

# ANTIBIOTIKY INDUKOVANÁ ORGÁNOVÁ DYSFUNKCE

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1896



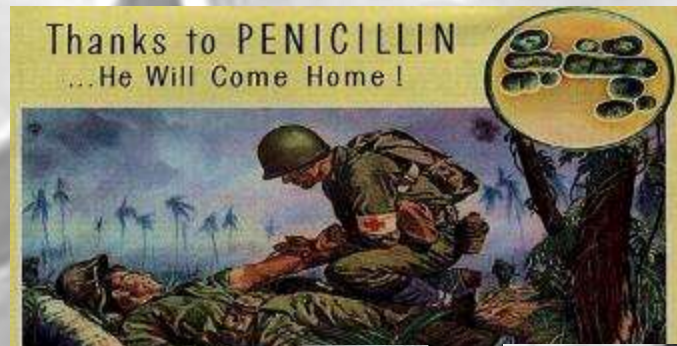
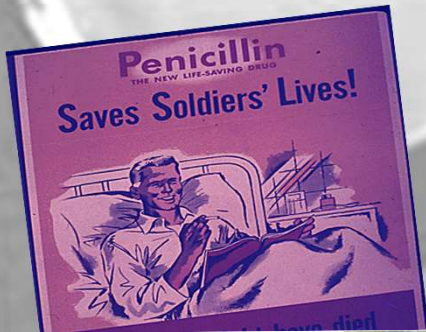
THE SMITHFIELD ENTRANCE.

[From a Photo. by F. C. O. Stuart, Southampton.]



Life expectancy:

- 46 let pro muže
- 48 let pro ženy



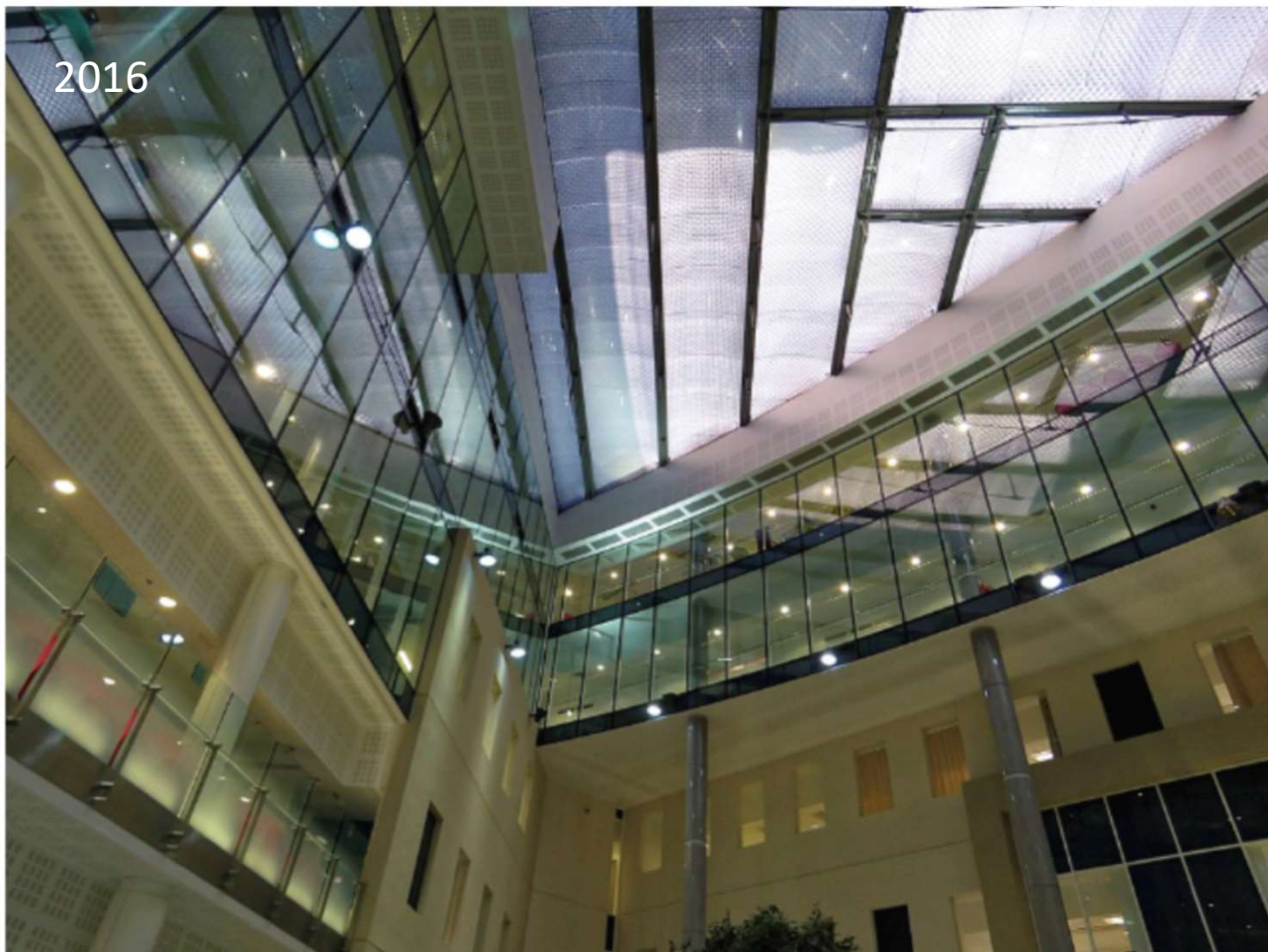
**PENICILLIN**  
New  
Wonder Drug  
from Mold

By IRMIS JOHNSON

**A** GREENISH BLUE MASS OF THE ONE that grows on water mold, on bread, on cheese and other foodstuffs, is now guaranteed to be an important ally in helping wounded soldiers fight their way back to health.



2016



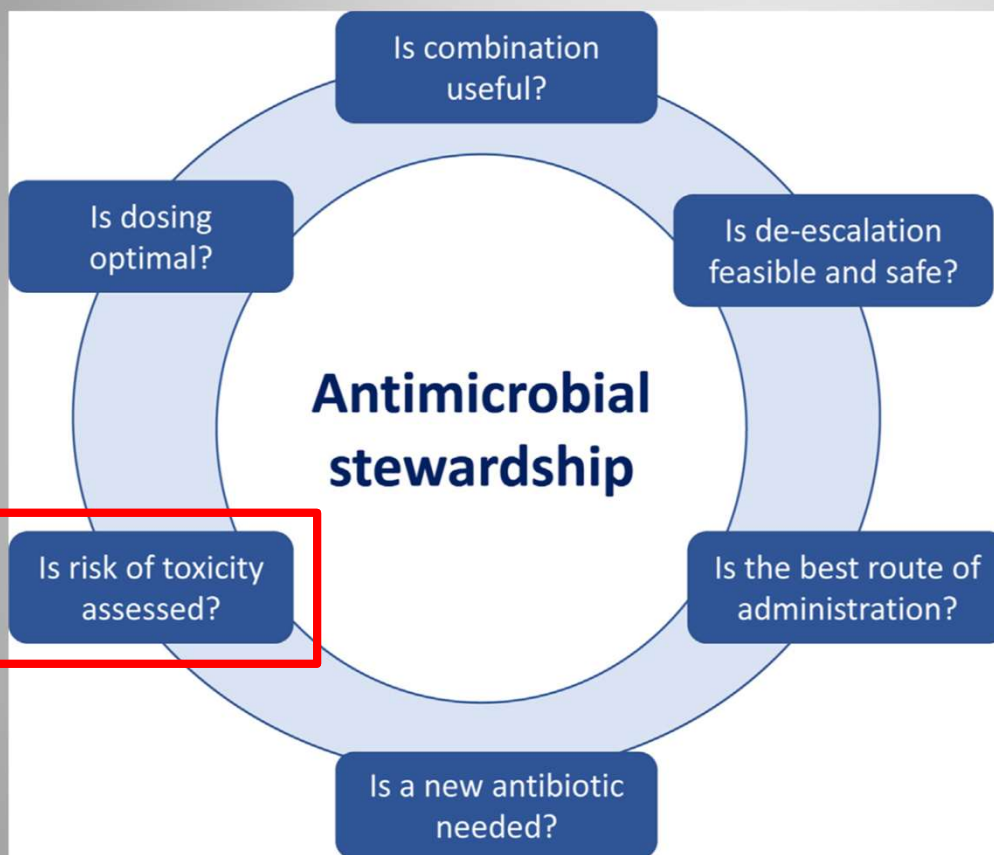
Life expectancy:

- 70 let pro muže
- 72 let pro ženy





- Nejčastěji ordinované léky
- Pilíř antiinfekční terapie nejen v IM
- Nárůst rezistence
- Ekonomický dopad

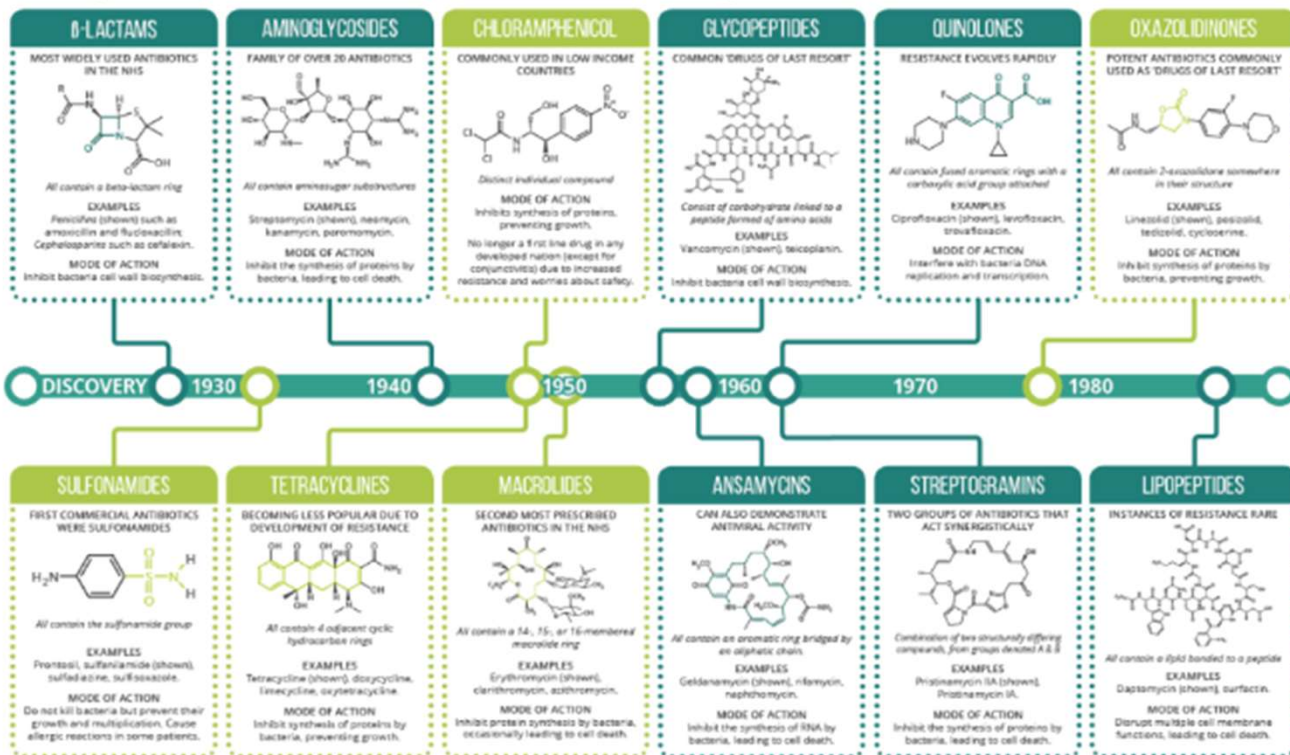


ATB v nemocnici:

- 50% hospitalizovaných
- 20-30% zbytečně

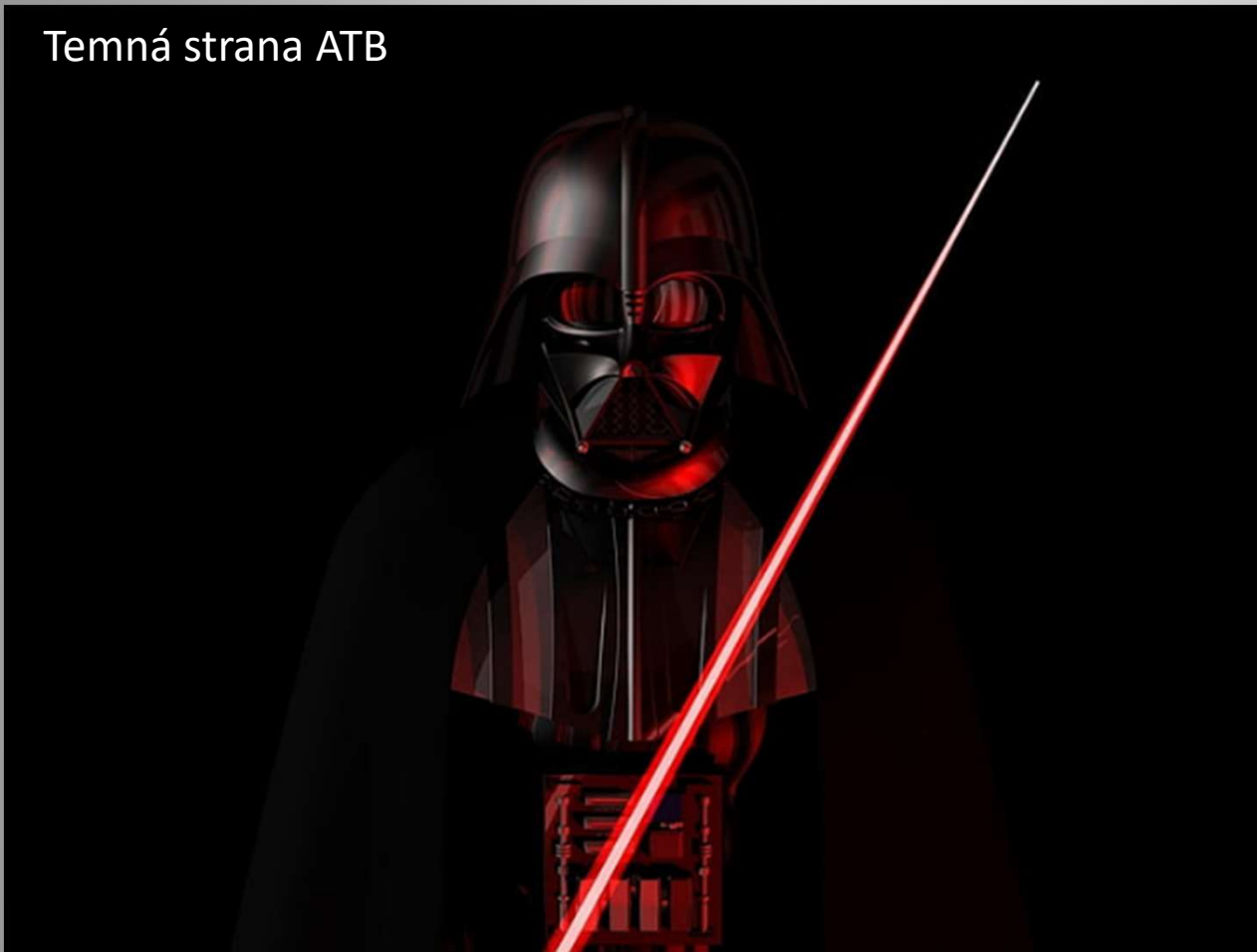
# DIFFERENT CLASSES OF ANTIBIOTICS - AN OVERVIEW

**Key:** ● COMMONLY ACT AS BACTERIOSTATIC AGENTS, RESTRICTING GROWTH & REPRODUCTION ● COMMONLY ACT AS BACTERICIDAL AGENTS, CAUSING BACTERIAL CELL DEATH





## Temná strana ATB



Alergické reakce

Orgánová toxicita

Clostridiové infekce

Vznik rezistence

### Neurotoxicita

Cefalosporiny

Karbapenemy

Chinolony

### Hematotoxicita

$\beta$ -laktamy

Linezolid

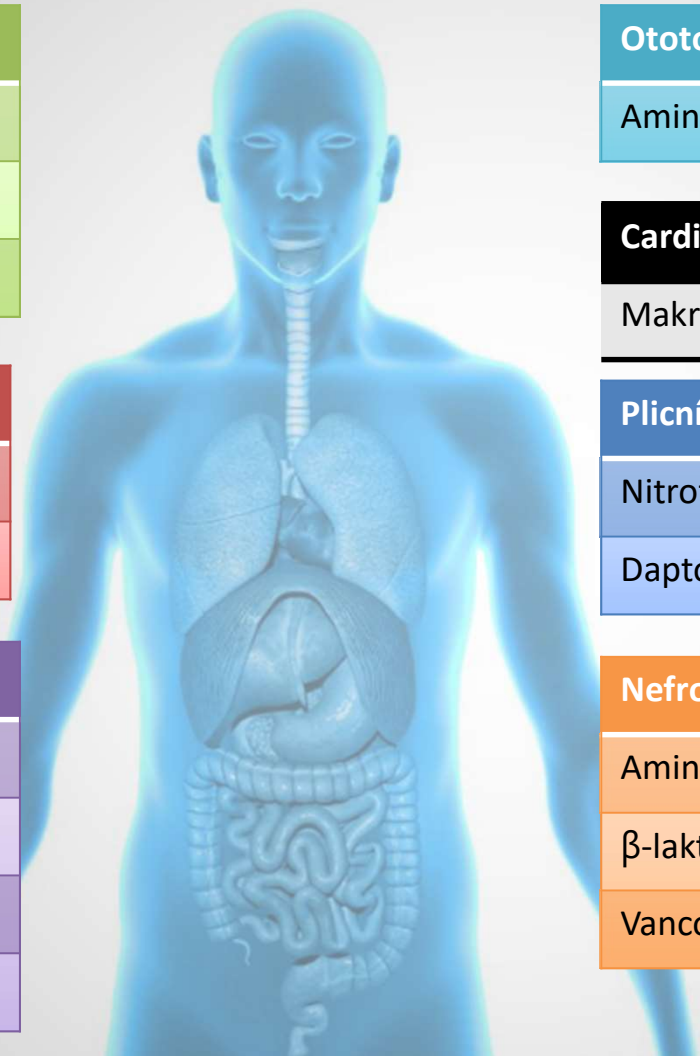
### Hepatotoxicita

Amox/klav

Oxacilin

Chinolony

Karbapenemy



### Ototoxicita

Aminoglykosidy

### Cardiotoxicita

Makrolidy

### Plicní toxicita

Nitrofurantoin

Daptomycin

### Nefrotoxicita

Aminoglykosidy

$\beta$ -laktamy

Vancomycin

## Predispozice kriticky nemocných ke vzniku orgánové toxicity



1. Preexistující org. dysfce
2. Polymorbidita
3. Synergie s jinými léky
4. Vysoké dávky i.v.

*File TM, Antimicrob Agents Chemother, 1997  
Hammond DA, Clin Infect Disease, 2017*



## Association of Adverse Events With Antibiotic Use in Hospitalized Patients

Pranita D. Tamma, MD, MHS; Edina Avdic, PharmD, MBA; David X. Li, BS; Kathryn Dzintars, PharmD; Sara E. Cosgrove, MD, MS



Table 3. Proportion of 30-Day Antibiotic-Associated Adverse Drug Events in 1488 Hospitalized Patients Receiving Systemic Antibiotic Therapy<sup>a</sup>

| Antibiotic Agent              | No. of Patients Receiving Agent | No. (%)        |                                |                 |                 |                 |                 |                           |
|-------------------------------|---------------------------------|----------------|--------------------------------|-----------------|-----------------|-----------------|-----------------|---------------------------|
|                               |                                 | Cardiac        | Gastro-intestinal <sup>b</sup> | Hematologic     | Hepato-biliary  | Renal           | Neurologic      | Other Events <sup>c</sup> |
| <b>β-Lactams<sup>d</sup></b>  | 1187                            | 0              | 59 (5.0)                       | 27 (2.3)        | 6 (0.5)         | 17 (1.4)        | 10 (0.8)        | 2 (0.2)                   |
| Ampicillin                    | 63                              | 0              | 2 (3.2)                        | 1 (1.6)         | 1 (1.6)         | 1 (1.6)         | 0               | 0                         |
| Amoxicillin-clavulanate       | 102                             | 0              | 3 (2.9)                        | 0               | 0               | 0               | 0               | 0                         |
| Ampicillin-sulbactam          | 52                              | 0              | 1 (1.9)                        | 0               | 0               | 2 (3.8)         | 0               | 0                         |
| Oxacillin                     | 33                              | 0              | 4 (12.1)                       | 1 (3.0)         | 2 (6.0)         | 0               | 0               | 0                         |
| Piperacillin-tazobactam       | 315                             | 0              | 16 (5.1)                       | 4 (1.3)         | 1 (0.3)         | 1 (0.3)         | 1 (0.3)         | 1 (0.3)                   |
| Cefazolin                     | 79                              | 0              | 0                              | 1 (1.3)         | 0               | 2 (2.5)         | 0               | 0                         |
| Ceftriaxone                   | 607                             | 0              | 14 (2.3)                       | 11 (1.8)        | 3 (0.5)         | 5 (0.8)         | 1 (0.2)         | 0                         |
| Cefpodoxime                   | 89                              | 0              | 2 (2.2)                        | 0               | 0               | 0               | 0               | 0                         |
| Cefepime                      | 414                             | 0              | 10 (2.4)                       | 6 (1.4)         | 0               | 6 (1.4)         | 7 (1.7)         | 1 (0.2)                   |
| Ertapenem                     | 85                              | 0              | 3 (3.5)                        | 0               | 0               | 0               | 0               | 0                         |
| Meropenem                     | 80                              | 0              | 4 (5.0)                        | 3 (3.8)         | 0               | 0               | 1 (1.3)         | 0                         |
| <b>Non-β-lactams</b>          |                                 |                |                                |                 |                 |                 |                 |                           |
| Aminoglycosides               | 32                              | 0              | 0                              | 0               | 0               | 2 (6.3)         | 0               | 0                         |
| Azithromycin                  | 400                             | 1 (0.3)        | 1 (0.3)                        | 0               | 4 (1.0)         | 0               | 0               | 0                         |
| Clindamycin                   | 193                             | 0              | 3 (1.6)                        | 0               | 0               | 0               | 0               | 0                         |
| Daptomycin                    | 8                               | 0              | 0                              | 0               | 0               | 0               | 0               | 1 (12.5)                  |
| Doxycycline                   | 57                              | 0              | 2 (3.5)                        | 0               | 0               | 0               | 0               | 0                         |
| Fluoroquinolones              | 394                             | 1 (0.3)        | 5 (1.3)                        | 1 (0.3)         | 3 (0.8)         | 1 (0.3)         | 1 (0.3)         | 1 (0.3)                   |
| Linezolid                     | 23                              | 0              | 0                              | 0               | 0               | 0               | 1 (4.3)         | 0                         |
| Metronidazole                 | 175                             | 0              | 1 (0.6)                        | 0               | 0               | 0               | 1 (0.6)         | 0                         |
| Trimethoprim-sulfamethoxazole | 155                             | 0              | 5 (3.2)                        | 0               | 0               | 6 (3.9)         | 0               | 1 (0.6)                   |
| Intravenous vancomycin        | 544                             | 0              | 2 (0.4)                        | 0               | 0               | 19 (3.5)        | 0               | 2 (0.4)                   |
| <b>Any antibiotics</b>        | <b>1488<sup>e</sup></b>         | <b>2 (0.1)</b> | <b>78 (5.2)</b>                | <b>28 (1.9)</b> | <b>13 (0.9)</b> | <b>45 (3.0)</b> | <b>13 (0.9)</b> | <b>7 (0.5)</b>            |

RESEARCH

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## Nephrotoxic drug burden among 1001 critically ill patients: impact on acute kidney injury

**Table 3 Nephrotoxic drugs most frequently prescribed among exposed patients**

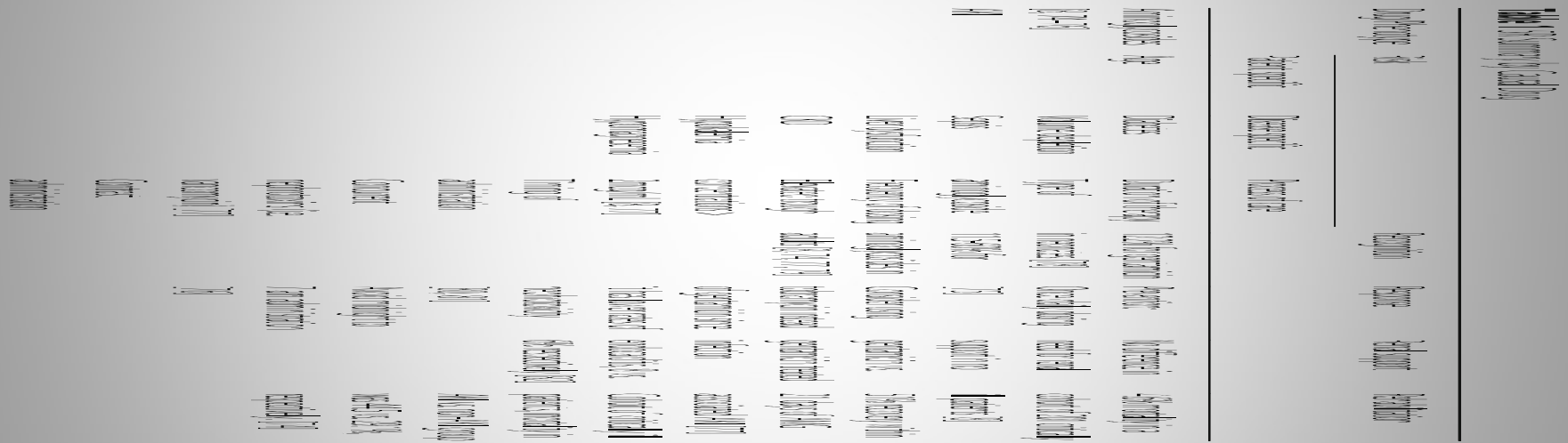
| Drugs                         | <i>n</i> = 617 |
|-------------------------------|----------------|
| Iodinated contrast media      | 154 (25%)      |
| Diuretics                     | 356 (58%)      |
| Loop diuretics                | 346 (97%)      |
| Thiazide diuretics            | 18 (5%)        |
| Potassium sparing diuretics   | 10 (3%)        |
| Antibiotics                   | 227 (37%)      |
| Vancomycin                    | 77 (34%)       |
| Aminoglycosides               | 139 (61%)      |
| High-dose beta-lactams        | 57 (25%)       |
| Sulfamethoxazole trimethoprim | 25 (11%)       |
| Rifampicin                    | 12 (5%)        |
| Antiviral agents              | 58 (9%)        |
| Acyclovir                     | 36 (62%)       |
| Other                         | 22 (38%)       |
| Antifungal agents             | 27 (4%)        |
| Amphotericin B                | 9 (33%)        |
| Voriconazole                  | 12 (44%)       |
| Other                         | 6 (22%)        |

REVIEW

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# The 6R's of drug induced nephrotoxicity

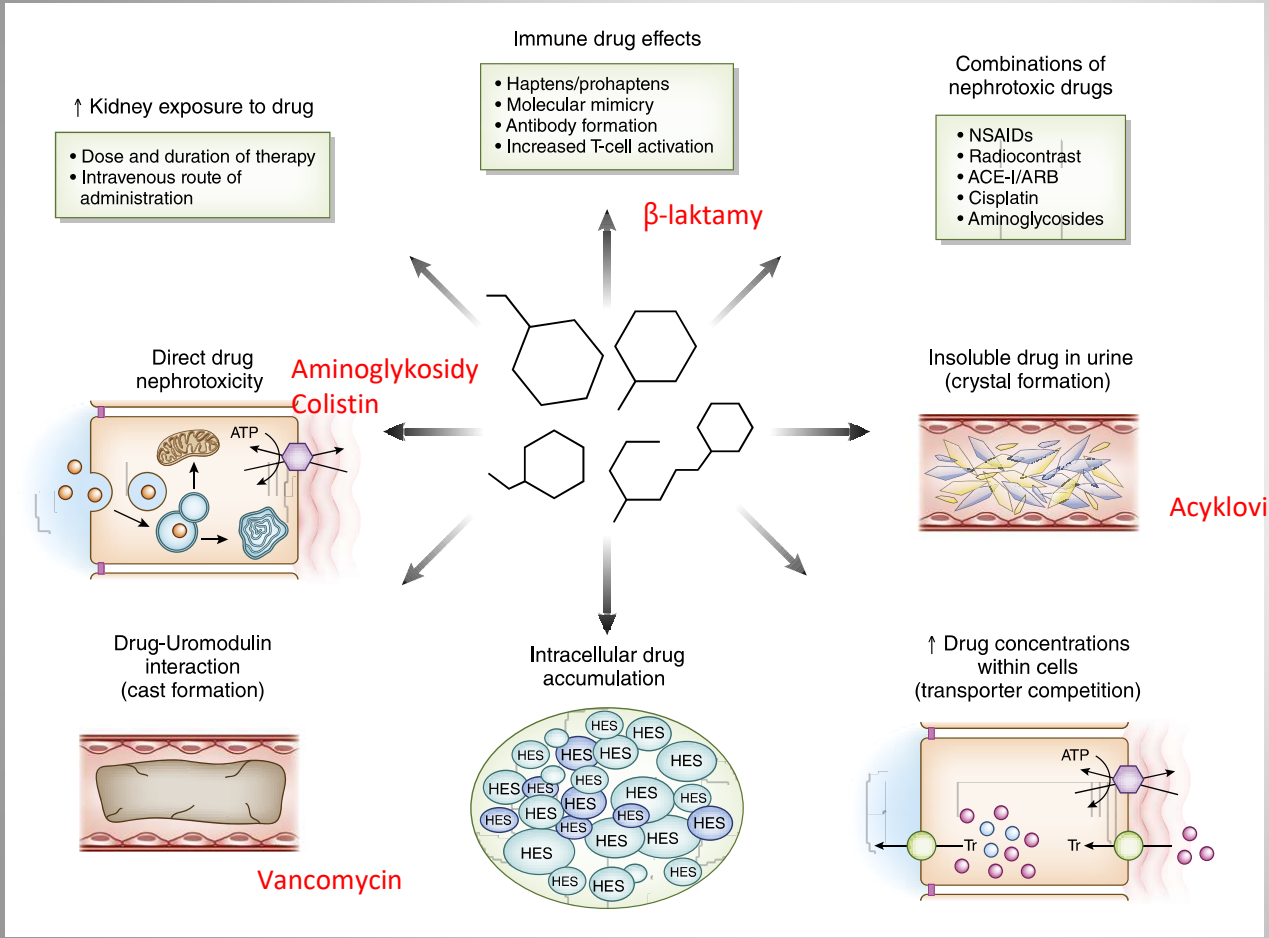


- Neexistuje jednotná definice ATB-indukovaného AKI
- Poškození ledvin může být trvalé



# Pharmacology behind Common Drug Nephrotoxicities

Mark A. Perazella



## Neurotoxic effects associated with antibiotic use: management considerations

Marie F. Grill<sup>1</sup> & Rama K. Maganti<sup>2</sup>



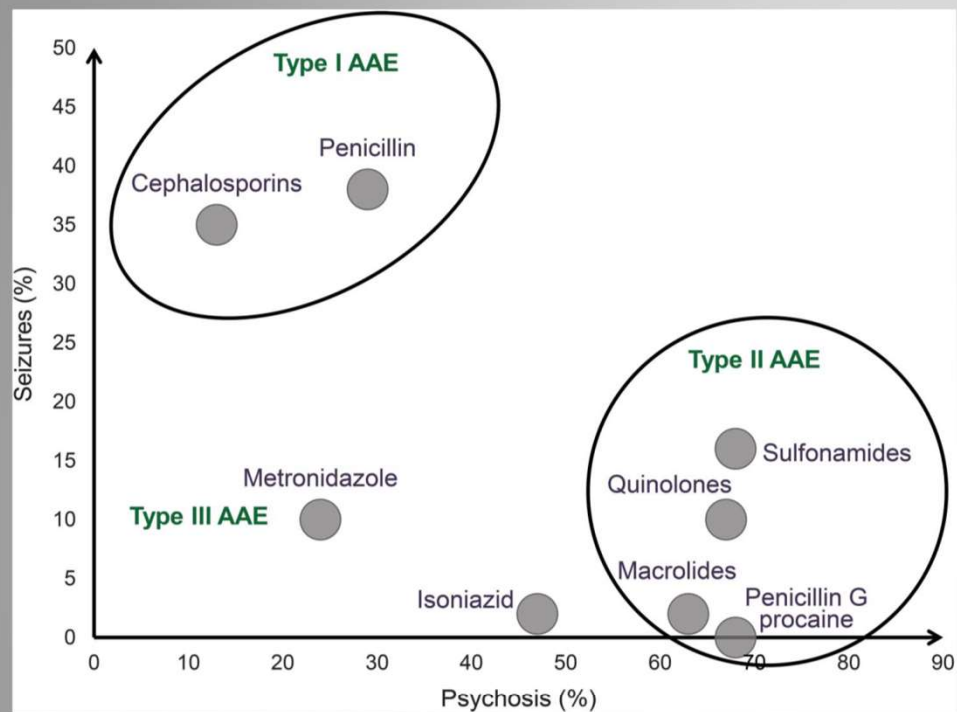
| Antibiotic class  | Number of publications                                   | Neurotoxic effects  | Mechanism of neurotoxicity   | Risk factors   |
|---|--|---|--|--|
| <b>Aminoglycosides:</b><br>1. Gentamicin<br>2. Streptomycin<br>3. Amikacin<br>4. Tobramycin<br>5. Neomicin<br>6. Kanamycin  | 5: retrospective case reviews; case series; case reports | Ototoxicity-class effect<br>Peripheral neuropathy; encephalopathy (gentamicin)<br>Neuromuscular blockade-class effect | Activation of NMDA receptors<br>Lysosomal abnormality; Axonal loss; Inflammatory response<br>Inhibition of pre-synaptic quantal release of acetylcholine and binding of drug to postsynaptic receptors | Increased CNS permeability<br>Intrathecal administration         |
| <b>Beta lactams-<br/>Cephalosporins:</b><br><i>High risk agents:</i><br>1. Cefazolin<br>2. Cefesolis<br>3. Ceftazidime<br>4. Cefoperazone<br>5. Cefepime<br><i>Low risk agents:</i><br>1. Cephalexin<br>2. Cefatoxime<br>3. Ceftriaxone | 24- Case reports; retrospective reviews; review articles | Encephalopathy with Triphasic waves on EEG<br>Tardive seizures<br>Seizures<br>NCSE<br>Myoclonus<br>Asterexis          | Inhibition of GABA-A release;<br>Increased glutamate; Induction of endotoxins; Cytokine release  | Renal failure<br>Prior CNS disease<br>Older age<br>Excess dosage |
| <b>Beta-lactams-<br/>Penicillins:</b><br>1. Benzylpenicillin<br>2. Penicillin G<br>3. Piperacillin<br>4. Ticarillin<br>5. Ampicillin<br>6. Amoxicillin<br>7. Oxacillin  | 4: Case reports; case series                             | Seizures<br>Tardive seizures<br>Encephalopa<br>Tremors  | Inhibition of GABA-A receptors   | Renal failure; low birth weight-neonates                         |
| <b>Beta-lactams<br/>Carbapenems</b><br>1. Imepenem<br>2. Meropenem<br>3. Paripenem<br>4. Ertapenem<br>5. Doripenem<br>6. Ceftaroline  | 4: Case reports  | Encephalopathy<br>Seizures<br>Myoclonus<br>Headache   | Inhibition of GABA-A receptors;<br>Possibly binding of glutamate   | Renal failure  |



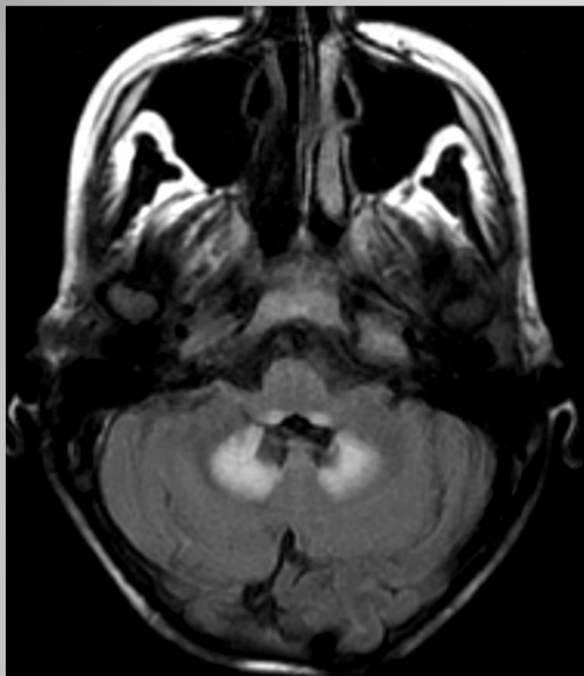
## NCSE/CSE

- Až 8% komatózních pacientů
- Vysoké riziko u predisponovaných
- Cefalosporiny, karbapenemy, chinolony
- cEEG, **redukce dávky či změna ATB**





- NCSE/CSE, křeče
- Zmatenost, psychóza halucinace
- Nystagmus, ataxie (metronidazol)



## Encefalopatie

- Až 70-80% pacientů na MICU
- ATB mohou mít významný vliv
- $\beta$ -laktamy, chinolony, makrolidy, metronidazol

*Kuriyama, Clinic Neuropharmacol, 2011*



**High risk patients:**

- Renal failure
- Prior CNS disease
- Elderly
- Very young

1. Adjust dose of antibiotic
2. Avoid potential neurotoxic agents

Drug administered

Neurotoxic effect identified (encephalopathy, neuromuscular weakness)

Discontinue offending agent

Unresolved

Resolved

Persistent encephalopathy

EEG/Continuous EEG monitoring

Replace with non-neurotoxic antibiotic

Seizures/NCSE

Non specific slowing

1. Replace non neurotoxic antibiotic
2. Observation

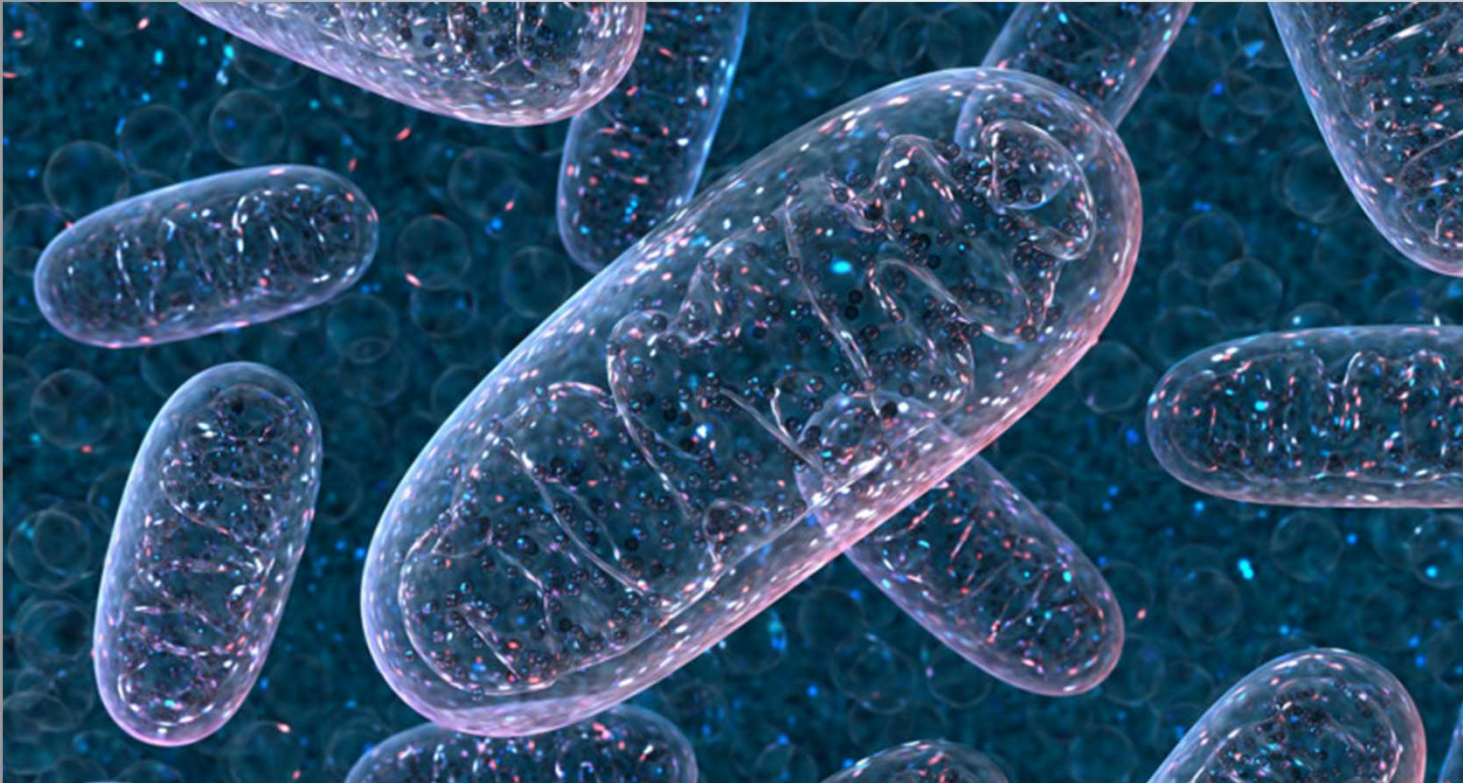
Consider hemodialysis or CVVHF (especially for cephalosporin, quinolones or polymyxin)

Persistent mental status change

1. AEDs (lorazepam, phenytoin or valproate)
2. Change to non neurotoxic antibiotic



ATB-indukovaná mitochondriální dysfunkce?

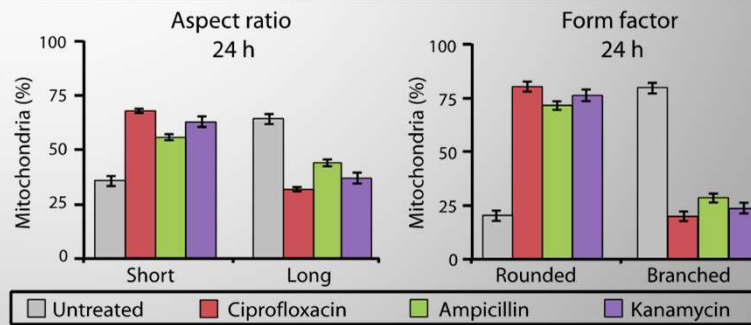
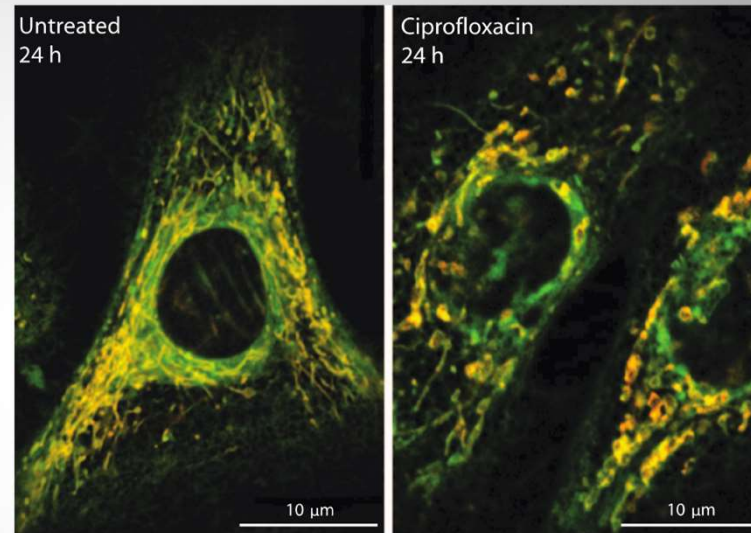
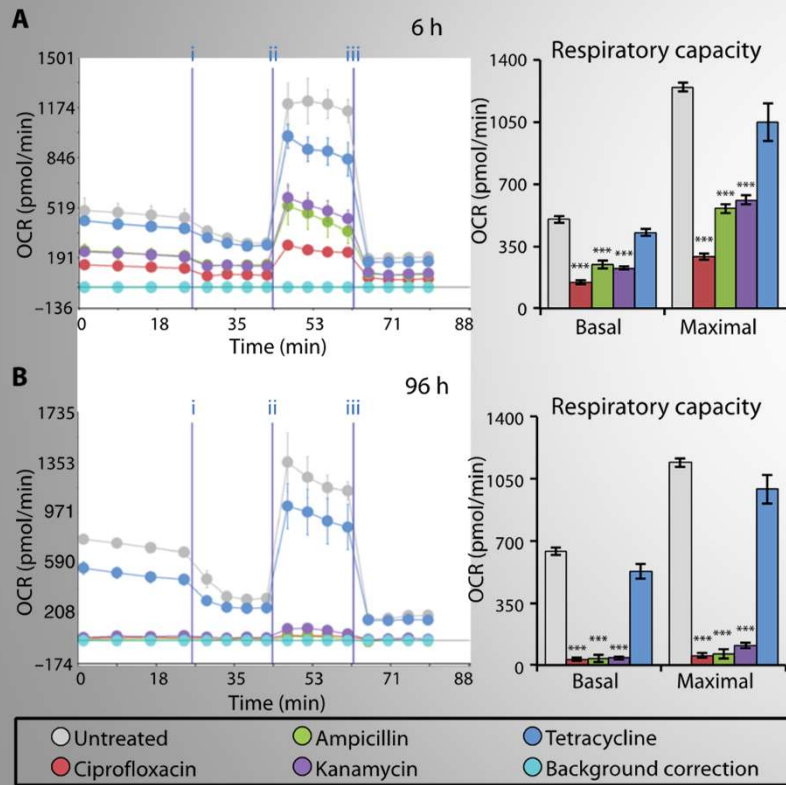




ANTIBIOTICS

# Bactericidal Antibiotics Induce Mitochondrial Dysfunction and Oxidative Damage in Mammalian Cells

Sameer Kalghatgi,<sup>1\*</sup> Catherine S. Spina,<sup>1,2,3\*</sup> James C. Costello,<sup>1</sup> Marc Liesa,<sup>3</sup>  
 J. Ruben Morones-Ramirez,<sup>1</sup> Shimyn Slomovic,<sup>1</sup> Anthony Molina,<sup>3,4</sup>  
 Orlan S. Shirihai,<sup>3</sup> James J. Collins<sup>1,2,3†</sup>



*Review Article*

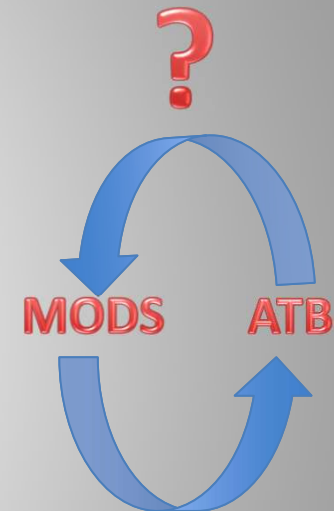
## **Role of Oxidative Stress and Mitochondrial Dysfunction in Sepsis and Potential Therapies**

REVIEW

Virulence 5:1, 66–72; January 1, 2014; © 2014 Landes Bioscience

### **The role of mitochondrial dysfunction in sepsis-induced multi-organ failure**

Mervyn Singer



A co mikrobiom?



## The Gut as the Motor of Multiple Organ Dysfunction in Critical Illness

Otani and Coopersmith *Journal of Intensive Care* (2019) 7:17  
https://doi.org/10.1186/s40560-019-0372-6

Journal of Intensive Care

REVIEW

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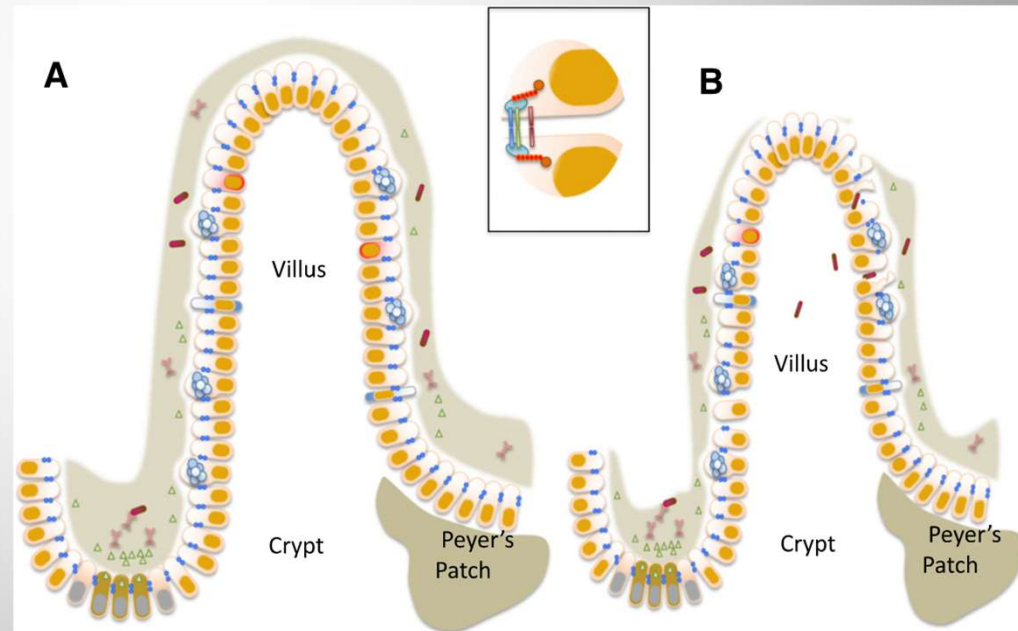
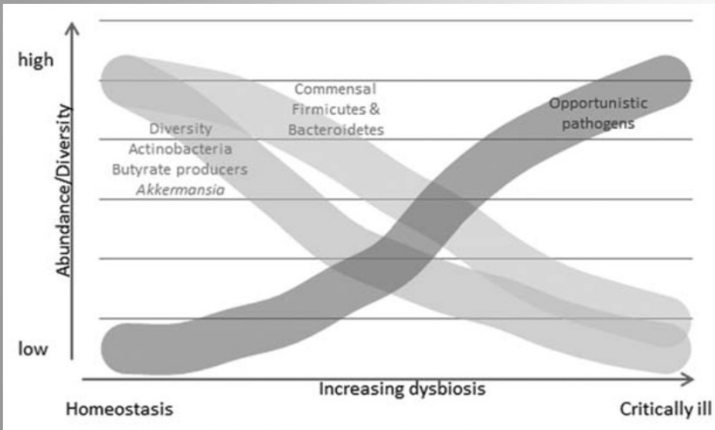
### Gut integrity in critical illness

Shunsuke Otani<sup>1,2,3</sup> and Craig M. Coopersmith<sup>1\*</sup>



### Gut microbiota and host defense in critical illness

Max C. Jacobs<sup>a</sup>, Bastiaan W. Haak<sup>a</sup>, Floor Hugenholtz<sup>a</sup>,  
and W. Joost Wiersinga<sup>a,b</sup>

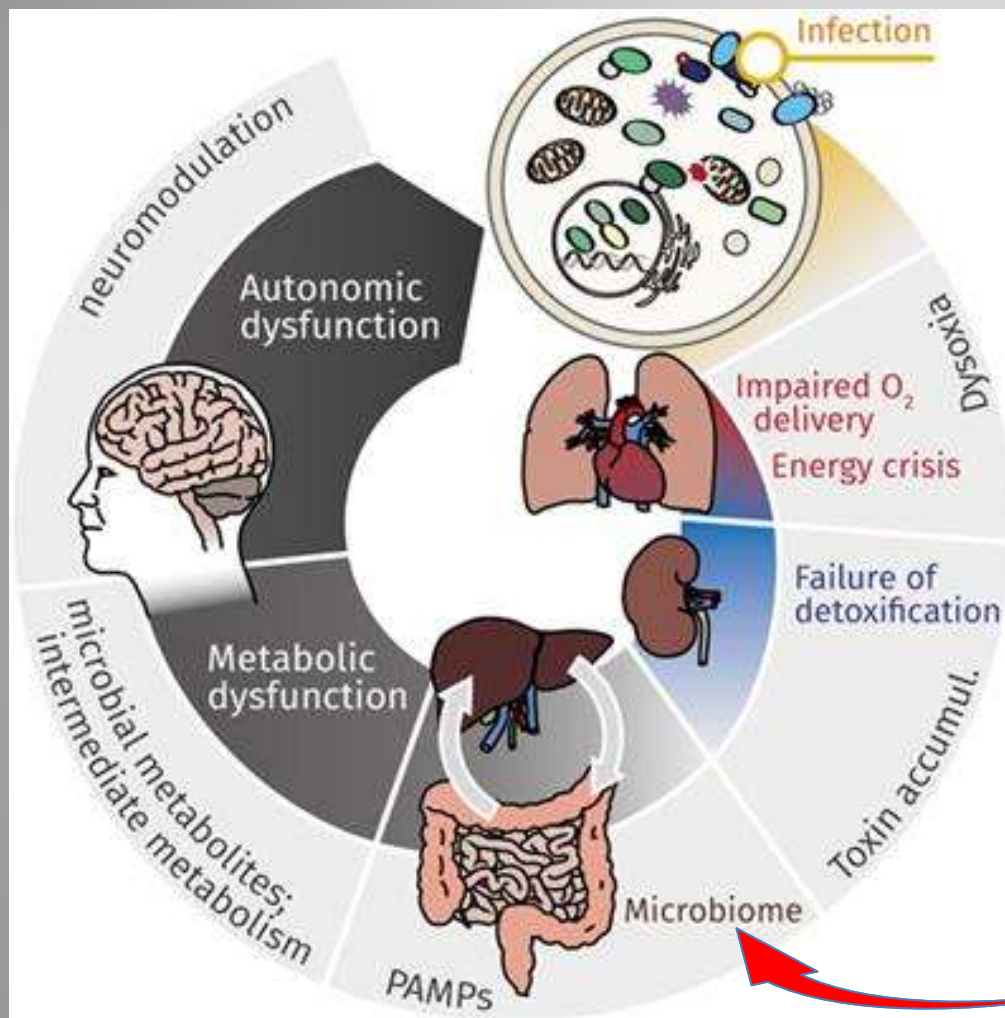




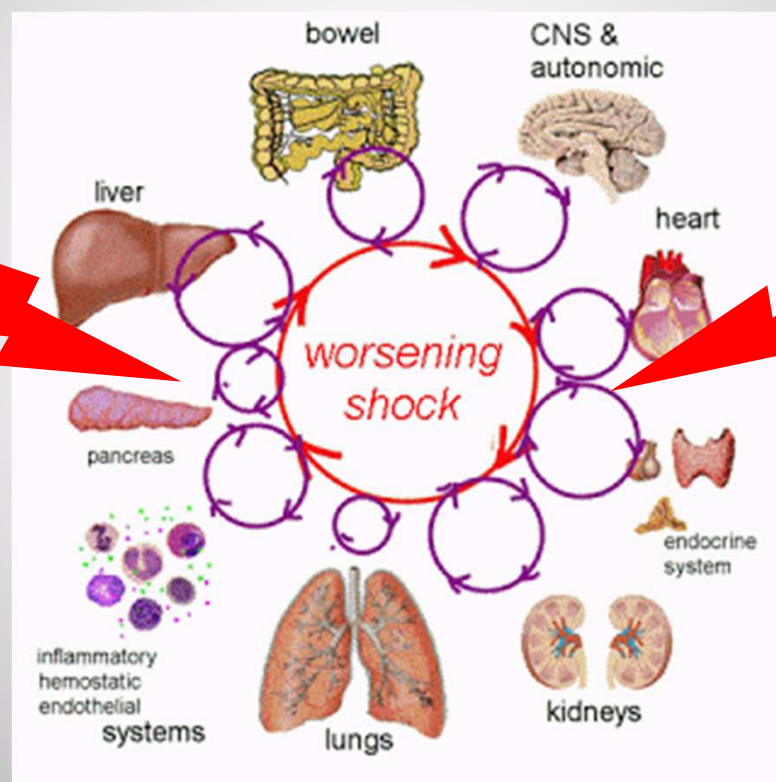
### Impact of antimicrobial therapy on the gut microbiome

Amira A. Bhalodi<sup>1\*</sup>, Tjitske S. R. van Engelen<sup>2†</sup>, Harjeet S. Virk<sup>2†</sup> and W. Joost Wiersinga<sup>2,3</sup>

| Antimicrobial class | Antimicrobial           | Effects on faecal microbiota  |             |   |
|---------------------|-------------------------|---|-------------|---|
|                     |                         | decrease  | increase    | stable  |
| Penicillins         | piperacillin/tazobactam | Enterobacteriaceae<br>bifidobacteria<br>Eubacteria<br>lactobacilli                                      |             | <i>Bacteroides</i><br>enterococci<br>clostridia   |
| Cephalosporins      | cefepime                | <i>E. coli</i><br>bifidobacteria  |             | <i>Bacteroides</i><br>clostridia  |
|                     | ceftazidime             | Enterobacteriaceae<br>lactobacilli  |             | enterococci<br><i>Bacteroides</i>   |
|                     | ceftriaxone             | Enterobacteriaceae<br><i>E. coli</i><br>lactobacilli<br>bifidobacteria<br>clostridia                    | enterococci | <i>Bacteroides</i>  |
| Carbapenems         | meropenem               | Enterobacteriaceae<br>clostridia<br><i>Bacteroides</i>  | enterococci | yeast<br>lactobacilli<br>bifidobacteria<br>Eubacteria<br>clostridia                       |
|                     | imipenem                | Enterobacteriaceae<br>enterococci<br>bifidobacteria<br>Eubacteria<br>lactobacilli<br><i>Bacteroides</i> |             |   |
|                     | ertapenem               | <i>E. coli</i><br>bifidobacteria<br><i>Bacteroides</i>  | enterococci | lactobacilli<br>clostridia  |
| Fluoroquinolones    | ciprofloxacin           | Enterobacteriaceae  | enterococci | anaerobic flora<br>bifidobacteria<br>bifidobacteria<br>lactobacilli<br><i>Bacteroides</i> |
|                     | levofloxacin            | <i>E. coli</i>  |             |   |
|                     | moxifloxacin            | enterococci<br>clostridia<br><i>E. coli</i><br>enterococci<br>bifidobacteria<br>clostridia              |             | lactobacilli<br><i>Bacteroides</i><br>fusobacteria  |



Kde je hranice mezi progresí MODS způsobenou primárním inzultem či naší vlastní léčbou, např. extenzivní ATB léčbou?

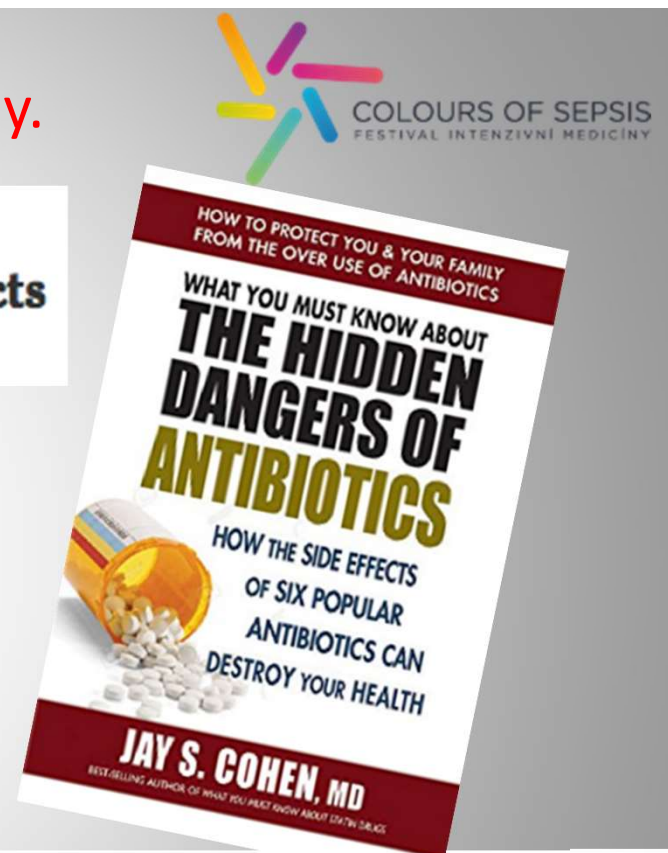


Mám-li jinou možnost, nikdy nevolím chinolony.

PERSONAL HEALTH

## Popular Antibiotics May Carry Serious Side Effects

BY JANE E. BRODY SEPTEMBER 10, 2012 12:01 AM 651



Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics

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## **Jsou-li ATB nezbytná:**

- **Znát rizika**
- **ANTIBIOTIC STEWARDSHIP**
- **Therapeutic drug monitoring**
- **Adekvátní dávkování**
- **Při nežádoucích účincích změna ATB**
- **Včasná deeskalace a ukončení ATB terapie**
- ***(Nestačil by někdy jeden dva dny ATB?)***



She's doing better.



Oh, thank God.



Technically, Alexander Fleming.  
He developed antibiotics



**Děkuji vám za pozornost**

14.

**XIV. kongres České společnosti intenzivní medicíny  
s mezinárodní účastí  
3-6.června 2020, Hotel Galant, Mikulov  
[www.csimkongres.cz](http://www.csimkongres.cz)**

