Antimicrobial Drugs short review

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Approach to the Antibiotic therapy

- Host factors
- Site of infection
- Local resistance profiles of suspected or known pathogens
- Regularly monitoring of the patients and collection of laboratory data

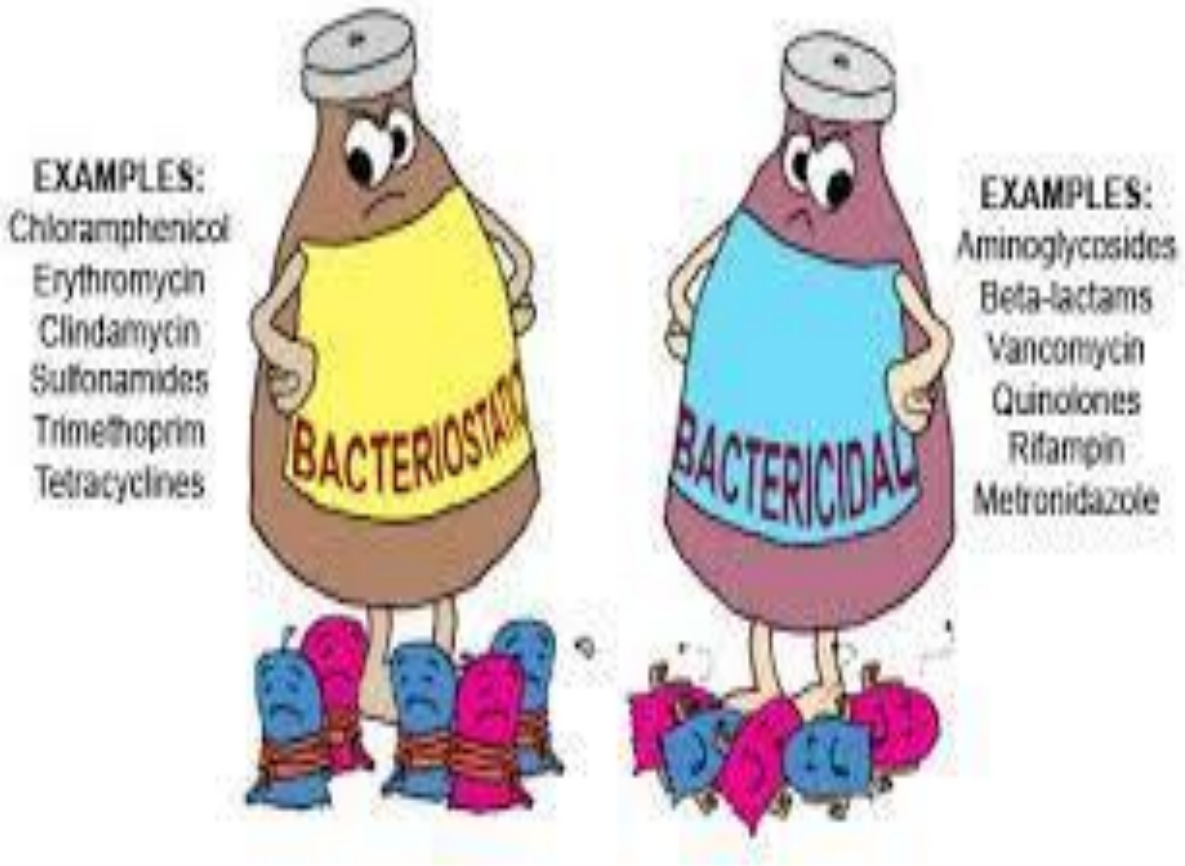
Empirical and directed therapy

- **Empirical therapy** is considered when the causative agent has yet to be determined and therapeutic decisions are based on the severity of illness and the clinicians assessment likely pathogens.
- **Directed therapy** is predicated on identification of the pathogen.

Directed therapy generally allows the use of **more targeted** and **narrower- spectrum** antibacterial agents than does **empirical therapy**.

When **empirical treatment** is clinically appropriate, care should be taken to obtain **clinical specimens** for microbiologic analysis **before the initiation of the therapy** and to **de-escalate therapy** as new information is obtained about the patients clinical conditions and the casual pathogens.

Multiple essential components of **bacterial cell structures** and **metabolism** have been the targets of antibacterial agents used in clinical medicine, and the interaction of an agent with its target results in either **inhibition of bacterial growth and replication*(bacteriostatic effect)*** or **bacterial killing *(bactericidal effect).***


EXAMPLES:
Chloramphenicol
Erythromycin
Clindamycin
Sulfonamides
Trimethoprim
Tetracyclines
BACTERIOSTATIC
BACTERICIDAL
EXAMPLES:
Aminoglycosides
Beta-lactams
Vancomycin
Quinolones
Rifampin
Metronidazole

Treatment with bacteriostatic agents is effective when the patient host **defenses are sufficient** to contribute to eradication of the infecting pathogen. In patient with **impaired host defenses (neutropenia)** or **infections in special body sites(meningitis & endocarditis)** **bactericidal agents** are generally preferred.

This understanding that **shorter antibiotic courses** are **less likely** than **longer** ones to promote the **emergence of *resistance* is true**.


Shorter Is Better With Antibiotics:
Lessons & Resources

Beta-lactam antibiotics:

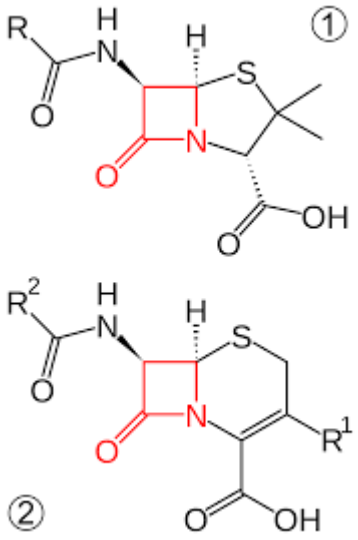
* Penicillins

* Cephalosporins

* Carbapenems

* Monobactams

* Beta-lactamase inhibitors



All Beta-lactams exert a **bactericidal effect**

by inhibiting

bacterial cell-wall synthesis.

They are **time dependent** killing agents.

Penicillins

is the first beta-lactam that was discovered in **1928** by **Alexander Fleming**.

❖ **Penicillins can be divided into five classes** on the basis of antibacterial activity :

Natural penicillins—penicillin G, penicillinV

Penicillinase-resistant penicillins—methicillin, nafcillin,

Aminopenicillins—ampicillin and amoxicillin

Carboxypenicillins—carbenicillin , ticarcillin

Acyl ureidopenicillins—piperacillin.

Penicillin G

Highly active against **Gram positive cocci**:

Streptococus pyogen , bovis , viridance

Most anaerobes (with certain **exceptions, such as Bacteroides**)

Treponema pallidum

Penicillin G

remains the primary agent for treatment of infections due to **Streptococcus pyogenes or Group A streptococcus (GAS)**

IV penicillin G

remains the treatment of choice for susceptible **pneumococcal and meningococcal meningitis**, **streptococcal and enterococcal endocarditis**, and **neurosyphilis**.

Neisseria gonorrhoeae strains frequently are ***resistant*** to penicillin, which is ***no longer recommended*** for treatment of gonorrhea.

***Penicillin G is the drug of choice for syphilis at all stages.**

Puerperal infections

due to **anaerobic streptococci** or **group B streptococci** (**Streptococcus agalactiae**), as well as genital clostridial infections, are treated with **penicillin G.**

Penicillinase-Resistance penicillins(PRP)

Anti staphylococcal penicillins (**nafcillin**, **oxacillin**, **cloxacillin** and **dicloxacillin, flucloxacillin)**

inhibit penicillinase-producing

S. aureus and **S.epidermidis**

The **penicillinase-resistant penicillins** are indicated **solely** for the treatment of infections caused by **methicillin-susceptible strains of staphylococci(MSSA)**, for which they are the agents of choice.

Ampicillin, Amoxicillin

are able to penetrate the porin channel of

Gram negative bacteria

but **not stable to *beta-lactamases***.

Active against the **E. coli, Proteus, Salmonella, Shigella, and Haemophilus influenzae , Enterococci, Listeria**

***None**

of the broad spectrum penicillins are

effective against

penicillinase-producing

staphylococci

Aminopenicillins

are indicated for treatment of **upper and lower respiratory tract infections**, **gastroenteritis**, **endocarditis**, **meningitis**, and **UTI** caused by **susceptible organisms**.

Amoxicillin, because of

its excellent bioavailability, is the preferred

agent for

oral administration in most situations;

it is well tolerated even in

high doses **up to** ***4 g/day*****.**

Amoxicillin is recommended as a ***single 2-g oral dose*** for prophylaxis of ***bacterial endocarditis*** for those with the **highest risk** of adverse outcome.

beta-lactamase inhibitors

Clavulanate,

Sulbactam,

Tazobactam

inhibitors which have little intrinsic anti bacterial activity but **inhibit** the activity of a number of **plasmid-mediated beta-lactamases**

Amoxicillin-clavulanate
has proved useful as therapy for
acute otitis media, sinusitis
or ***pneumonia***.
It is particularly useful to treat
polymicrobial infections including
bite wounds
of human or animal origin.

Cephalosporins

In clinical practice, grouped into five "generations" based upon their spectrum of activity against aerobic and facultative Gram negative bacilli.

First-Generation Cephalosporins

The first-generation cephalosporins available in IRAN are ***cefazolin, cephalotin, cefadroxil , cephalexin***.

They have been extensively used as alternatives to penicillin for ***staphylococcal (MSSA)***.

Most commonly,

these include ***skin and soft tissue infections***.

Cefazolin

is still recommended in

penicillin-allergic patients for **more serious staphylococcal** infections,

such as **endocarditis**

Cefazolin

is recommended as the

prophylactic antibiotic of

choice for **foreign-body implantation**

and for many

clean and clean contaminated

surgical procedures in which there is a

high risk of infection.

The **oral** first-generation cephalosporins,

cephalexin

have **very high oral bioavailability**.

These drugs provide appropriate

outpatient

therapy for many

Cephalexin has
poor activity against pneumococci,
H. influenzae, M. catarrhalis
and **is not recommended** for
sinusitis, otitis media,
or lower respiratory tract infections.
*The drug is effective in
uncomplicated urinary tract infections

Third-generation cephalosporins

available in the **Iran** are

cefixime, cefotaxime, ceftazidime,

and ceftriaxone.

(cefoperazone, cefpodoxime)

Third-generation cephalosporins are major drugs for the treatment of many important infections because of their high antibacterial **potency**, **wide spectrum of activity**, low **potential for toxicity**, and favorable pharmacokinetics (*enhanced drug concentrations in the CSF*).

They have been especially useful in infections resulting from ***gram-negative bacilli*** that are **resistant to other β-lactam antibiotics**.

Ceftriaxone has the **longest half-life** and is usually administered **once or tiwce daily**.

Ceftazidime is dosed **two or three times daily**.

Cefotaxime has the shortest half-life, has varied from every **4 h** to **three times daily**.

Treatment of meningitis requires ***maximal doses*** of these cephalosporins, such as ***2 g every 12 hours for ceftriaxone***, and **2 g every 4 to 6 hours in adults for cefotaxime**.

Cefotaxime and ceftriaxone continue to be active against most bacteria producing **CAP**.

The oral third-generation cephalosporin ,*cefixime** is approved for **oral therapy** of **mild-to-moderate respiratory infections, such as *otitis media, sinusitis.

Ceftriaxone 250 to 500 mg IM

is **highly active against**

N. Gonorrhoeae.

It is the drug of choice for

all forms of gonococcal infection and is used **in combination** with a

single oral dose of azithromycin or 7 days of oral doxycycline.

Ceftriaxone and Cefixime

are a recommended

alternative therapy for ***typhoid fever***

and for severe infections caused by

Shigella.

Fluoroquinolones

- nalidixic acid
- ofloxacin
- lomefloxacin,
- Levofloxacin,
- gatifloxacin,
- ciprofloxacin
- norfloxacin,
- enoxacin,
- trovafloxacin,
- moxifloxacin

Quinolones

Quinolones are **most active against aerobic** ***gram-negative bacilli***, particularly **Enterobacteriaceae** and **Haemophilus** and **against gram-negative cocci**, such as **Neisseria** and **Moraxella catarrhalis.**

Relative to nalidixic acid**, the fluoroquinolones also have additional activity against ***P. aeruginosa

Because of the ***risk of selection*** of resistance during fluoroquinolone treatment of ***serious pseudomonal*** infections, these agents are usually used ***in combination*** with an **antipseudomonal Beta lactam**.

Ciprofloxacin and ***levofloxacin*** have the broadest spectrum of the activity against ***gram-negative bacteria***, including ***P.aeuroginosa***

Levofloxacin, moxifloxacin, and gemifloxacin

have improved activity against *S. pneumoniae* and have been referred to *respiratory quinolones*.

Ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin

are active against

***M. tuberculosis*.**

CLINICAL USES

Urinary Tract Infections

Concentrations of many quinolones in urine are *usually sufficient.*

For *uncomplicated UTI*, usually *in symptomatic young women* with cystitis, most quinolones are likely to be highly effective when given for brief courses of 3 to 10 days, and have been found to be comparable to TMP-SMX and nitrofurantoin

Fluoroquinolones *concentrate in prostatic* tissue.

In one small comparative study of men with predominantly E. coli infections, norfloxacin given for 4 to 6 weeks was superior (92% eradication) to TMP-SMX (67% eradication) at 1-month follow-up.

After the emergence of ***quinolone resistance*** among ***N. gonorrhoeae***, the Centers for Disease Control and Prevention (**CDC**), updated its recommendations and **removed fluoroquinolones from the treatment guidelines**.

Aminoglycosides

- Aminoglycosides are highly potent, broad-spectrum antibiotics
  - with **Gram-negative antibacterial** therapeutic coverage that **inhibit protein synthesis**
  - Their history begins in **1944 with streptomycin**

Aminoglycosides

Although marked **regional and individual hospital differences** exist for in vitro susceptibility patterns, the majority of aerobic and facultative ***gram-negative bacilli, including Enterobacteriaceae, P. aeruginosa, and Acinetobacter remain*** susceptible to **gentamicin, tobramycin, and amikacin**.

Aminoglycosides are used successfully in the treatment of intracellular infections, such as **brucellosis, tuberculosis.**

Clinical uses

*most commonly in ***combination*** with other antibacterial agents (synergism)

complicated urinary tract infections

intra abdominal infections

*selected aminoglycosides clinically relevant activity against

protozoa (paromomycin),

N. gonorrhoeae (spectinomycin)

Mycobacterial infections (amikacin)

Clindamycin

- is a **lincosamide** antibiotic and is ***bacteriostatic*** against some organisms and ***bactericidal*** against others.
- Chemical modification of lincomycin provided clindamycin with increased **antibacterial potency** and **absorption after oral administration**.

Treatment against

anaerobic and **aerobic streptococci**

(**except enterococci**)

most staphylococci

Bacteroides.fragilis, clostridium

perferigens, fusobacterium and

Actinomyces, bacterial vaginosis

Clindamycin is used for treatment of

dental infections,

lung abscess and

skin soft tissue infections.

Metronidazole

- is one of the mainstay drugs for the treatment of **anaerobic infections**.
- Despite extensive worldwide use, acquired **resistance to metronidazole among anaerobic bacteria is rare**.
- Metronidazole is **well absorbed** after **oral** administration and is virtually **100 percent** bioavailable

Metronidazole

Treatment of

- ***anaerobic bacterial***
- ***Amebiasis***
- ***symptomatic and asymptomatic trichomoniasis;***
- ***intra-abdominal infections***

(as part of combination regimen)

*treatment of

pseudomembranous colitis

**bacterial vaginosis*

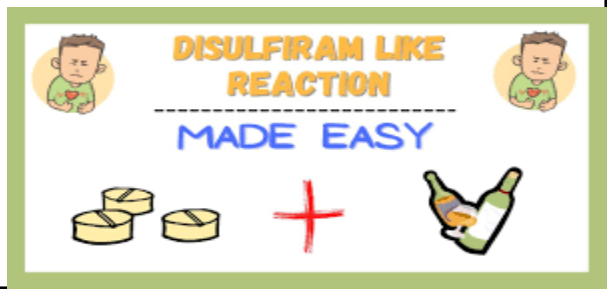
*as part of a multidrug regimen for

H. pylori eradication

Some studies have demonstrated that elimination of metronidazole metabolites may be reduced among those with ***renal insufficiency***, but **there are no specific recommendations for dose reduction in this patient population**

Disulfiram-like reactions

- There have been case reports suggesting a possible disulfiram-like reaction **when metronidazole is administered systemically or vaginally to patients drinking ethanol**.
- causes **flushing, tachycardia, palpitations, nausea, and vomiting**
- recommends ***avoiding alcohol ingestion during metronidazole therapy and for at least 48 hours afterwards***



Tetracyclines

- ***Chlortetracycline*** was the first tetracycline discovered, ***in 1948***.
- ***Tigecycline*** is the first of this new class of agents and exhibits ***broad-spectrum antibacterial activity*** similar to the tetracyclines.

Tetracyclines

- ***Doxycycline, Minocycline, Tetracycline*** *and* ***Tigecycline*** inhibit protein synthesis and are ***bacteriostatic.***

- **They have wide clinical use:** skin soft tissue infections (MRSA), Spirochetal infections (Lyme dis, syphilis, leptospirosis and relapsing fever), atypical pneumonia, STI(C.trachomatis, LGV) & Brucellosis.

Doxycycline may **be an alternative for use in children** since it binds calcium to a lesser extent than tetracycline, which can cause tooth discoloration and bony growth retardation.

Tigecycline has a broader spectrum of activity.

Tigecycline has activity against gram-positive pathogens including: Enterococcus (VRE), Listeria, Streptococcus, both methicillin-susceptible and -resistant S. aureus, and S. epidermidis. Its gram-negative activity includes: Acinetobacter, Citrobacter, Enterobacter, Escherichia coli, Klebsiella.

Dose adjustment is not necessary for doxycycline or tigecycline in patients with **renal dysfunction**, and thus, these are the preferred tetracyclines in this population

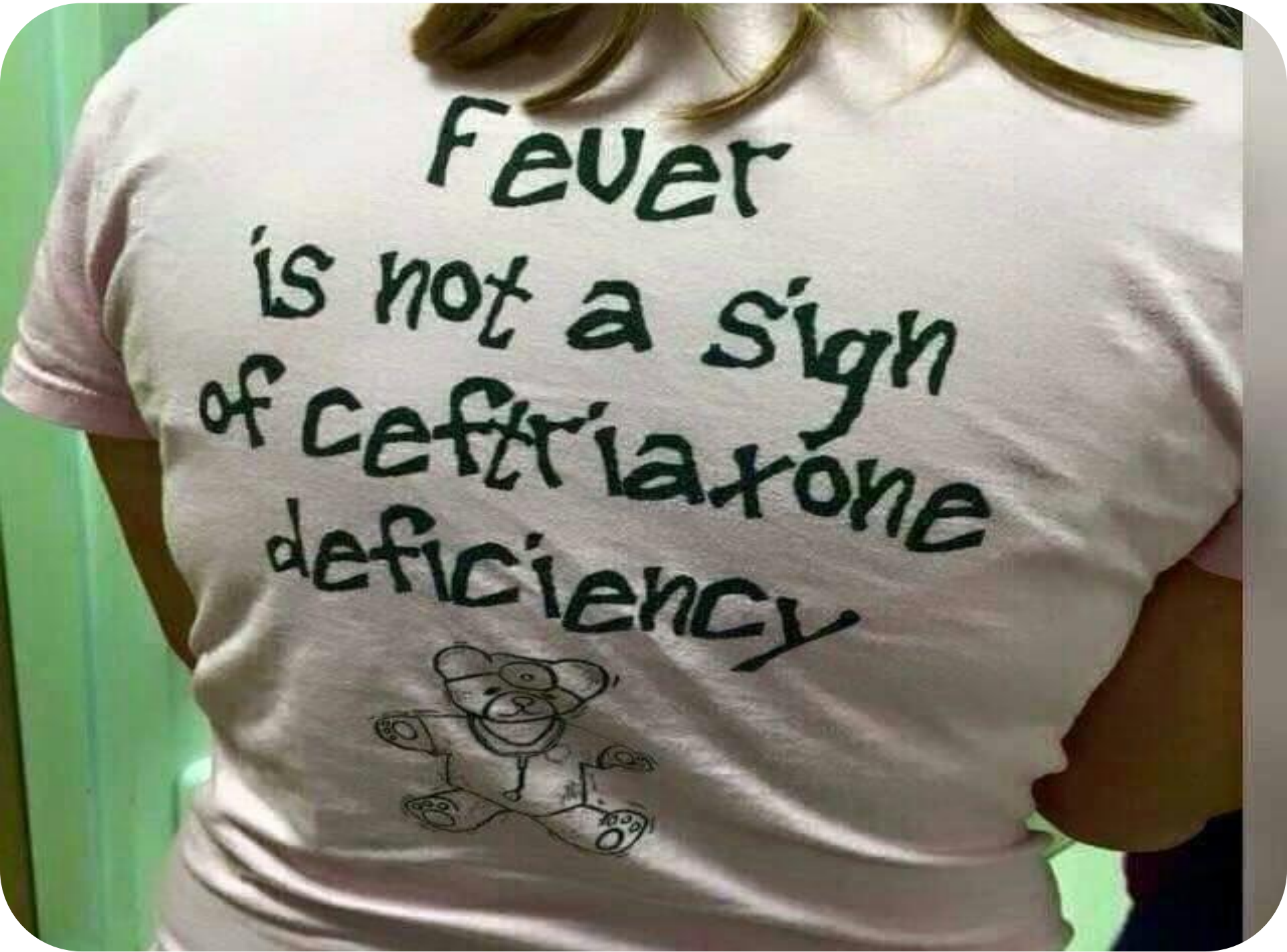
Tetracyclines can cause ***fetal toxicity*** when given to ***pregnant women*** and **should generally not be used in pregnant** women or **children under the age of eight** years.

Antimicrobial stewardship

- ***Increasing prevalence of MDR bacteria*** with a substantial amount of inappropriate antimicrobial use, the need for rational antimicrobial prescribing has never been greater.
- The practice of promoting the **selection** of the ***appropriate drug, dosage rout*** and **duration** of antimicrobial therapy.

Antimicrobial stewardship gold

- ***Improve patient care*** through appropriate antimicrobial use
- ***Decrease the development of resistance*** within patient and population
- ***Reduce the incidence of adverse effects***
- ***Control costs***


fever
is not a sign
of ceftriaxone
deficiency