratory confirmed influenza and 8 children to prevent one symptomatic case

under age of 2 no benefit CD 004879

in adults vaccine reduced the number of people with influenza symptoms from 4% down to 1% CD001269

elderly - poor quality dataCD004876

COPD - reduced exacerbations/patient but no difference in number of patients CD002733

The flu vaccine
How well does it work?

Vancouver Sun from Oct 15 - New report questions science behind flu vaccine efficacy and use policy

Report from the university of Minnesota entitled “ The compelling need for game-changing vaccines”

It's all about the numbers

Previous evaluations - 70-90% effective

Every year 1-10% per year adults – roughly 5% - chance reduced to 1% - less if unmatched

5-20% in children – roughly 10% - therefore reduced to 2%

New report - no new studies - but looked at different diagnostic endpoints – earlier evaluations used studies that used antibodies as the diagnosis – this one used culture

Instead of the effect being 70-90% - they found 60% for the flu shot – nasal spray was 85% effective in children 6 months to 6 years old

5% down to 2% in adults

10% goes down to 4% in children

Other flu evidence

In patients with asthma

No effect seen in reducing exacerbations caused by influenza

In patients with COPD

Does reduce the number of exacerbations

In the elderly – some effect but

The available evidence is of poor quality BUT SUGGESTS BENEFIT and provides no guidance regarding the safety, efficacy or effectiveness of influenza vaccines for people aged 65 years or older.

Safety

Guillain-Barre syndrome relatively rare neurologic disorder a condition in which the body damages its own nerve cells (outside of the brain and spinal cord), resulting in muscle weakness and, in some cases, paralysis.
Febrile seizures

Skin and soft tissue infections

In an otherwise healthy individual

Cloxacillin/cephalexin - erythromycin or clindamycin if penicillin allergic

5 days has been shown to be as good as 10 days

In areas where CA-MRSA has become clinically important (10-15% resistance) - risk factors include children, competitive atheletes, Native Ameicans, IVDU

Trimethoprim/sulphamethoxazole or clindamycin? or doxycycline have been shown to work BUT clinical trials are lacking

UTIs

Duration - 3 days is long enough - single dose?

Prevention - half a regular DS tablet daily or just treat when symptoms occur

Sulfamethoxazole/trimethoprim - rash issues – use trimethoprim

Ciprofloxacin

For UTI's - break a 500 mg tablet in 4

¼ tablet BID x 3 days – two tablets

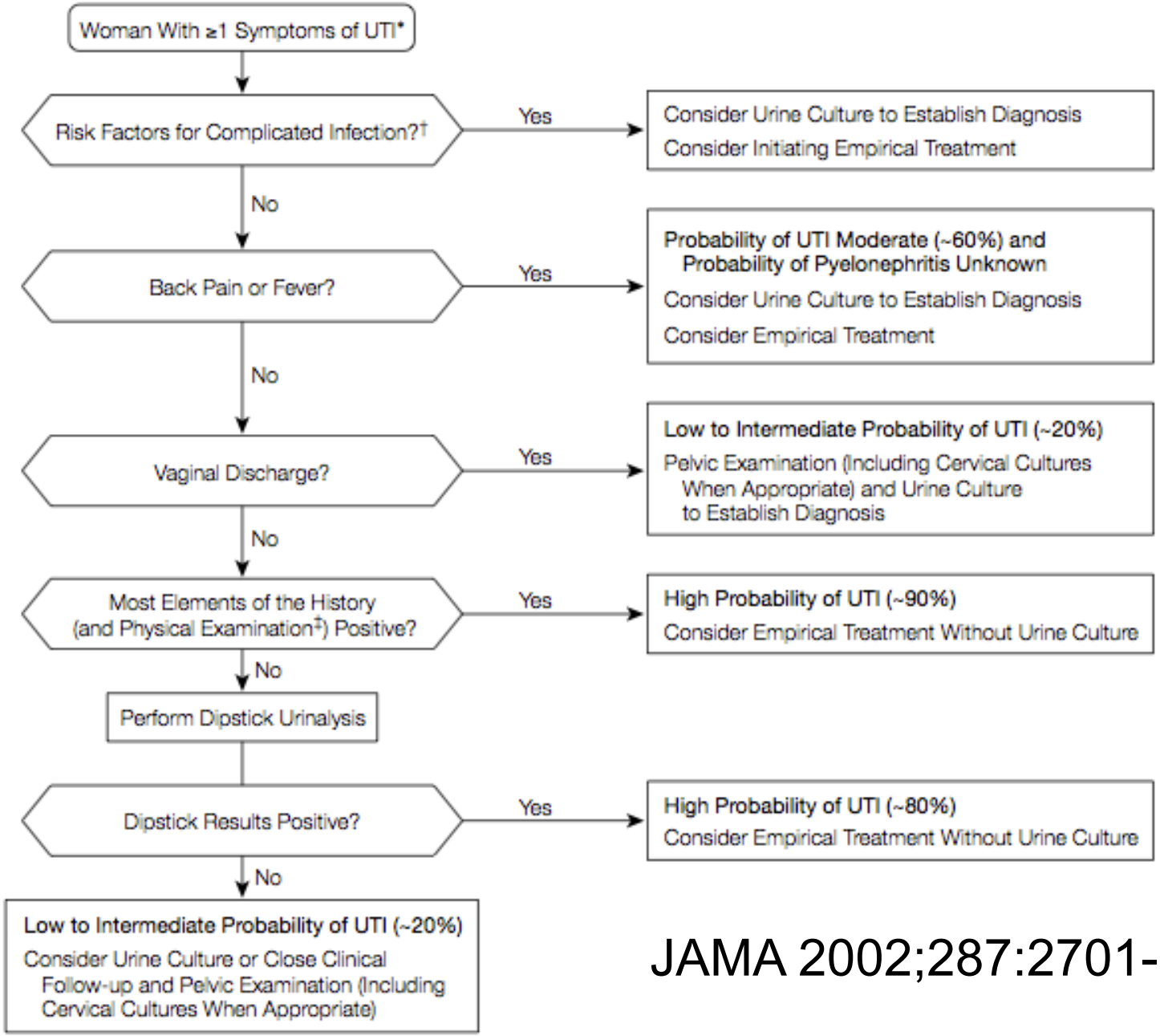
Nitrofurantoin

100 mg BID

Do you need a dipstick urinalysis?

In women with dysuria, frequency, and no vaginal discharge the probability of UTI is 96%

JAMA 2002;287:2701-10



JAMA 2002;287:2701-10

Abx Choice

21 studies (6016 participants)

Trimethoprim-sulfamethoxazole (TMP-SMX) was as effective as fluoroquinolones in achieving short-term (RR 1.00, 95% CI 0.97 to 1.03) and long-term (RR 0.99, 95% CI 0.94 to 1.05) symptomatic cure.

Beta-lactam drugs were as effective as TMP-SMX for short-term (RR 0.95, 95% CI 0.81 to 1.12) and long-term (RR 1.06, 95% CI 0.93 to 1.21) symptomatic cure.

Short-term cure for nitrofurantoin was similar to that of TMP-SMX (RR 0.99, 95% CI 0.95 to 1.04) as was long-term symptomatic cure (RR 1.01, 95% CI 0.94 to 1.09)

No differences were observed between the classes of antimicrobials included in this review for the symptomatic cure of acute uncomplicated UTI

Fluoroquinolones proved more effective than beta-lactams for the short-term bacteriological outcome, probably with little clinical significance.

Individualised treatment should take into consideration the predictable susceptibility of urinary pathogens in local areas, possible adverse events and resistance development, and patient preference.

Cochrane Library CD007182

Nitrofurantoin vs placebo for UTIs

78 patients randomised to nitro 100 mg QID or placebo for three days

Improved and cure	3 days (%)	7 days (%)
Nitrofurantoin	77	88
Placebo	54	52

Another study suggested a 24% spontaneous cure rate for bladder infections
Scand J Infect Dis 2004;36:296-301

Br J Gen Pract 2002;52:708-10

UTI Prevention

50% recurrence per year on placebo

"clinical recurrences (CRPY) the RR was 0.15 (95% CI 0.08 to 0.28)"

"One RCT compared postcoital versus continuous daily ciprofloxacin and found no significant difference in rates of UTIs, suggesting that postcoital treatment could be offered to woman who have UTI associated with sexual intercourse."

Cochrane Library

Ciprofloxacin for 7 days vs14 days
pyelonephritis

Women with acute pyelonephritis - fever and at least one other symptom - 44 years old – 90% E. coli

7 days or 14 days of cipro 500 mg BID

Clinical and bacteriological outcome 10-14 days after completion of active treatment

248 patients - only 156 assessed – because randomnly assigned before a definitive diagnosis was established

Short term/cumulative efficacy – roughly 95% success rate both groups

Side effects – 0 patients in 7 day had mucosal candida infection – 5 in the 14 day group

Lancet August 4, 2012

	No history of allergy to sulfonamide antibiotic	History of allergy to sulfonamide antibiotic	History of allergy to penicillin
Reaction within 30 days of a sulfonamide non-antibiotic	1.6%	9.1%	14.6%

N Engl J Med 2003;349:1628-35

Things to think about

Ask patients if they have used erythromycin previously

Consider doxycycline

Consider high-dose amoxicillin

Consider cutting ciprofloxacin tablets

Is resistance futile?

Patients are not more adherent to once a day vs twice a day therapy

If you are an allergic person you are an allergic person

The dose and duration of treatment with antibiotics is often not well-defined

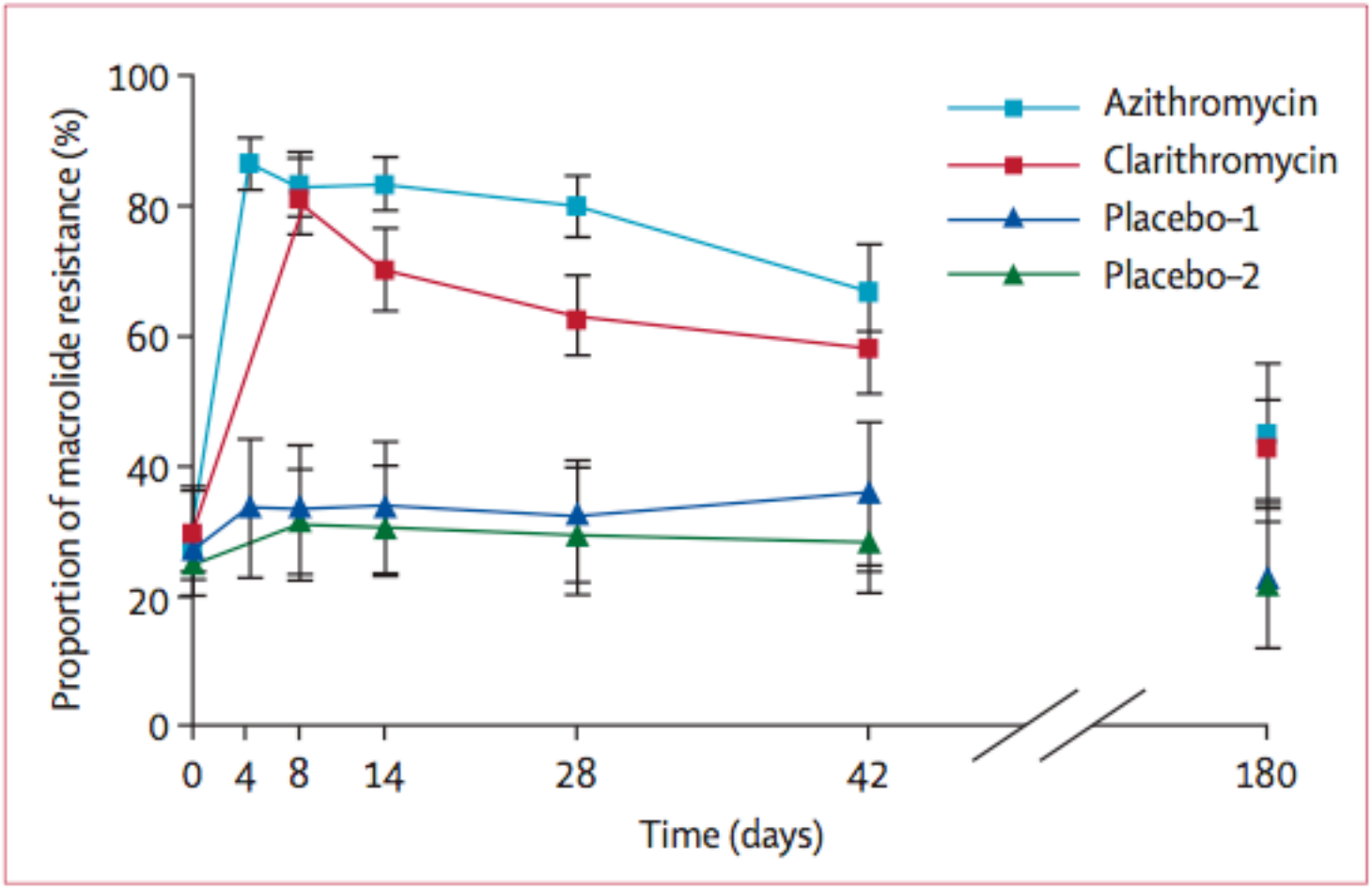


Figure 2: **Temporal changes in the proportion of macrolide-resistant streptococci after azithromycin and clarithromycin use**

Data shown are for all 204 volunteers followed through to day 42, and for 99 volunteers followed through to day 180. Error bars are 95% CI.

Withdrawal from market

Grepafloxacin/sparfloxacin - withdrawn because of concerns about cardiac toxicity associated with prolongation of the Q-T interval

Temafloxacin - withdrawn because of serious hemolysis

Trovafloxacin - has been reported to be associated with life-threatening toxicity