

**Ach tie
ANTIBIOTIKÁ ...**

**Roman Kula
KARIM FN Ostrava**



Inšpirácia ...

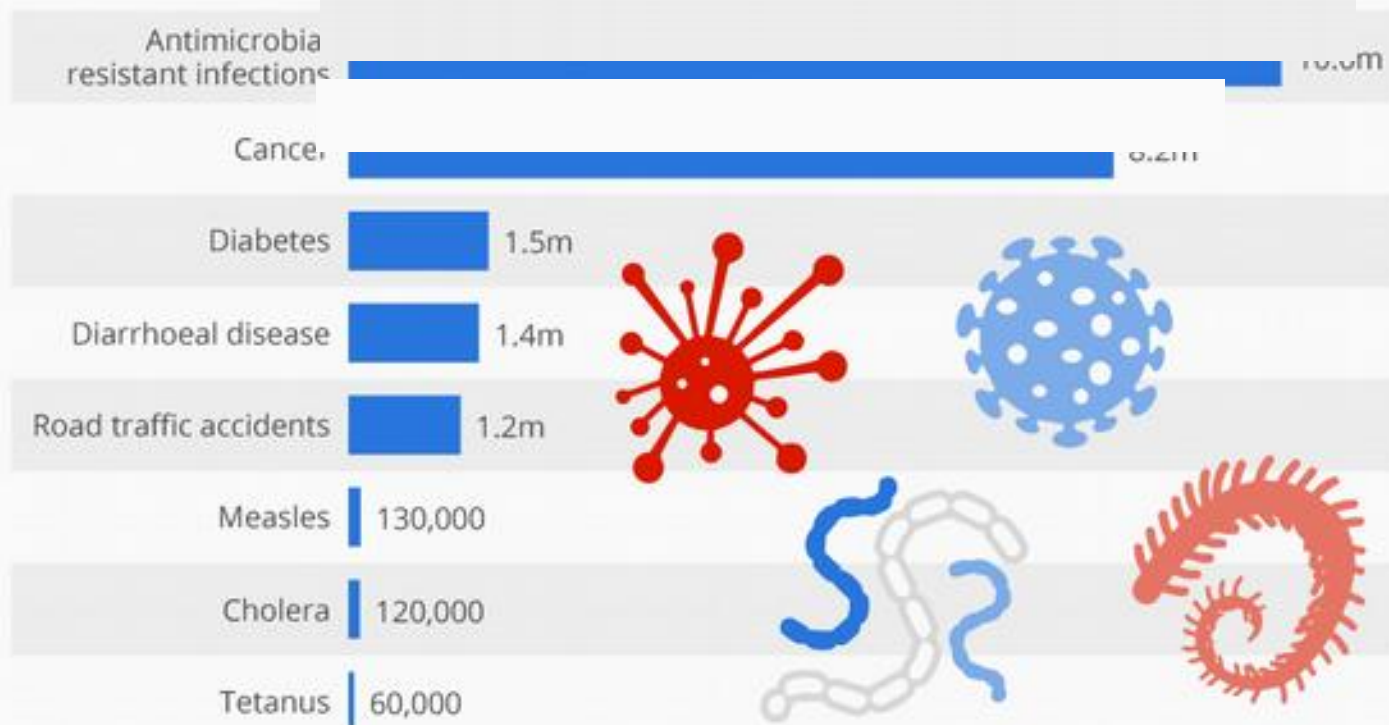


Inšpirácia ...



Deaths From Drug-Resistant Infections Set To Skyrocket

Deaths from antimicrobial resistant infections and other causes in 2050



@StatistaCharts · Source: Review on Antimicrobial Resistance

statista

Na margo „rezistencie“ ...



Na margo „rezistencie“ ...



Amanda Jezek



We can only really slow the development of resistance. We're not going to stop it completely. Even appropriate use of antibiotics does contribute to resistance – Amanda Jezek, Vice President for Public Policy and Government Relations, Infectious Diseases Society of America

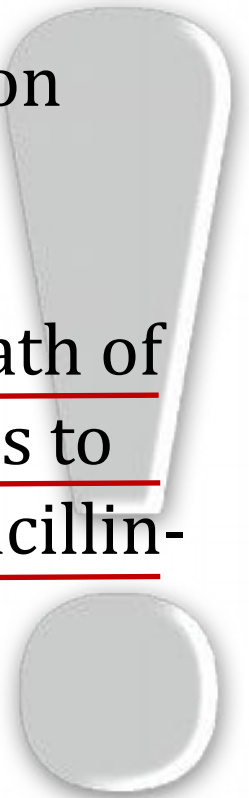
Na margo „rezistencie“ ...



Sir. A. Fleming

„The thoughtless person playing with penicillin treatment is morally responsible for the death of the man who succumbs to infection with the penicillin-resistant organism.“

... from Nobel Prize Lecture 1945





NATURE 2012

Get pigs off antibiotics

Frank Aarestrup explains how he helped Denmark to cut the use of antibiotics in its livestock by 60%, and calls on the rest of the world to follow suit.

The amount of antibiotics consumed by livestock worldwide is almost double that used by humans, according to some estimates^{1,2}. In the United States, for instance, about 300 milligrams of antibiotics are used to produce every kilogram of meat and eggs^{3,4}. These drugs are administered not just to treat or to prevent infections. In many countries, they are used to help the animals to grow faster. This is an unsustainable situation. Since many farmers began giving antibiotics to livestock in the late 1940s, people have been infected with strains of bacteria that are resistant to those antibiotics^{1,2,5}.

RESEARCH ARTICLE

Science 2019

ONE HEALTH

Global trends in antimicrobial resistance in animals in low- and middle-income countries

Thomas P. Van Boeckel^{1,2,6,†}, João Pires^{1,6,†}, Reshma Silvester², Cheng Zhao¹, Julia Song^{3,4}, Nicola G. Criscuolo¹, Marius Gilbert², Sebastian Bonhoeffer^{6,†}, Ramanan Laxminarayan^{1,2,4,†}

... počet ATB, na ktoré su mikróby rezistentné v 50% prípadov **stúpil o 300%**

Nadužívanie ATB ...



NATURE 2013

THIS WEEK

EDITORIALS

CANCER Talk is so not cheap at the US National Cancer Institute p.142

WORLD VIEW The unlikely scientific wisdom of Chairman Mao p.143



NEWS New proteins could help explain regeneration game p.145

The antibiotic alarm

2010 - 2015 (Nature 2015)

- vzostup spotreby ATB o **30%**
- vzostup výskytu CAR^r enterobakterií **z 30 na 60%**

“Antibiotics remain heavily over-prescribed by doctors around the world.”

Nadužívanie ATB ... **na ICU**



Nadužívanie ATB ... **na ICU**



... na ICU je **celá rada stavov pripomínajúcich odpoved' na infekciu**

- **elevácia prokalcitoninu neinfekčnej etiológie**
(šokové stavy, kardiálne zlyhávanie, fyziologická elevácia...)
- **imitátory sepsy** *(HLH, tumor lysis syndrom ...)*

Karvunidis T. et al. *Vnitř Lék* 2019; 65: 440-448

Nadužívanie ATB ... **na ICU**



... na ICU je celá rada stavov pripomínajúcich odpoveď na infekciu

- elevácia procalcitoninu/presepsinu neinfekčnej etiológie (šokové stavy, kardiálne zlyhávanie, fyziologická elevácia)
- imitátory sepsy (HLH, tumor lysis syndrom ...)

Karvunidis T. et al. *Vnitř Lék* 2019; 65: 440-448

Antibiotikami liečime pacientov už takmer 100 rokov, ale bohužiaľ stále si nie sme istí, či antibiotikami liečime skutočne sepsu ... (teda aspoň nie v akútnej fáze) ☹ ☹

Špecifické problémy ATB liečby na ICU ...

... u ostatných pacientov sa nevyskytujú

... sú rizikové pre vývoj rezistencie

... môžu dokonca zhoršiť stav pacienta



Dávkovanie ATB ... **na ICU**



Dávkovanie ATB ... na ICU



= STEP into
the UNKNOWN ☹️



Dávkovanie ATB ... **na ICU**



- chceme dosiahnuť „cídnu“ koncentráciu ATB v infikovanom tkanive, ale ...
 - ... v klinickej praxi o tom, či sme ju dosiahli **nič nevieme!***
 - ... ak sme ju **nedosiahli**, potom platí: „**položivá baktéria rada mutuje, mŕtva NIKDY!**“*
- chceme dosiahnuť koncentráciu ATB v sére niekoľko násobne nad MIC, ale ...
 - ... v klinickej praxi o tom, či sme ju dosiahli **nič nevieme!***
- dávkovanie ATB riadime liekopisom, ale ...
 - ... ten je postavený pre „zdravých ľudí“ a nie pre pacientov so sepsou ☹*

Dávkovanie ATB ... na ICU



Clin Infect Dis. 2014 ;58:1072-83.

DALI: Defining Antibiotic Levels in Intensive Care Unit Patients: Are Current β -Lactam Antibiotic Doses Sufficient for Critically Ill Patients?

Jason A. Roberts,^{1,2} Sanjoy K. Paul,^{3,4} Murat Akova,⁵ Matteo Bassetti,⁶ Jan J. De Waele,⁷ George Dimopoulos,⁸ Kirsi-Maija Kaukonen,⁹ Despoina Koulenti,^{1,8} Claude Martin,^{10,11} Philippe Montravers,¹² Jordi Rello,¹³ Andrew Rhodes,¹⁴ Therese Starr,² Steven C. Wallis,¹ and Jeffrey Lipman^{1,2}; for the DALI Study^a

... 25-50% pacientov na ICU má **pri liekopisnom dávkovaní** neadekvátnu expozíciu β -laktamovými antibiotikami !!

= HORŠIA PROGNOZA x REZISTENCIA

Dávkovanie ATB ... **na ICU**



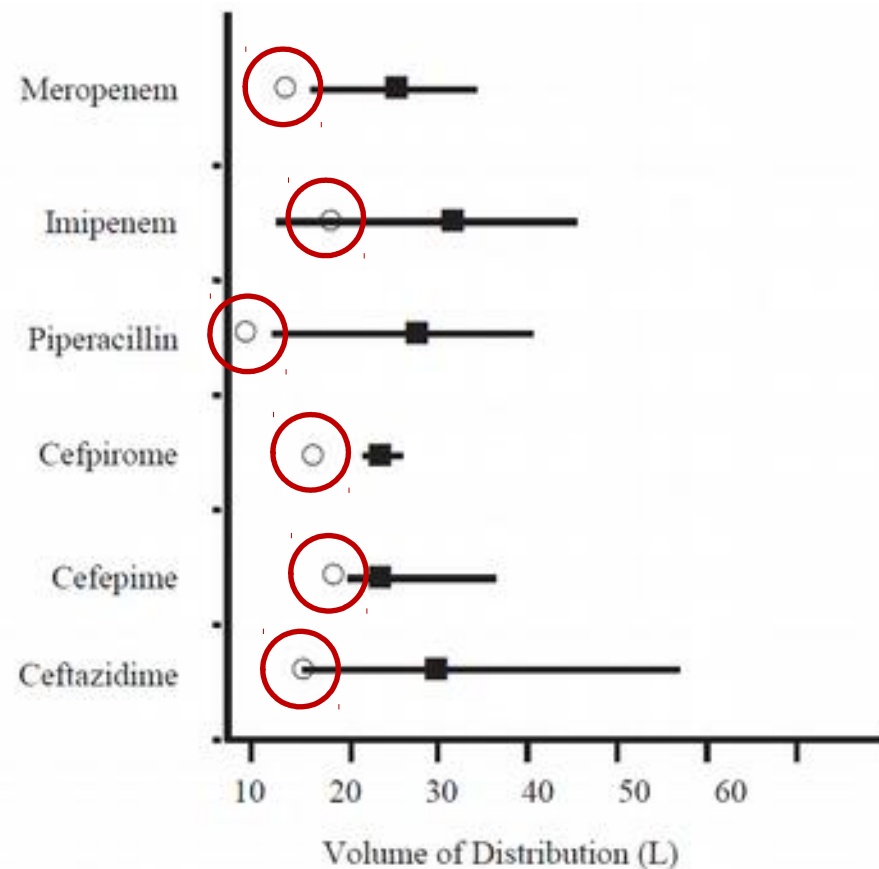
... farmakokinetika ATB u kriticky chorých **je úplne iná**, než u zdravých ľudí **!!**

Dávkovanie ATB ... na ICU



... farmakokinetika ATB u kriticky chorých **je úplne iná**, než u zdravých ľudí !!

- ↑ **Volume of distribution**



Dávkovanie ATB ... na ICU

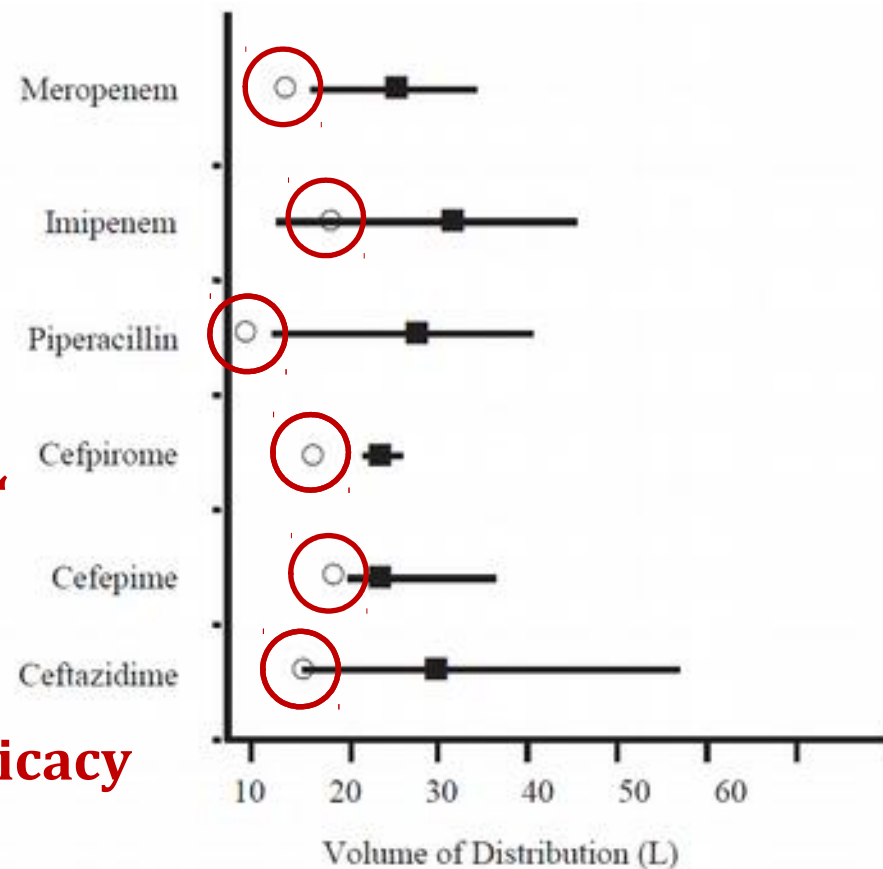


... farmakokinetika ATB u kriticky chorých **je úplne iná**, než u zdravých ľudí !!

- ↑ **Volume of distribution**
- ↑ **Clearance**

... „dosage and schedule regimens based on data from healthy volunteers **may be misleading**“

... therapeutic **drug monitoring** of β -lactam antibiotic concentration **may help to improve its efficacy**





*Čím sa pri dávkovaní ATB riadiť
v praxi ... ??*

*MUDr. K. Galková, Ph.D.,
(Nitra)*

Délka léčby ATB ... **na ICU**



Dĺžka liečby ATB ... **na ICU**



... zdá sa, že dnes už asi „málokoho“ zaujíma,
že **skrátением ATB liečby sa dá:**



IGNORE

Dĺžka liečby ATB ... **na ICU**



... zdá sa, že dnes už asi „málokoho“ zaujíma,
že **skrátением ATB liečby sa dá:**



Crit Care Med **2016** , 44: 256-64

Duration of Antimicrobial Treatment for Bacteremia in Canadian Critically Ill Patients*

Nick Daneman, MD¹; Asgar H. Rishu, MBBS²; Wei Xiong, MSc³; Sean M. Bagshaw, MD⁴;
Peter Dodek, MD⁵; Richard Hall, MD⁶; Anand Kumar, MD⁶; Francois Lamontagne, MD⁷;
Francois Lauzier, MD⁸; John Marshall, MD⁹; Claudio M. Martin, MD¹⁰; Lauralyn McIntyre, MD¹¹;
John Muscedere, MD¹²; Steve Reynolds, MD¹³; Henry T. Stelfox, MD¹⁴; Deborah J. Cook, MD¹⁵;
Robert A. Fowler, MD¹⁶; on behalf of the Canadian Critical Care Trials Group



IGNORE

Medián trvania ATB liečby = 14 dní ☹️☹️

Dĺžka liečby ATB ... **na ICU**



... zdá sa, že dnes už asi „málokoho“ zaujíma, že **skrátением ATB liečby sa dá:**

- ušetriť
- znížiť riziko vývoja CDI
- znížiť riziko vývoja rezistence

... snád' ale *zbystríme svoju pozornosť* pri zistení, že **skrátением ATB liečby sa dá:**



OBSERVANT

Dĺžka liečby ATB ... **na ICU**



... ATB sú **TOXICKÉ LÁTKY !!**

RESEARCH ARTICLE

Sci Transl Med. 2013 Jul 3; 5(192): 192ra85.

ANTIBIOTICS

Bactericidal Antibiotics Induce Mitochondrial Dysfunction and Oxidative Damage in Mammalian Cells

Sameer Kalghatgi,^{1*} Catherine S. Spina,^{1,2,3*} James C. Costello,¹ Marc Liesa,³
J. Ruben Morones-Ramirez,¹ Shimyn Slomovic,¹ Anthony Molina,^{3,4}
Orlan S. Shirihai,³ James J. Collins^{1,2,3†}

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... something INVISIBLE for intensivists



www.impactjournals.com/oncotarget/

Oncotarget, Advance Publications 2015

Antibiotics that target mitochondria effectively eradicate cancer stem cells, across multiple tumor types: Treating cancer like an infectious disease

Rebecca Lamb^{1,2,*}, Bela Ozsvari^{1,2,*}, Camilla L. Lisanti³, Herbert B. Tanowitz⁴, Anthony Howell^{1,2}, Ubaldo E. Martinez-Outschoorn⁵, Federica Sotgia^{1,2} and Michael P. Lisanti^{1,2}

... something **VISIBLE** for oncologists



www.impactjournals.com/oncotarget/

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 **frontiers**
in Oncology

ORIGINAL RESEARCH
published: 12 October 2018
doi: 10.3389/fonc.2018.00452

Doxycycline, an Inhibitor of Mitochondrial Biogenesis, Effectively Reduces Cancer Stem Cells (CSCs) in Early Breast Cancer Patients: A Clinical Pilot Study

Cristian Scatena¹, Manuela Roncolla^{1,2}, Antonello Di Paolo³, Paolo Aretini⁴, Michele Menicagli⁴, Giovanni Fanelli⁴, Carolina Marini⁴, Chiara Maria Mazzanti⁴, Matteo Ghilli², Federica Sotgia², Michael P. Lisanti^{1*} and Antonio Giuseppe Naccarato^{1*}



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Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

Biochemical and Biophysical Research Communications xxx (2017) 1e7



Antibiotic tigecycline enhances cisplatin activity against human hepatocellular carcinoma through inducing mitochondrial dysfunction and oxidative damage

Jun Tan ^a, Meijun Song ^b, Mi Zhou ^{c,*}, Yaoren Hu ^{a,**}



www.impactjournals.com/oncotarget/

Oncotarget, Advance Publications 2015

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Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc



Inhibition of mitochondrial translation as a therapeutic strategy for human ovarian cancer to overcome chemoresistance

Bo Hu^{*.1}, Yue Guo^{**.1}



www.impactjournals.com/oncotarget/

Oncotarget, Advance Publications 2015

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SCIENTIFIC
REPORTS

OPEN

Tigecycline as a dual inhibitor of retinoblastoma and angiogenesis via inducing mitochondrial dysfunctions and oxidative damage

Ying Xiong¹, Wei Liu², Qian Huang¹, Jierong Wang¹, Yanjun Wang¹, Huijuan Li¹ & Xuedong Fu¹



Antibiotics that target mitochondria effectively eradicate cancer stem cells, across multiple tumor types: Treating cancer like an infectious disease

Rebecca Lamb^{1,2,*}, Bela Ozsvari^{1,2,*}, Camilla L. Lisanti³, Herbert B. Tanowitz⁴, Anthony Howell^{1,2}, Ubaldo E. Martinez-Outschoorn⁵, Federica Sotgia^{1,2} and Michael P. Lisanti^{1,2}

*Nucleic Acids Research, 2018 1
doi: 10.1093/nar/ky793*

Ciprofloxacin impairs mitochondrial DNA replication initiation through inhibition of Topoisomerase 2

Anu Hangas¹, Koit Aasumets², Nina J. Kekäläinen¹, Mika Paloheinä¹, Jaakko L. Pohjoismäki¹, Joachim M. Gerhold² and Steffi Goffart^{1,*}



www.impactjournals.com/oncotarget/

Oncotarget, Advance Publications 2015

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... rovnakú „mitochondriálnú paseku“ robia aj aminoglykosidy a β -laktamy ☹



... a my ich dávame v situácii už „rozbehnutej“ ...

Virulence 5:1, 66–72; January 1, 2014

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

Burns 43 (2017) 471 – 485

Review

Oxidative stress in sepsis: Pathophysiological implications justifying antioxidant co-therapy



Carlos André Prauchner

Departamento de Química, Centro de Ciências Naturais e Exatas, Universidade Federal de Santa Maria, Avenida Roraima, número 1000, CEP 97105-900 Santa Maria, RS, Brazil

Dĺžka liečby ATB ... **na ICU**



... ATB sú **TOXICKÉ LÁTKY !!**

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... zbytočne dlhá antibiotická liečba **môže potencovať mechanizmy zodpovedné za vývoj, či perzistenciu MODS**



Evelien de Jong

Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial

Evelien de Jong, Jos A van Oers, Albertus Beishuizen, Piet Vos, Wytze J Vermeijden, Lenneke E Haas, Bert G Loef, Tom Dormans, Gertrude C van Melsen, Yvette C Kluiters, Hans Kemperman, Maarten J van den Elsen, Jeroen A Schouten, Jörn O Streefkerk, Hans G Krabbe, Hans Kieft, Georg H Kluge, Veerle C van Dam, Joost van Pelt, Laura Bormans, Martine Bokelman Otten, Auke C Reidinga, Henrik Endeman, Jos W Twisk, Ewoudt M W van de Garde, Anne Marie G A de Smet, Jozef Kesecioglu, Armand R Girbes, Maarten W Nijsten, Dylan W de Lange

... z tohoto uhla pohľadu je celkom pochopiteľný **náhodný nález** pri testovaní non-inferiority PCT riadenej ATB liečby u kriticky chorých

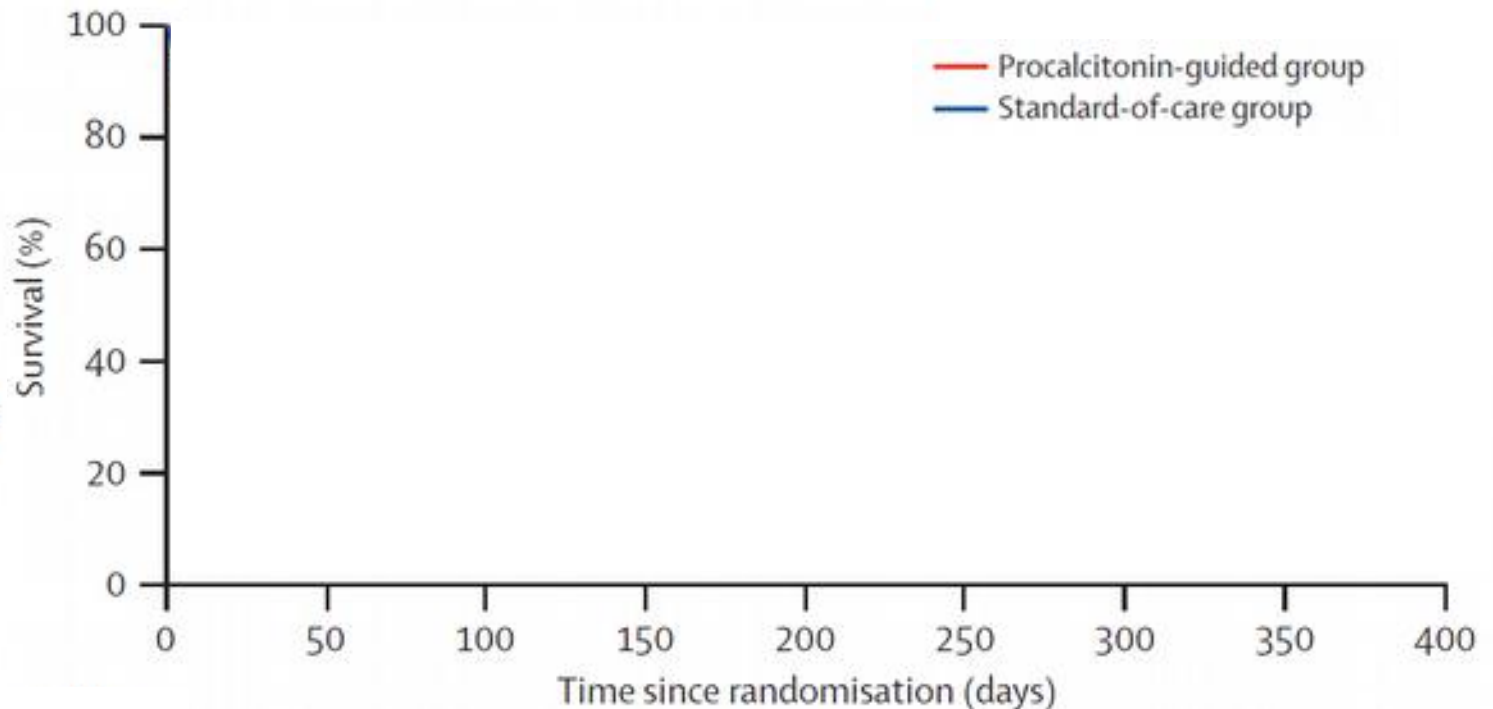




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... čo sa doposiaľ nikomu nepodarilo
byť sa ATB liečba skrakuje ...

Délka ATB léčby - control arm

Chastre J et al. *JAMA* 2003; 290:2588-98

Briel M et al. *Arch Intern Med* 2008;168:2000-7

Nobre V et al. *Am J Respir Crit Care Med* 2008;177:498-505

Hochreiter M et al. *Crit Care* 2009;13:R83

Schuetz P et al. *JAMA* 2009;302:1059-66

Stolz D et al. *Eur Respir J* 2009;34:1364-75

Bouadma L et al. (**PRORATA Trial**) *Lancet* 2010;375:463-74

De Jong E et al., *Lancet Infect Dis* 2016; 16: 819-27



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... čo sa doposiaľ nikomu nepodarilo
byť sa ATB liečba skracuje ...

Délka ATB léčby - control arm

Chastre J et al. <i>JAMA</i> 2003; 290:2588-98	15 dnů
Briel M et al. <i>Arch Intern Med</i> 2008;168:2000-7	13 dnů
Nobre V et al. <i>Am J Respir Crit Care Med</i> 2008;177:498-505	13 dnů
Hochreiter M et al. <i>Crit Care</i> 2009;13:R83	10 dnů
Schuetz P et al. <i>JAMA</i> 2009;302:1059-66	8 dnů
Stolz D et al. <i>Eur Respir J</i> 2009;34:1364-75	9 dnů

... pretože liečbu neskrátili dostatočne 😊

J. Garnacho-Montero
A. Gutiérrez-Pizarra
A. Escobedo-Ortega
Y. Corcia-Palomo
Esperanza Fernández-Delgado
I. Herrera-Melero
C. Ortiz-Leyba
J. A. Márquez-Vácara

De-escalation of empirical therapy is associated with lower mortality in patients with severe sepsis and septic shock



POSTER, Colours of Sepsis 2019



K vyléčení sepse je nutné vysadit ATB

¹Šumanová M., ¹Pěkná J., ²Glasnák M.

¹Anesteziologicko-resuscitační oddělení, ²Oddělení klinické mikrobiologie Nemocnice Rudolfa a Stefanie Benešov

Prezentujeme kauzistiku 23-leté pacientky (bifázická afektivní porucha se sklony k sebepoškození, jinak bez závažných komorbidit) operované akutně pro intracerebrální krvácení z AV malformace frontálního vlevo, pooperačně s nálezem ileotemorální trombozy PDK řešené zavedením kaválního filtru. Stav byl komplikován recidivujícími sepsemi, opakovaně přeléčena ATB, etiologie sepse stále nejasná. Ke konečnému odhalení původce pomohlo úplné vysazení ATB terapie.



Délka léčby ATB ... **na ICU**



Less than
5 days ??

Dĺžka liečby ATB ... **na ICU**



Eur Respir J 2002; 19: 944–951

Effects of antibiotics on protected specimen brush sampling in ventilator-associated pneumonia

E. Prats*, J. Dorca*, M. Pujol[#], L. Garcia[¶], B. Barreiro*, R. Verdaguer⁺, F. Gudiol[#], F. Manresa*

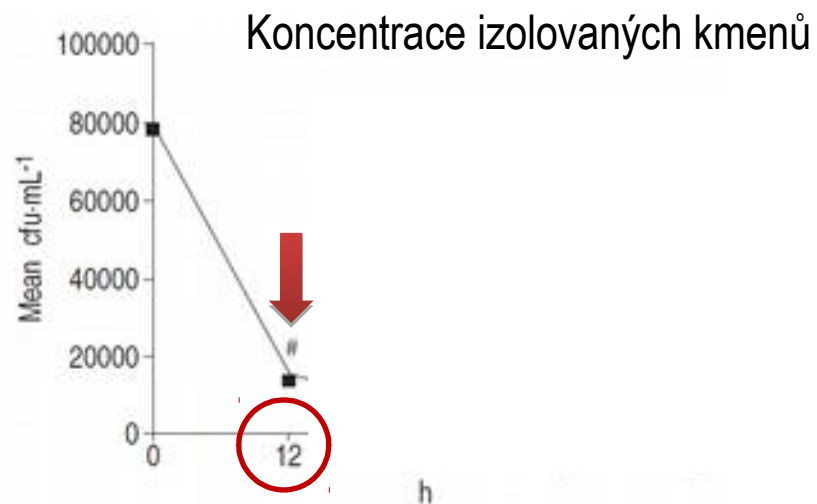
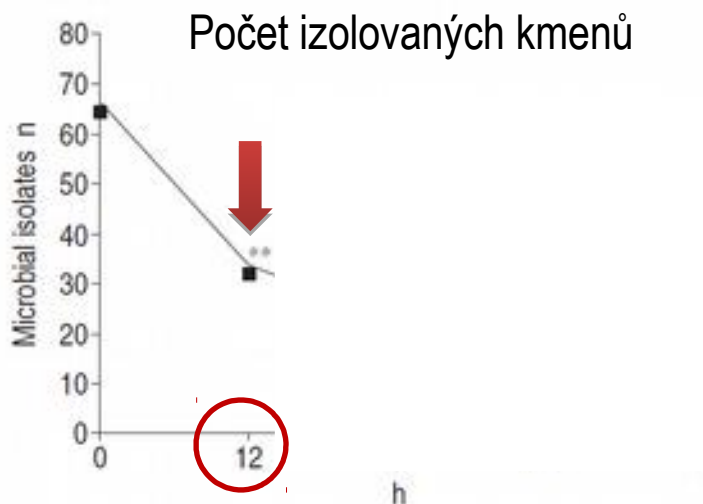
Délka léčby ATB ... na ICU



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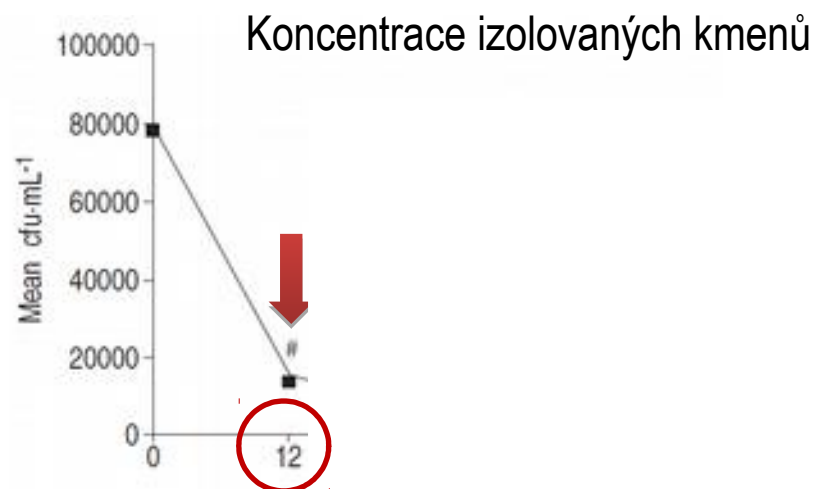
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Dĺžka liečby ATB ... na ICU



Eur Respir J 2002;

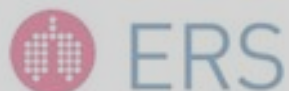
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Zamestnávajte antibiotiká LEN „ZABÍJANÍM MIKROORGANIZMOV“ !!

Dĺžka liečby ATB ... **na ICU**



Eur Respir J 2002;

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ventilator-associated pneumonia

E. Prats*, J. Dorca*, M. Pujol[#], L. Garcia[¶], B. Barreiro*, R. Verdaguer⁺, F. Guzmán[¶], F. Manresa*



**Zamestnávajte antibiotiká LEN „ZABÍJANÍM
MIKROORGANIZMOV“ !!**

**V súčinnosti s funkčným imunitným systémom je doba
na eradikáciu mikroorganizmov pri antibiotickej liečbe
zrejme veľmi krátka 😊**





*Ako v praxi skrátit' ATB
liečbu ... ??*

*MUDr. M. Káňová, Ph.D.,
(Ostrava)*



*Existuje ATB indukované
MODS... ??*

*MUDr. J. Chvojka, Ph.D.,
(Plzeň)*



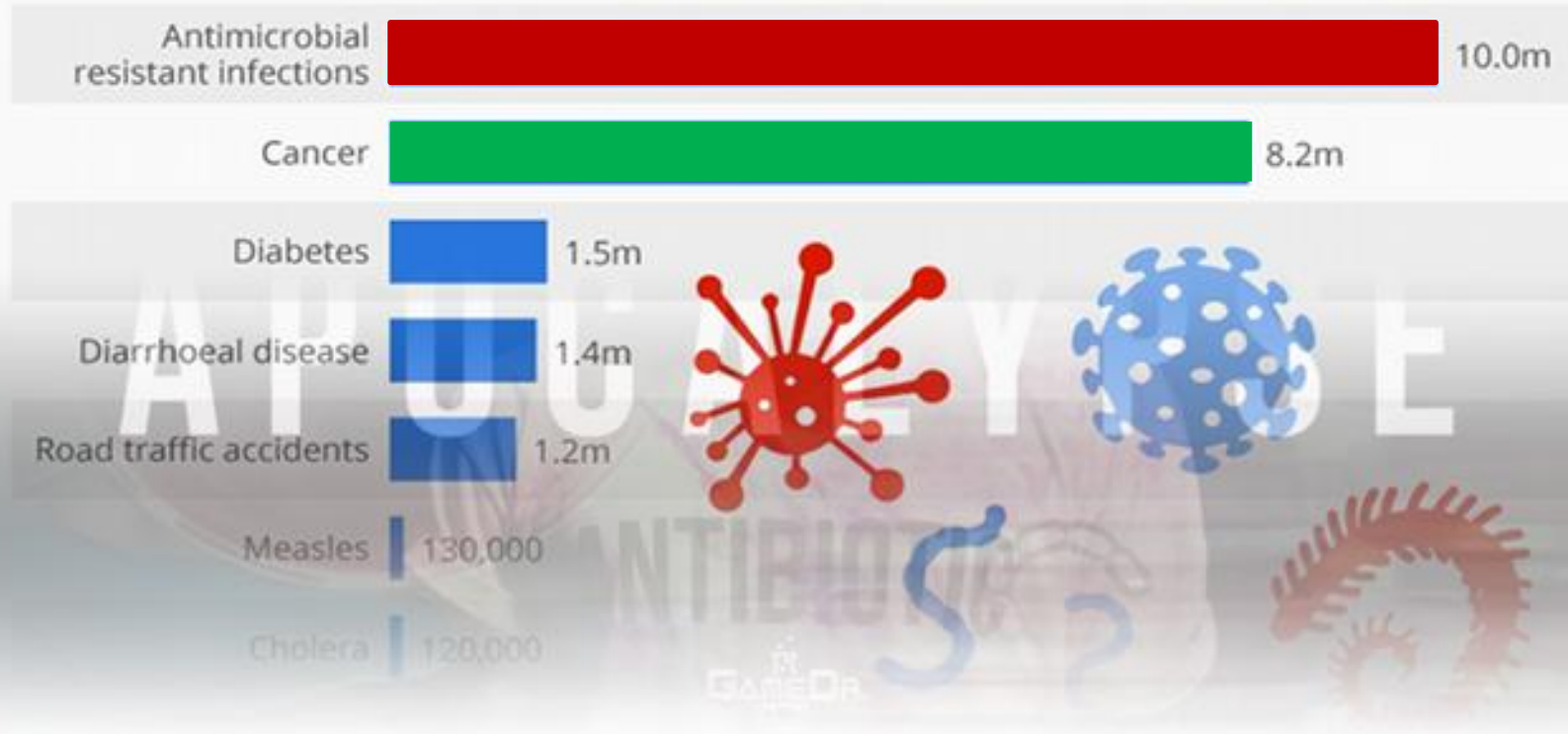
... nad čím v tejto súvislosti premýšľam?
- aký dopad na vývoj bakteriálnej rezistencie bude mať poznanie, že
„ATB sa budú používať ako cytostatika“ ...

Antibiotics that target mitochondria effectively eradicate cancer stem cells, across multiple tumor types: Treating cancer like an infectious disease

Rebecca Lamb^{1,2,*}, Bela Ozsvari^{1,2,*}, Camilla L. Lisanti³, Herbert B. Tanowitz⁴, Anthony Howell^{1,2}, Ubaldo E. Martinez-Outschoorn⁵, Federica Sotgia^{1,2} and Michael P. Lisanti^{1,2}

Deaths From Drug-Resistant Infections Set To Skyrocket

Deaths from antimicrobial resistant infections and other causes in 2050



.. nebude pokles úmrtnosti na rakovinu (z dôvodu využitia ATB ako „cytostatík“) „vykúpený“ vzostupom úmrtnosti na rezistentné bakteriálne kmene ???

Take-home message ...



... v duchu odkazu Alexandra Fleminga



*Nehrajme sa
nezodpovedne
s antibiotikami!*



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NEW ANTIBIOTICS WITH CYTOSTATIC ACTIVITY

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Okrém iného aj preto, že to sú
CYTOSTATIKA



ATB ako cytostatika ... ??

*MUDr. J. Sagan
(Ostrava)*