Antibiotics

Geoffrey A. Cannon: Superbug, Nature's revenge, Why antibiotics can breed disease (published in 1995 by Virgin books) (**Excerpt):**

http://ummafrapp.de/skandal/versch.%20Texte/Cannon_Superbug.pdf

Geoffrey A. Cannon: Superbug Antibiotics A-Z

http://ummafrapp.de/skandal/versch.%20Texte/Antibiotics_A-Z.pdf

Heinrich Kremer: Acquired Iatrogenic Death Syndrome

http://ummafrapp.de/skandal/Acquired%20Iatrogenic%20Death%20Syndrome,%20H.%20Kremer%201996.pdf

When wonder drugs don't work

http://www.keepantibioticsworking.com/library/uploadedfiles/When_Wonder_Drugs_Dont_Work_How_Antibiotic_Res.pdf

Resistance to Antibiotics:

Antimicrobial resistance profiles of enterococci isolated from poultry meat and pasteurized milk in Rio de Janeiro, Brazil

http://www.scielo.br/pdf/mioc/v102n7/5878.pdf

Bacterial Disease and Antimicrobial Susceptibility Patterns in HIV-Infected, Hospitalized Children: A Retrospective Cohort Study

http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=18813340

Spread of Low Fitness Drug resistant Mycobacterium tuberculosis Strain in a Setting of High Human Immunodeficiency Virus Prevalence

http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=2292903&blobtype=pdf

Multiple Mechanisms of Antimicrobial Resistance in *Pseudomonas aeruginosa:* Our Worst Nightmare?

http://www.journals.uchicago.edu/doi/pdf/10.1086/338782

Emergence of High Rates of Antimicrobial Resistance among Viridans Group Streptococci in the United States

http://aac.asm.org/cgi/reprint/40/4/891

New b-Lactamases in Gram-Negative Bacteria: Diversity and Impact on the Selection of Antimicrobial Therapy

http://www.journals.uchicago.edu/doi/pdf/10.1086/319610

Increasing Prevalence of Antimicrobial Resistance Among Uropathogens Causing Acute Uncomplicated Cystitis in Women

http://jama.ama-assn.org/cgi/reprint/281/8/736

Antimicrobial Resistance among *Streptococcus pneumoniae* in the United States: Have We Begun to Turn the Corner on Resistance to Certain Antimicrobial Classes?

http://www.journals.uchicago.edu/doi/pdf/10.1086/430906

High-Level Tetracycline Resistance in Neisseria gonorrhoeae Is Result of Acquisition of Streptococcal tetM Determinant

http://aac.asm.org/cgi/reprint/30/5/664

Widespread Quinolone Resistance among Methicillin-Resistant Staphylococcus aureus Isolates in a General Hospital

http://aac.asm.org/cgi/reprint/33/4/593?view=long&pmid=2729953

Prevention of Resistance: A Goal for Dose Selection for Antimicrobial Agents

http://www.journals.uchicago.edu/doi/pdf/10.1086/344653

Novel Antibiotic Combinations against Infections with Almost Completely Resistant *Pseudomonas aeruginosa* and *Acinetobacter* Species

http://www.journals.uchicago.edu/doi/pdf/10.1086/504486

Clinical evaluation of 12 cases of Antimicrobial Drug induced Pneumonitis

http://www.journalarchive.jst.go.jp/jnlpdf.php?cdjournal=internalmedicine1962&cdvol=29&noissue=3&startpage=248&lang=en&from=jnlabstract

ADVERSE EFFECTS OF ANTIBIOTICS

AMINOGLYCOSIDES

An aminoglycoside antibiotic gentamycin induces oxidative stress reduces antioxydative reserve and reduces spermatogenesis in rats

http://www.jstage.jst.go.jp/article/jts/33/1/85/_pdf

AMINOPENICILLIN

Adverse drug reactions amoxicillin and clavulanit acid

http://jac.oxfordjournals.org/cgi/reprint/60/1/121

ANTIMYCOTICA

Lyosomal Alterations induced in cultured rat fibroblasts by long time exposure to low concentrations of azythromycin.

http://jac.oxfordjournals.org/cgi/reprint/42/6/761

Clarithromycin Inhibits NF-kB Activation in Human Peripheral Blood Mononuclear Cells and Pulmonary Epithelial Cells

http://aac.asm.org/cgi/reprint/45/1/44

BETA-LACTAMES

A Novel _-Lactam Antibiotic Activates Tumor Cell Apoptotic Program by Inducing DNA Damage

http://molpharm.aspetjournals.org/cgi/reprint/61/6/1348

CEPHALOSPORINS

Rapid Detection of the mosaic structure of the Neisseria Gonorrhoeae penAgene which is associated with decreased Susceptibilities to oral Cephalosporins

http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=2395096&blobtype=pdf

Decreased affinity of mosaic-structure recombinant penicillin-binding protein 2 for oral cephalosporins in Neisseria gonorrhoeae

http://jac.oxfordjournals.org/cgi/reprint/60/1/54

GLYCOPEPTIDS

Counterpoint: Vancomycin and *Staphylococcus aureus*—An Antibiotic Enters Obsolescence

http://www.journals.uchicago.edu/doi/pdf/10.1086/518452

MACROLIDES

Macrolide induced clinically relevant drug interactions with Cytochrome P-450A (CYP) 3A4 an update focussed on Claritromycin, azytromycin and diritromycin

http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=2015000&blobtype=pdf

QUINOLONES

Several gene programs are induced in ciprofloxacin-treated human lymphocytes as revealed by microarray analysis

http://www.jleukbio.org/cgi/reprint/74/3/456

Immunomodulatory and Protective Effects of Moxifloxacin against *Candida albicans*-Induced Bronchopneumonia in Mice Injected with Cyclophosphamide

http://aac.asm.org/cgi/reprint/46/8/2442

Immunemodulatory Effects of Ciprofloxacin in TNBS-induced colitis in mice

http://www3.interscience.wiley.com/cgi-bin/fulltext/114091393/PDFSTART

Moxifloxacin but not Ciprofloxacin or Azithromycin selectively inhibits IL-8, IL-6 ERK 1 / 2, JNK, NFK-B activation

http://ajplung.physiology.org/cgi/reprint/292/1/L343

Ciprofloxacin induces an immunemodulatory stress in human T-lymphocytes

http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1479116&blobtype=pdf

Limited effects of Temafloxacin on T-Lymphocyte function

http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=284561&blobtype=pdf

Ciprofloxacin induces an immunomodulatory stress response in human T-lymphocytes

http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=105711&blobtype=pdf

Fluorinated 4-quinolones induce hyperproduction of interleukine 2

http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=287008&blobtype=pdf

TETRACYCLINE

Hepatic Gene Expression Profiling and Lipid Homeostatsis in Mice exposed to Steatogenic Drug Tetracycline

http://toxsci.oxfordjournals.org/cgi/reprint/94/1/206

Tetracycline alters drugs susceptibility in Candida albicans and other pathogenic fungi

http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=2615396&blobtype=pdf

TMPSMX

Acute Lymphoblastic leukemia in Association with long Term exposure to TMPSMX

http://www.indianpediatrics.net/apr2007/311.pdf

Impact of Trimethoprim-Sulfamethoxazole Prophylaxis on Etiology and Susceptibilities of Pathogens Causing Human Immunodeficiency Virus-Associated Bacteremia

http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=127034&blobtype=pdf

Co-trimoxazole red cell aplasia in leukaemia.

http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1778150&blobtype=pdf

Trimethoprim-sulfonamide combination therapy in early pregnancy.

http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=2214286&blobtype=pdf

Acute Lymphoblastic Leukemia in Association with Long Term Exposure to Trimethoprim-Sulfomethaxozole

http://www.indianpediatrics.net/apr2007/311.pdf

Co-trimoxazole induced acute thrombocytopenic purpura

http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1726081&blobtype=pdf

The Effects of Lincomycin-Spectinomycin and Sulfamethoxazole-Trimethoprim on Hyaluronidase Activities and Sperm Characteristics of Rams

http://www.jstage.jst.go.jp/article/jvms/65/7/775/_pdf

Abstracts:

: Rev Infect Dis. 1989 Jul-Aug;11 Suppl 5:S1382-9. Links

New quinolones: in vitro effects as a potential source of clinical toxicity.

Forsgren A, **Bredberg A**, **Riesbeck K**.

Department of Medical Microbiology, University of Lund, Malmö General Hospital, Sweden.

4-Quinolones affect mammalian cellular functions in vitro in several ways. High concentrations inhibit DNA replication, but individual genes are perhaps sensitive to lower concentrations of drug. Inhibition of cell proliferation differs widely among 4-quinolones. Ciprofloxacin and norfloxacin are the most antiproliferative, inhibiting cell growth by approximately 30% at 20 mg/L. Genotoxicity tests with 4-quinolones are probably "false-positive" as a result of increased [3H]thymidine uptake that is not related to DNA damage. Ciprofloxacin at greater than or equal to 10 mg/L causes significant strand breaks in DNA, which seemingly are quickly repaired and do not cause mutations or cancer. Production of immunoglobulin is inhibited by ciprofloxacin at a concentration of 5 mg/L, but production of the growth factor interleukin 2 (IL-2) is increased by 4-quinolones at the same concentration and is hyperinduced at higher concentrations. Thus the effects are very contradictory. Increased production of IL-2 may contribute to central nervous system adverse effects. 4-Quinolones in combination with theophylline or antiinflammatory drugs may inhibit gamma-aminobutyric acid receptor binding and thereby have adverse effects on the central nervous system. Some 4-quinolones induce crystalluria, which may be nephropathic.

J Leukoc Biol. 2003 Sep;74(3):456-63. 

Links

Several gene programs are induced in ciprofloxacin-treated human lymphocytes as revealed by microarray analysis.

Eriksson E, **Forsgren A**, **Riesbeck K**.

Department of Medical Microbiology, Lund University, Malmö University Hospital, Sweden.

Fluoroquinolones have immunomodulatory properties and interfere with cytokine production. The aim of this study was to characterize the extent of the superinduced mRNA levels in activated human lymphocytes incubated with ciprofloxacin (5 and 80 micro g/ml) using a cytokine gene expression microarray from R and D Systems (Abingdon, UK). Several gene transcripts (n=104) were up-regulated in cells treated with ciprofloxacin at 80 micro g/ml, whereas 98 transcripts were down-regulated out of 847 total genes included on the microarray. The increased mRNAs were distributed between major gene programs, including interleukins (36.5%), signal-transduction molecules (13.5%), adhesion molecules (10.6%), tumor necrosis factor and transforming growth factor-beta superfamilies (10.6%), cell-cycle regulators (9.6%), and apoptosis-related molecules (8.7%). To determine the specificity of the microarray, a quantitative reverse transcriptase-polymerase chain reaction (RT-PCR), which contained a panel of 12 different cytokine mRNAs, was used. Eleven out of the 12 gene transcripts were up-regulated in the specific RT-PCR, whereas only eight were found to be increased in the microarray. A microarray from Clontech (Hampshire, UK), containing 588 different genes, was also included. Results obtained with this broad-coverage expression array slightly differed compared with the other

microarray. We conclude that the fluoroquinolone ciprofloxacin at high concentrations interferes with several gene programs, which is in accordance with a mammalian stress response. From a technical point of view, a discrepancy may exist between data obtained by different microarrays and more specific methods such as quantitative RT-PCR.

J Chemother. 2002 Feb;14(1):3-12. Links

Immunomodulating activity of quinolones: review.

Riesbeck K.

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Fluorinated quinolones exert their bactericidal activity by inhibiting bacterial type II topoisomerases. At therapeutic concentrations, quinolones superinduce interleukin-2 (IL-2) and interferon-gamma production by mitogen-activated human peripheral blood T lymphocytes. At the molecular level, a stronger activation of the nuclear factor AP-1 ('activator protein-1') is observed in cells incubated with ciprofloxacin, resulting in enhanced cytokine gene transcription. Several cytokine and immediate early (e.g., c-fos and c-jun) mRNAs are upregulated by ciprofloxacin, possibly reflecting a mammalian stress response. In cultures with murine splenocytes, quinolones enhance IL-3 and granulocyte-macrophage colony stimulating factor (GM-CSF) synthesis. The stimulation of these hematopoietic growth factors prolongs survival of mice with depressed bone marrow and prevents experimental antiphospholipid syndrome (APS). In contrast, quinolones inhibit both human and mouse monocytic IL-1 and TNF-alpha synthesis, an effect that is beneficial in rat experimental type II collagen induced arthritis and LPS-induced septic chock in mice. The intriguing immunomodulatory activities of fluoroquinolones warrant future investigations with new tailored derivatives.

Antimicrob Agents Chemother. 1998 Aug;42(8):1923-30. Final Version FREE aac.asm.org
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Ciprofloxacin induces an immunomodulatory stress response in human T lymphocytes.

Riesbeck K, **Forsgren A**, **Henriksson A**, **Bredberg A**.

Department of Medical Microbiology, Lund University, Malmö University Hospital, S-205 02 Malmö, Sweden. riesbeck@mikrobiol.mas.lu.se

Exposure of cells to adverse environmental conditions invokes a genetically programmed series of events resulting in the induction of specific genes. The fluoroquinolone antibiotic ciprofloxacin has recently been reported to upregulate interleukin-2 (IL-2) gene induction. In the present investigation, the effect of ciprofloxacin at supratherapeutic concentrations on immediate-early (<2 h) gene expression in primary human peripheral blood lymphocytes was studied with Northern blots. In addition, transcriptional activity of IL-2 and metallothionein enhancer and promoter regions and transcription factors AP-1, NF-kappaB, and NF-AT were analyzed by chloramphenicol acetyltransferase (CAT) and electrophoretic mobility shift assays, respectively. The concentration of c-fos, c-jun, c-myc, junB, and fra-1 mRNAs was increased in activated peripheral blood lymphocytes incubated with ciprofloxacin compared to that in untreated controls. Ciprofloxacin increased CAT activity in stimulated lymphocytes transfected with plasmids containing either the IL-2 or metallothionein enhancer. Furthermore, among the transcription factors tested, AP-1 activity was increased in stimulated purified T helper lymphocytes incubated with ciprofloxacin compared to drug-free controls. Taken together, ciprofloxacin increased the levels of immediate-early transcripts, enhanced IL-2 and metallothionein promoter induction, and upregulated AP-1 concentrations in primary lymphocytes, reflecting a program commonly observed in mammalian stress responses.

: Antimicrob Agents Chemother. 1994 Apr;38(4):879-82.

Limited effects of temafloxacin compared with ciprofloxacin on T-lymphocyte function.

Riesbeck K, **Forsgren A**.

Department of Medical Microbiology, Lund University, Malmö General Hospital, Sweden.

Temafloxacin increased interleukin-2 production and mRNA levels and enhanced thymidine incorporation in stimulated lymphocyte cultures. Gamma interferon mRNA levels were unaffected. Temafloxacin also stimulated interleukin-2 gene induction, as revealed in a chloramphenicol acetyltransferase reporter gene system. However, temafloxacin exerted significantly weaker effects in these respects than did ciprofloxacin.

1: Proc Natl Acad Sci U S A. 1989 Apr;86(8):2809-13.

Fluorinated 4-quinolones induce hyperproduction of interleukin 2.

Riesbeck K, **Andersson J**, **Gullberg M**, **Forsgren A**.

Department of Medical Microbiology, University of Lund, Malmö General Hospital, Sweden.

The fluorinated 4-quinolones are a "new" group of antibiotics with a broad antibacterial spectrum. They are already widely used in clinical practice. Previous studies have shown that these drugs increase the uptake of [3H]thymidine into DNA of mitogen-stimulated lymphocytes but inhibit cell growth and immunoglobulin secretion. This study shows that the 4-quinolones strongly (up to 100 times) increase the recovery of interleukin 2 (IL-2) in culture supernatants of phytohemagglutinin (PHA)-stimulated normal human lymphocytes and also prolong the kinetics of IL-2 production. The effect was significant at clinically achievable concentrations (5 micrograms/ml). In addition to hyperproduction of IL-2, the level of RNA hybridizing with a human IL-2 cDNA probe was also intensely elevated (16-32 times) in PHA-stimulated lymphocytes cultured with ciprofloxacin (80 micrograms/ml). The mechanism responsible for 4-quinolone-mediated effects on T cells is at present unclear, but evidence is presented that suggests the effect is not exerted at the level of protein kinase C activation. Ciprofloxacin at 80 micrograms/ml also decreased the expression of IL-2 receptors measured by immunofluorescence with CD 25 antibodies and a radiolabeled IL-2 binding assay. At the same concentration of ciprofloxacin, there was a very low expression of the transferrin receptor and the cell size increased very little in human lymphocytes after PHA stimulation. The enhanced IL-2 production by 4-quinolones may contribute to side effects reported when these drugs are used for treatment of patients.

1: Eur J Clin Invest. 2006 Oct;36(10):671-3. FULL TEXT AVAILABLE ONLINE WILEY InterScience Links
Comment on:
Eur J Clin Invest. 2006 Oct;36(10):720-9.

Immunomodulation by fluoroquinolones and other antibacterial agents.

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Hyperactivity of cathepsin B and other lysosomal enzymes in fibroblasts exposed to azithromycin, a dicationic macrolide antibiotic with exceptional tissue accumulation.

Gerbaux C, **Van Bambeke F**, **Montenez JP**, **Piret J**, **Morlighem G**, **Tulkens PM**.

Unité de Pharmacologie Cellulaire et Moléculaire, Université Catholique de Louvain, Bruxelles, Belgium. gerbaux@facm.ucl.ac.be

Azithromycin accumulates in lysosomes where it causes phospholipidosis. In homogenates prepared by sonication of fibroblasts incubated for 3 days with azithromycin (66 microM), the activities of sulfatase A, phospholipase A1, N-acetyl-beta-hexosaminidase and cathepsin B increased from 180 to 330%, but not those of 3 non-lysosomal enzymes. The level of cathepsin B mRNA was unaffected. The hyperactivity induced by azithromycin is non-reversible upon drug withdrawal, prevented by coincubation with cycloheximide, affects the Vmax but not the Km, and is not reproduced with gentamicin, another drug also causing lysosomal phospholipidosis. The data therefore suggest that azithromycin increases the level of lysosomal enzymes by a mechanism distinct from the stimulation of gene expression but requiring protein synthesis, and is not in direct relation to the lysosomal phospholipidosis.

1: J Antimicrob Chemother. 1998 Dec;42(6):761-7.

Lysosomal alterations induced in cultured rat fibroblasts by long-term exposure to low concentrations of azithromycin.

Van Bambeke F, **Gerbaux C**, **Michot JM**, **d'Yvoire MB**, **Montenez JP**, **Tulkens PM**.

Unité de Pharmacologie Cellulaire et Moléculaire, Uinversité Catholique de Louvain, Brussels, Belgium. vanbambeke@facm.ucl.ac.be

Computer-aided simulations suggest that the doses and schedules of administration of azithromycin proposed in treatment and prophylaxis of Mycobacterium avium complex (MAC) in AIDS patients will result in drug concentrations in serum and extracellular fluids remaining for sustained periods of time in the 0.03-0.1 mg/L range. We exposed cultured rat embryo fibroblasts to these concentrations (and multiples up to 20 mg/L) for up to 16 days. Electron microscopy showed that after 7 days' incubation in 0.03 mg/L azithromycin, there was conspicuous accumulation of osmiophilic, lamellar structures (myeloid bodies) in lysosomes, suggesting the onset of a phospholipidosis. Assay of total cell phospholipids and cholesterol showed significant increases in cells exposed to > or = 1 to 5 mg/L of azithromycin in association with hyperactivity of the lysosomal enzyme cathepsin B. The data suggest that azithromycin, at extracellular concentrations pertinent to its use for MAC treatment, and perhaps also prophylaxis, causes limited morphological alterations of the lysosomes in cultured cells which are of the same nature as those developing rapidly and extensively at higher concentrations.

1: J Orthop Res. 2001 Sep;19(5):950-4.

1: Toxicol Appl Pharmacol. 1999 Apr 15;156(2):129-40. ELSEVIER FULL-TEXT ARTICLE Links

Interactions of macrolide antibiotics (Erythromycin A, roxithromycin, erythromycylamine [Dirithromycin], and azithromycin) with phospholipids: computer-aided conformational analysis and studies on acellular and cell culture models.

Montenez JP, **Van Bambeke F**, **Piret J**, **Brasseur R**, **Tulkens PM**, **Mingeot-Leclercq MP**.

Unité de Pharmacologie Cellulaire et Moléculaire, Université Catholique de Louvain, Brussels, B-1200, Belgium.

The potential of 14/15 membered macrolides to cause phospholipidosis has been prospectively assessed, and structure-effects examined, using combined experimental and conformational approaches. Biochemical studies demonstrated drug binding to phosphatidylinositol-containing liposomes and inhibition of the activity of lysosomal phospholipase A1 toward phosphatidylcholine included in the bilayer, in close correlation with the number of cationic groups carried by the drugs (erythromycin A </= roxithromycin < erythromycylamine </= azithromycin). In cultured cells (fibroblasts), phospholipidosis (affecting all major phospholipids except sphingomyelin) was observed after 3 days with the following ranking: erythromycin A </= roxithromycin < erythromycylamine < azithromycin (roxithromycin could, however, not be studied in detail due to intrinsic toxicity). The difference between erythromycylamine and azithromycin was accounted for by the lower cellular accumulation of erythromycylamine. In parallel, based on a methodology developed and validated to study drug-membrane interactions, the conformational analyses revealed that erythromycin A, roxithromycin, erythromycylamine, and azithromycin penetrate into the hydrophobic domain of a phosphatidylinositol monolayer through their desosamine and cladinose moieties, whereas their macrocycle is found close to the interface. This position allows the aminogroups carried by the macrocycle of the diaminated macrolides (erythromycylamine and azithromycin) to come into close contact with the negatively charged phosphogroup of phosphatidylinositol, whereas the amine located on the C-3 of the desosamine, common to all four drugs, is located at a greater distance from this phosphogroup. Our study suggests that all macrolides have the potential to cause phospholipidosis but that this effect is modulated by toxicodynamic and toxicokinetic parameters related to the drug structure and mainly to their cationic character.

Toxic effect of rifampicin on human osteoblast-like cells.

Isefuku S, **Joyner CJ**, **Simpson AH**.

Nuffield Department of Orthopaedic Surgery, Nuffield Orthopaedic Centre, Headlington, Oxford, UK.

We examined the effects of rifampicin on osteoblast-like cells derived from adult human bone in vitro. Cancellous bone was collected from five different individuals during elective orthopaedic operations and cultured in antibiotic-free media. Total DNA, 3H-thymidine incorporation and alkaline phosphatase (ALP) activity were measured after the cells were cultured for 4 days in media containing concentrations of rifampicin ranging from 0 to 1000 microg/ml. Mean total DNA was decreased at concentrations of 10 microg/ml and above in the cultures obtained from four out of five individuals but these decreases were significant in the cultures from only two individuals. 3H-thymidine incorporation, a more sensitive indicator of change in cell proliferation, and ALP activity were significantly decreased ($P < 0.05$) in all of the cultures containing 3 and 7 microg/ml, respectively. In the clinical setting, serum concentrations of rifampicin often exceed 10 microg/ml after systemic administration. The present study has shown that rifampicin, at these concentrations, can inhibit the proliferation of osteoblast-like cells in vitro. Further studies should be carried out to assess whether rifampicin is detrimental to the bone repair process in vivo.

1: Curr Top Med Chem. 2003;3(9):1021-42.

1: J Orthop Trauma. 2003 Mar;17(3):212-6.

Gentamicin may have an adverse effect on osteogenesis.

Isefuku S, **Joyner CJ**, **Simpson AH**.

Nuffield Department of Orthopaedic Surgery, University of Oxford, Headington, England, United Kingdom.

OBJECTIVE: To investigate the toxic effect of gentamicin at the high concentrations that can be achieved by local administration in the management of bone infection. DESIGN: Randomized, prospective study in cultured cells, with drug exposure duration of 4 days. SETTING: Cell culture in Dulbecco's modification of Eagle's minimal essential medium with supplements at 37 degrees C in air:CO2 (v:v, 95:5). MATERIALS: Human osteoblastlike cells derived from cancellous bone collected from four adult patients without systemic disease during total hip replacement were cultured in antibiotic-free medium for 4 weeks. INTERVENTION: The cultured cells were exposed to media containing various concentrations of gentamicin (0-1000 microg/mL) for 4 days. MAIN OUTCOME MEASUREMENTS: Alkaline phosphatase activity, total DNA, and 3H-thymidine incorporation. RESULT: Alkaline phosphatase activity was significantly decreased ($p < 0.05$) in all of the cultures at gentamicin concentrations of 100 microg/mL and above. 3H-thymidine incorporation was also decreased ($p < 0.05$) in three out of four cultures at 100 microg/mL and above. Total DNA was significantly decreased ($p < 0.05$) at 700 microg/mL and above. CONCLUSION: Gentamicin, at high concentrations, as achieved following topical application, inhibits cell proliferation in vitro and, therefore, may be detrimental to the repair process in vivo.

Oxazolidinone antibacterial agents: a critical review.

Hutchinson DK.

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This review covers recent developments in several important aspects of research on oxazolidinone antibacterial agents. Structure-activity relationships are first discussed, emphasizing bioisosteric replacements for the both the oxazolidinone ring and the N-acetylaminomethyl group at C-5. The oxazolidinones have a mechanism of action that is distinct from other antibacterial agents, whereby protein synthesis is inhibited prior to initiation. Studies aimed at determining how the oxazolidinones bind to the bacterial ribosome and interfere with peptidyl transferase activity are described in detail, and are then related to the nature of the changes in the ribosomal RNA leading to resistance. Toxicity of the oxazolidinones remains a critical issue, in that early lead compounds exhibited lethal toxicity in animal studies. Preclinical and clinical safety studies of both eperezolid and linezolid are summarized, giving emphasis to histopathological effects observed in early animal studies. These studies are then related to thrombocytopenia and pancytopenia observed in patients treated with linezolid for extended time periods. Finally, studies to determine the nature and potential severity of drug-drug interactions in patients undergoing linezolid therapy are discussed.

: Behav Brain Res. 2009 Jan 23;196(2):168-79. Epub 2008 Oct 11.  Links

Minocycline and neurodegenerative diseases.

Kim HS, **Suh YH**.

Department of Pharmacology, Seoul National University, College of Medicine, Seoul, Republic of Korea.

Minocycline is a semi-synthetic, second-generation tetracycline analog which is effectively crossing the blood-brain barrier, effective against gram-positive and -negative infections. In addition to its own antimicrobacterial properties, minocycline has been reported to exert neuroprotective effects over various experimental models such as cerebral ischemia, traumatic brain injury, amyotrophic lateral sclerosis, Parkinson's disease, kainic acid treatment, Huntington' disease and multiple sclerosis. Minocycline has been focused as a neuroprotective agent over neurodegenerative disease since it has been first reported that minocycline has neuroprotective effects in animal models of ischemic injury [Yrjanheikki J, Keinanen R, Pellikka M, Hokfelt T, Koisinaho J. Tetracyclines inhibit microglial activation and are neuroprotective in global brain ischemia. Proc Natl Acad Sci USA 1998;95:15769-74; Yrjanheikki J, Tikka T, Keinanen R, Goldsteins G, Chan PH, Koistinaho J. A tetracycline derivative, minocycline, reduces inflammation and protects against focal cerebral ischemia with a wide therapeutic window. Proc Natl Acad Sci USA 1999;96:13496-500]. Recently, the effect of minocycline on Alzheimer's disease has been also reported. Although its precise primary target is not clear, the action mechanisms of minocycline for

neuroprotection reported so far are; via; the inhibition of mitochondrial permeability-transition mediated cytochrome c release from mitochondria, the inhibition of caspase-1 and -3 expressions, and the suppression of microglial activation, involvement in some signaling pathways, metalloprotease activity inhibition. Because of the high tolerance and the excellent penetration into the brain, minocycline has been clinically tried for some neurodegenerative diseases such as stroke, multiple sclerosis, spinal cord injury, amyotropic lateral sclerosis, Hungtington's disease and Parkinson's disease. This review will briefly summarize the effects and action mechanisms of minocycline on neurodegenerative diseases.

1: Science. 2008 Aug 29;321(5893):1203-6. Links

Redox-active antibiotics control gene expression and community behavior in divergent bacteria.

Dietrich LE, **Teal TK**, **Price-Whelan A**, **Newman DK**.

Department of Biology, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 01239, USA.

It is thought that bacteria excrete redox-active pigments as antibiotics to inhibit competitors. In Pseudomonas aeruginosa, the endogenous antibiotic pyocyanin activates SoxR, a transcription factor conserved in Proteo- and Actinobacteria. In Escherichia coli, SoxR regulates the superoxide stress response. Bioinformatic analysis coupled with gene expression studies in P. aeruginosa and Streptomyces coelicolor revealed that the majority of SoxR regulons in bacteria lack the genes required for stress responses, despite the fact that many of these organisms still produce redox-active small molecules, which indicates that redox-active pigments play a role independent of oxidative stress. These compounds had profound effects on the structural organization of colony biofilms in both P. aeruginosa and S. coelicolor, which shows that "secondary metabolites" play important conserved roles in gene expression and development.

PMID: 18755976 [PubMed - indexed for MEDLINE]

1: Exp Toxicol Pathol. 2008 Jun;60(1):77-85. Epub 2008 Apr 11. Links

Tetracycline-induced reproductive toxicity in male rats: effects of vitamin C and N-acetylcysteine.

Farombi EO, **Ugwuezunmba MC**, **Ezenwadu TT**, **Oyeyemi MO**, **Ekor M**.

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Tetracycline, a broad-spectrum antibiotic employed clinically in the treatment of bacteria infections, is known to cause a number of biochemical dysfunctions and

suspected to induce testicular damage to animals and humans, but there is paucity of data on its effect and mechanism of action on the male reproductive system. The present study therefore evaluates its spermatotoxic and testicular toxicity in male rats and the chemoprotective effects of Vitamin C (Vit C) and N-acetylcysteine (NAC). Tetracycline was administered orally at the dose level of 28.6 mg/kg body weight per day in two equal divided doses (12h interval). Vit C and NAC were also administered orally to the rats at doses of 200 and 50 mg/kg body weight per day, respectively, for the 14 days of the experiment. While there was no change in the body weights of rats, tetracycline administration caused significant decrease in the relative weights of testis, epididymis and seminal vesicles ($P<0.05$). Administration of tetracycline caused a reduction in the epididymal sperm motility, percentage of live spermatozoa, sperm count, and an increase in abnormal sperm morphology, as well as induction of adverse histopathologic changes in the testes. While Vit C and NAC significantly mitigated the toxic effect of tetracycline on sperm parameters, the antioxidants did not improve the adverse histopathologic changes induced by antibiotic. Treatment of rats with tetracycline significantly decreased the activities of superoxide dismutase, catalase (CAT), glucose-6-phosphate dehydrogenase, glutathione-S-transferase (GST) and the levels of GSH and serum testosterone, while the activity of gamma-glutamyltranspeptidase and the formation of malondialdehyde (MDA) increased. Both Vit C and NAC significantly attenuated the toxic effects of tetracycline to the antioxidant and testicular marker enzymes as well as markers of oxidative stress. Collectively, the results suggest that therapeutic dose of tetracycline elicits spermatotoxic and testicular toxicity in male rats through induction of oxidative stress. The chemoprotective effects of Vit C and NAC during tetracycline treatment suggest that these antioxidants may find clinical application in cellular damage involving reactive oxygen species (ROS).

J Toxicol Sci. 2008 Feb;33(1):85-96.

An aminoglycoside antibiotic gentamycin induces oxidative stress, reduces antioxidant reserve and impairs spermatogenesis in rats.

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Gentamycin (GS) is an aminoglycoside antibiotic used to treat infections of various Gram-negative organisms. The present study was designed to investigate the effects of GS on oxidative stress, antioxidant levels, testicular structure and sperm parameters in the rat. Adult Wistar rats (12 week old; N=7/group) were treated (i. p.) with 0 mg/kg, 3 mg/kg and 5 mg/kg for 10 days at an interval of 24 hr between subsequent treatments. Animals were sacrificed on days 1 and 35 after the last treatment, and the reproductive organs were removed and weights of testis and seminal vesicle were recorded. The right testis was processed for light microscopic analysis. The left testis was homogenized and step 19 spermatids were counted to determine the daily sperm production (DSP) and daily abnormal sperm production (DASP). The sperm count, sperm motility and incidence of abnormal sperms were

estimated in the epididymis. In testicular sections, along with the evaluation of qualitative changes, the seminiferous tubule diameter (STD) and the epithelial height (SE) were measured. The incidence of stage XIV tubules in testicular sections, meiotic figures and step 14 spermatids/stage XIV tubule, and step 19 spermatids/stage VII tubule were estimated. Intra-testicular levels of superoxide anion, lipid peroxidation and antioxidants-superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx) and ascorbic acid were measured. GS did not affect the body weight, but the testis weight and DSP were decreased at 5 mg/kg dose-level on both days ($p<0.05$), and the weight of seminal vesicle decreased on day 35 at both dose-levels. The DASP was increased in a dose-dependent manner ($p<0.05$) on days 1 and 35 at both dose-levels. The sperm count was decreased at both dose-levels on day 35, whereas the sperm motility was decreased and sperm abnormality was increased on day 1 at 5 mg/kg and on day 35 at both dose-levels. GS induced structural changes such as sloughing of seminiferous epithelium, vacuoles and gaps in the epithelium, nuclear pyknosis and atrophic changes in a few tubules. The tubular shrinkage was observed as indicated by decreased STD and SE on both days at 5 mg/kg dose-level. Incidence of stage XIV tubules and step 19 spermatids/stage VII tubule decreased on all time points at all dose-levels, whereas the step 14 spermatids and meiotic figures decreased on day 35 at both dose-levels ($p<0.05$). The free radical- superoxide anion concentration was significantly increased on day 1 in a dose-dependent pattern ($p<0.05$). However, activities of all 3 enzymatic antioxidants and ascorbic acid level decreased in a dose-dependent pattern on day 1 ($p<0.05$), except the GPx, which was also decreased on day 35 at 5 mg/kg dose-level. There was a significant rise in the thiobarbituric acid reactive substances on day 1 indicating increased lipid peroxidation in the testis. In conclusion, GS induces an oxidative stress-status in the testis by increasing free radical formation and lipid peroxidation, and by decreasing the antioxidant reserves. These biochemical changes manifest as structural and cytotoxic changes in the testis. Further, GS also affects the spermatozoa by affecting their number, motility and morphology.

J Econ Entomol. 2007 Oct;100(5):1533-41. Links

Penicillin-induced oxidative stress: effects on antioxidative response of midgut tissues in instars of Galleria mellonella.

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Penicillin and other antibiotics are routinely incorporated in insect culture media. Although culturing insects in the presence of antibiotics is a decades-old practice, antibiotics can exert deleterious influences on insects. In this article, we test the hypothesis that one of the effects of dietary penicillin is to increase oxidative stress on insects. The effects of penicillin on midgut concentrations of the oxidative stress indicator malondialdehyde (MDA) and on midgut antioxidant enzyme (superoxide dismutase [SOD], catalase [CAT], glutathione S-transferase [GST], and glutathione peroxidase [GPx]) and transaminases (alanine aminotransferase and aspartate aminotransferase) activities in greater wax moth, Galleria mellonella (L.), were

investigated. The insects were reared from first instars on artificial diets containing 0.001, 0.01, 0.1, or 1.0 g penicillin per 100 g of diets. MDA content was significantly increased in the midgut tissues of each larval instar reared in the presence of high penicillin concentrations. Activities of antioxidant and transaminase enzymes did not show a consistent pattern with respect to penicillin concentrations in diet or age of larvae. Despite the increased penicillin-induced oxidative stress in gut tissue, antioxidant and transaminase enzymes did not correlate with oxidative stress level or between each other in larvae of other age stages except for the seventh instar. We found a significant negative correlation of MDA content with SOD and GST activities in seventh instars. SOD activity was also negatively correlated with CAT activity in seventh instars. These results suggest that exposure to dietary penicillin resulted in impaired enzymatic antioxidant defense capacity and metabolic functions in wax moth larval midgut tissues and that the resulting oxidative stress impacts midgut digestive physiology.

Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labour: 7-year follow-up of the ORACLE II trial.

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BACKGROUND: The ORACLE II trial compared the use of erythromycin and/or amoxicillin-clavulanate (co-amoxiclav) with that of placebo for women in spontaneous preterm labour and intact membranes, without overt signs of clinical infection, by use of a factorial randomised design. The aim of the present study--the ORACLE Children Study II--was to determine the long-term effects on children after exposure to antibiotics in this clinical situation. METHODS: We assessed children at age 7 years born to the 4221 women who had completed the ORACLE II study and who were eligible for follow-up with a structured parental questionnaire to assess the child's health status. Functional impairment was defined as the presence of any level of functional impairment (severe, moderate, or mild) derived from the mark III Multi-Attribute Health Status classification system. Educational outcomes were assessed with national curriculum test results for children resident in England. FINDINGS: Outcome was determined for 3196 (71%) eligible children. Overall, a greater proportion of children whose mothers had been prescribed erythromycin, with or without co-amoxiclav, had any functional impairment than did those whose mothers had received no erythromycin (658 [42.3%] of 1554 children vs 574 [38.3%] of 1498; odds ratio 1.18, 95% CI 1.02-1.37). Co-amoxiclav (with or without erythromycin) had no effect on the proportion of children with any functional impairment, compared with receipt of no co-amoxiclav (624 [40.7%] of 1523 vs 608 [40.0%] of 1520; 1.03, 0.89-1.19). No effects were seen with either antibiotic on the number of deaths, other medical conditions, behavioural patterns, or educational attainment. However, more children whose mothers had received erythromycin or co-amoxiclav developed cerebral palsy than did those born to mothers who received no erythromycin or no co-amoxiclav, respectively (erythromycin: 53 [3.3%] of 1611 vs 27 [1.7%] of 1562, 1.93,

1.21-3.09; co-amoxiclav: 50 [3.2%] of 1587 vs 30 [1.9%] of 1586, 1.69, 1.07-2.67). The number needed to harm with erythromycin was 64 (95% CI 37-209) and with co-amoxiclav 79 (42-591). INTERPRETATION: The prescription of erythromycin for women in spontaneous preterm labour with intact membranes was associated with an increase in functional impairment among their children at 7 years of age. The risk of cerebral palsy was increased by either antibiotic, although the overall risk of this condition was low. FUNDING: UK Medical Research Council.

1: Life Sci. 2008 Aug 1;83(5-6):155-63. Epub 2008 Jun 18. ELSEVIER FULL-TEXT ARTICLE Links

Dapsone induces oxidative stress and impairs antioxidant defenses in rat liver.

Veggi LM, **Pretto L**, **Ochoa EJ**, **Catania VA**, **Luquita MG**, **Taborda DR**, **Sánchez Pozzi EJ**, **Ikushiro S**, **Coleman MD**, **Roma MG**, **Mottino AD**.

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Dapsone (DDS) is currently used in the treatment of leprosy, malaria and in infections with Pneumocystis jirovecii and Toxoplasma gondii in AIDS patients. Adverse effects of DDS involve methemoglobinemia and hemolysis and, to a lower extent, liver damage, though the mechanism is poorly characterized. We evaluated the effect of DDS administration to male and female rats (30 mg/kg body wt, twice a day, for 4 days) on liver oxidative stress through assessment of biliary output and liver content of reduced (GSH) and oxidized (GSSG) glutathione, lipid peroxidation, and expression/activities of the main antioxidant enzymes glutathione peroxidase, superoxide dismutase, catalase and glutathione S-transferase. The influence of DDS treatment on expression/activity of the main DDS phase-II-metabolizing system, UDP-glucuronosyltransferase (UGT), was additionally evaluated. The involvement of dapsone hydroxylamine (DDS-NHOH) generation in these processes was estimated by comparing the data in male and female rats since N-hydroxylation of DDS mainly occurs in males. Our studies revealed an increase in the GSSG/GSH biliary output ratio, a sensitive indicator of oxidative stress, and in lipid peroxidation, in male but not in female rats treated with DDS. The activity of all antioxidant enzymes was significantly impaired by DDS treatment also in male rats, whereas UGT activity was not affected in any sex. Taken together, the evidence indicates that DDS induces oxidative stress in rat liver and that N-hydroxylation of DDS was the likely mediator. Impairment in the activity of enzymatic antioxidant systems, also associated with DDS-NHOH formation, constituted a key aggravating factor.

Clin Pharmacol Ther. 2004 Oct;76(4):313-22. npg nature publishing group Links

The effect of clarithromycin, fluconazole, and rifabutin on sulfamethoxazole hydroxylamine formation in individuals with human immunodeficiency virus infection (AACTG 283).

Winter HR, **Trapnell CB**, **Slattery JT**, **Jacobson M**, **Greenspan DL**, **Hooton TM**, **Unadkat JD**.

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BACKGROUND: Sulfamethoxazole hydroxylamine formation, in combination with long-term oxidative stress, is thought to be the cause of high rates of adverse drug reactions to sulfamethoxazole in human immunodeficiency virus (HIV)-infected subjects. Therefore the goal of this study was to determine the effect of fluconazole, clarithromycin, and rifabutin on sulfamethoxazole hydroxylamine formation in individuals with HIV-1 infection. METHODS: HIV-1-infected subjects (CD4 + count >/=200 cells/mm 3) were enrolled in a 2-part (A and B), open-label drug interaction study (Adult AIDS Clinical Trial Group [AACTG] 283). In part A (n = 9), subjects received cotrimoxazole (1 tablet of 800 mg sulfamethoxazole/160 mg trimethoprim daily) alone for 2 weeks and then, in a randomly assigned order, cotrimoxazole plus either fluconazole (200 mg daily), rifabutin (300 mg daily), or fluconazole plus rifabutin, each for a 2-week period. Part B (n = 12) was identical to part A except that clarithromycin (500 mg twice daily) was substituted for rifabutin. RESULTS: In part A, fluconazole decreased the area under the plasma concentration-time curve (AUC), percent of dose excreted in 24-hour urine, and formation clearance (CL f) of the hydroxylamine by 37%, 53%, and 61%, respectively (paired t test, P < .05). Rifabutin increased the AUC, percent excreted, and CL f of the hydroxylamine by 55%, 45%, and 53%, respectively (P < .05). Fluconazole plus rifabutin decreased the AUC, percent excreted, and CL f of the hydroxylamine by 21%, 37%, and 46%, respectively (P < .05). In part B the fluconazole data were similar to those of part A. Overall, clarithromycin had no effect on hydroxylamine production. CONCLUSIONS: If the exposure (AUC) to sulfamethoxazole hydroxylamine is predictive of sulfamethoxazole toxicity, then rifabutin will increase and clarithromycin plus fluconazole or rifabutin plus fluconazole will decrease the rates of adverse reactions to sulfamethoxazole in HIV-infected subjects.

PMID: 15470330 [PubMed - indexed for MEDLINE]

Lakartidningen. 2004 Jul 8;101(28-29):2332-5. Links

[Increasing incidence of ciprofloxacin resistant gonorrhea in Sweden. Choose a correct antibiotic and follow up the treatment!]

[Article in Swedish]

Berglund T, **Colucci B**, **Lund B**, **Qvarnström I**, **Sandström E**.

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The incidence of gonorrhoea has increased in Sweden and is now three times higher than in the middle of the 1990's. A remarkable increase of ciprofloxacin resistant

gonorrhoea has been reported in Stockholm and other parts of Sweden during 2003. Among men attending a clinic for homosexual men in Stockholm the ciprofloxacin resistant cases have increased from a low level to over 50% during the last year. Most of the homosexual men are exposed in Stockholm and one serotype is dominant. Also in the county of Gävleborg there has been an outbreak of ciprofloxacin resistant gonorrhoea among young heterosexual men and women. No resistance to cefixime, ceftriaxone and spectinomycin has been noted and these antibiotics are then a better first choice of treatment in a Swedish context.

1: J Vet Med Sci. 2003 Jul;65(7):775-80. Links

The effects of lincomycin-spectinomycin and sulfamethoxazole-trimethoprim on hyaluronidase activities and sperm characteristics of rams.

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The effects of lincomycin-spectinomycin and sulfamethoxazole-trimethoprim combinations on the hyaluronidase enzyme of serum and semen and on sperm characteristics in rams were determined. Thirthy-two Akkaraman rams were used. The rams were randomly divided into four groups. Group A and group B were determined as control groups of group C (lincomycin-spectinomycin) and D (sulfamethoxazole-trimethoprim), respectively. Combinations of lincomycin-spectinomycin and sulfamethoxazole-trimethoprim were administered at doses of 15 mg.kg(-1) intramuscularly and 12 mg.kg(-1) body weights orally, respectively. Blood and semen samples were collected at 4, 12, 24, 48, 72, 192 and 384 hr. Semen hyaluronidase activities of rams in group C increased significantly ($p<0.001$, <0.05) compared with the control group at 24 and 48 hr, respectively. Semen hyaluronidase activities in group D rams also increased significantly ($p<0.001$) in comparison with the control group at all times except 72 and 384 hr. Serum hyaluronidase activities increased significantly ($p<0.01$, <0.001) at 24 and 48 hr after treatment of lincomycin-spectinomycin. Additionally, significant ($p<0.05$, <0.001) increases were detected in the serum hyaluronidase activities of group D at 48 and 72 hr, respectively. No significant correlation was found between serum and semen hyaluronidase activities. Furthermore, significant increases ($p<0.05$) were observed in the percentages of motile sperm in the rams of group C and D compared with the control groups. The values of sperm concentration and total number of sperm in group C and D rams decreased significantly ($p<0.001$) in comparison with control groups. No significant correlations were found between the semen hyaluronidase activities and sperm characteristics. In conclusion, these findings show that the combinations of lincomycin-spectinomycin and sulfamethoxazole-trimethoprim do not have any harmful effects on hyaluronidase activities and sperm motility. However, the use of both antibiotic combinations in breeding rams during the ramming season is not advisable due to the decrease of sperm concentration.

1: Sex Transm Dis. 1988 Oct-Dec;15(4):234-43. Links

Therapy of uncomplicated gonorrhea due to antibiotic-resistant Neisseria gonorrhoeae.

Kraus SJ, **Reynolds GH**, **Rolfs RT Jr**.

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Antibiotics available to treat uncomplicated anogenital infections due to beta-lactamase-producing Neisseria gonorrhoeae include spectinomycin, ceftriaxone, and clavulanic acid added to aqueous procaine penicillin G or amoxicillin. Important variables in deciding which antibiotic regimen to use include effectiveness against urethral, cervical, pharyngeal, and rectal infections; cost; eradication of coexisting incubating syphilis; adverse effects; efficacy against strains of N. gonorrhoeae with chromosomally mediated resistance to antimicrobial agents; ease of administration; patient acceptance; and the potential for inducing resistance to antimicrobial agents in pathogens other than those causing sexually transmitted diseases. This review outlines the advantages and disadvantages of the various regimens.

Ann Intern Med. 1985 Jul;103(1):70-8. Links

Cefamandole and cefoxitin.

Sanders CV, **Greenberg RN**, **Marier RL**.

Cefamandole and cefoxitin, introduced only 7 years ago, are now the most commonly prescribed parenteral antibiotics in the United States. These drugs are similar to the first-generation cephalosporins in toxicity, but their in-vitro spectrum of activity is greater. Their serum half-lives are longer than those of cephalothin and cephapirin but shorter than that of cefazolin. Although cefamandole has been recommended in empiric therapy for patients with community-acquired pneumonia and as a prophylactic agent for patients having various surgical procedures, other regimens are less expensive and just as effective. Cefamandole should not be used to treat intra-abdominal, enterobacter, or ampicillin-resistant Haemophilus influenzae infections. Cefoxitin is effective in the treatment and prevention of mixed aerobic-anaerobic skin and soft-tissue, intra-abdominal, gynecologic, and penicillinase-producing, spectinomycin-resistant Neisseria gonorrhoeae infections. Cefoxitin represents a greater advance than cefamandole in our continuing search for safe and more effective antimicrobial agents.

Coll Antropol. 2008 Sep;32(3):919-25. Links

Teratogenicity of antibacterial agents.

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The aim of our study was to study the possible correlation between use of antibacterial drugs in pregnancy and occurrence of congenital malformations. Among 6099 investigated pregnant women, 392 (6.43%) used antibacterial drugs. The most frequently used antibacterials belonged to category B (75.77%), while 14.54% antibiotics belonged to category D and 1.02% to category X. The most often used antibiotics were cephalexin (22.19%), amoxicillin (20.66%) and ampicillin (14.29%). In 14 embryos exposed to effects of beta-lactams in utero, malformations were detected. The results of this study show possible teratogenic potential even with those antibacterials which are considered safe, but as those are usually minor malformations, they often pass undetected. Because of that and because of frequent use of antibacterials during pregnancy, detailed examinations concerning their safety should be made.

1: Lancet Infect Dis. 2008 Sep;8(9):543-52.  Links

Comparison of antibiotics with placebo for treatment of acute sinusitis: a meta-analysis of randomised controlled trials.

Falagas ME, **Giannopoulou KP**, **Vardakas KZ**, **Dimopoulos G**, **Karageorgopoulos DE**.

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We did a meta-analysis of randomised controlled trials (RCTs) to assess the therapeutic role of antibiotics for acute sinusitis compared with placebo. Eligible studies were retrieved from PubMed and Scopus. 17 double-blind RCTs were included (three involving children). Acute sinusitis was diagnosed with clinical criteria in nine RCTs, imaging studies in six RCTs, and microbiological or laboratory methods in two RCTs. Amoxicillin was used in ten of 23 antibiotic treatment groups. To account for potential statistical heterogeneity between studies, a random-effects model was used for all analyses. Compared with placebo, antibiotics were associated with a higher rate of cure or improvement (2648 patients, odds ratio [OR] 1.64 [95% CI 1.35-2.00], data from 16 RCTs), or cure alone (1813 patients, OR 1.82 [1.34-2.46], 12 RCTs), but also with more adverse events (1963 patients, OR 1.87 [1.21-2.90], 12 RCTs). The rate of symptom resolution was faster with antibiotics in most RCTs. Disease complications, disease recurrence, and study withdrawals because of adverse events did not differ between compared treatments. In conclusion, use of antibiotics for acute sinusitis confers a small therapeutic benefit over placebo with a corresponding rise in the risk for adverse events. We suggest that antibiotics should be reserved for carefully selected patients with a higher probability for bacterial disease.

1: BMC Gastroenterol. 2008 May 29;8:20.   Links

Short-term triple therapy with azithromycin for Helicobacter pylori eradication: low cost, high compliance, but low efficacy.

Silva FM, **Eisig JN**, **Teixeira AC**, **Barbuti RC**, **Navarro-Rodriguez T**, **Mattar R**.

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BACKGROUND: The Brazilian consensus recommends a short-term treatment course with clarithromycin, amoxicillin and proton-pump inhibitor for the eradication of Helicobacter pylori (H. pylori). This treatment course has good efficacy, but cannot be afforded by a large part of the population. Azithromycin, amoxicillin and omeprazole are subsidized, for several aims, by the Brazilian federal government. Therefore, a short-term treatment course that uses these drugs is a low-cost one, but its efficacy regarding the bacterium eradication is yet to be demonstrated. The study's purpose was to verify the efficacy of H. pylori eradication in infected patients who presented peptic ulcer disease, using the association of azithromycin, amoxicillin and omeprazole. METHODS: Sixty patients with peptic ulcer diagnosed by upper digestive endoscopy and H. pylori infection documented by rapid urease test, histological analysis and urea breath test were treated for six days with a combination of azithromycin 500 mg and omeprazole 20 mg, in a single daily dose, associated with amoxicillin 500 mg 3 times a day. The eradication control was carried out 12 weeks after the treatment by means of the same diagnostic tests. The eradication rates were calculated with 95% confidence interval. RESULTS: The eradication rate was 38% per intention to treat and 41% per protocol. Few adverse effects were observed and treatment compliance was high. CONCLUSION: Despite its low cost and high compliance, the low eradication rate does not allow the recommendation of the triple therapy with azithromycin as an adequate treatment for H. pylori infection.

1: Microb Ecol. 2008 Oct;56(3):395-402. Epub 2008 Jan 22. SpringerLink FULL-TEXT ARTICLE Links

Effect of antibiotic therapy on human fecal microbiota and the relation to the development of Clostridium difficile.

De La Cochetière MF, **Durand T**, **Lalande V**, **Petit JC**, **Potel G**, **Beaugerie L**.

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The gastrointestinal tract is a complex ecosystem. Recent studies have shown that the human fecal microbiota is composed of a consortium of microorganism. It is known that antibiotic treatment alters the microbiota, facilitating the proliferation of

opportunists that may occupy ecological niches previously unavailable to them. It is therefore important to characterize resident microbiota to evaluate its latent ability to permit the development of pathogens such as Clostridium difficile. Using samples from 260 subjects enrolled in a previously published clinical study on antibiotic-associated diarrhea, we investigated the possible relationship between the fecal dominant resident microbiota and the subsequent development of C. difficile. We used molecular profiling of bacterial 16S rDNA coupled with partial least square (PLS) regression analysis. Fecal samples were collected on day 0 (D0) before antibiotic treatment and on day 14 (D14) after the beginning of the treatment. Fecal DNA was isolated, and V6-to-V8 regions of the 16S rDNA were amplified by polymerase chain reaction with general primers and analyzed by temporal temperature gradient gel electrophoresis (TTGE). Main bacteria profiles were compared on the basis of similarity (Pearson correlation coefficient). The characteristics of the microbiota were determined using PLS discriminant analysis model. Eighty-seven TTGE profiles on D0 have been analyzed. The banding pattern was complex in all cases. The subsequent onset of C. difficile was not revealed by any clustering of TTGE profiles, but was explained up to 46% by the corresponding PLS model. Furthermore, 6 zones out of the 438 dispatched from the TTGE profiles by the software happened to be specific for the group of patients who acquired C. difficile. The first approach in the molecular phylogenetic analysis showed related sequences to uncultured clones. As for the 87 TTGE profiles on D14, no clustering could be found either, but the subsequent onset of C. difficile was explained up to 74.5% by the corresponding PLS model, thus corroborating the results found on D0. The non exhaustive data of the microbiota we found should be taken as the first step to assess the hypothesis of permissive microbiota. The PLS model was used successfully to predict C. difficile development. We found that important criteria in terms of main bacteria could be markedly considered as predisposing factors for C. difficile development. Yet, the resident microbiota in case of antibiotic-associated diarrhea has still to be analyzed. Furthermore, these findings suggest that strategies reinforcing the ability of the fecal microbiota to resist to modifications would be of clinical relevance

1: Chest. 2007 Aug;132(2):447-55. Epub 2007 Jun 15. Final Version FREE Chest Links
Comment in:
Chest. 2007 Dec;132(6):2063; author reply 2063-4.

Comparison of first-line with second-line antibiotics for acute exacerbations of chronic bronchitis: a metaanalysis of randomized controlled trials.

Dimopoulos G, **Siempos II**, **Korbila IP**, **Manta KG**, **Falagas ME**.

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BACKGROUND: Although acute exacerbations of chronic bronchitis (AECBs) are common, there has been no metaanalysis that focused on the optimum regimen.
METHODS: To evaluate the comparative effectiveness and safety of first-line antimicrobial agents (ie, amoxicillin, ampicillin, pivampicillin, trimethoprim/sulfamethoxazole, and doxycycline) and second-line antimicrobial

agents (ie, amoxicillin/clavulanic acid, macrolides, second-generation or third-generation cephalosporins, and quinolones) for the treatment of patients with AECB, in an era of increasing antimicrobial resistance among the microbes responsible for AECB, we performed a metaanalysis of randomized controlled trials (RCTs) retrieved through searches of the PubMed and the Cochrane databases. RESULTS: Twelve RCTs were included in the metaanalysis. First-line antibiotics were associated with lower treatment success compared to second-line antibiotics in the clinically evaluable patients (odds ratio [OR], 0.51; 95% confidence interval [CI], 0.34 to 0.75). There were no differences among the compared regimens regarding mortality (OR, 0.64; 95% CI, 0.25 to 1.66) or treatment success (OR, 0.56; 95% CI, 0.22 to 1.43) in microbiologically evaluable patients, or adverse effects in general (OR, 0.75; 95% CI, 0.39 to 1.45) or diarrhea in particular (OR, 1.58; 95% CI, 0.74 to 3.35). CONCLUSIONS: Compared to first-line antibiotics, second-line antibiotics are more effective, but not less safe, when administered to patients with AECB. The available data did not allow for stratified analyses according to the presence of risk factors for poor outcome, such as increased age, impaired lung function, airway obstruction, and frequency of exacerbations; this fact should be taken into consideration when interpreting the findings of this metaanalysis.

1: Mutat Res. 2007 May 18;629(2):133-9. Epub 2007 Feb 25. ELSEVIER FULL-TEXT ARTICLE Links

Antibiotic amoxicillin induces DNA lesions in mammalian cells possibly via the reactive oxygen species.

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Amoxicillin is a commonly prescribed drug for anti- bacterial infection. In this study, we are interested in the effect of the drug on the cellular DNA integrity. Amoxicillin was added to the human or hamster cells in culture, and the DNA lesions induced by the drug were assessed by a comet assay with nuclear extract incubation (Wang et al., 2005 Anal Biochem 337: 70-75). Amoxicillin at 5mM rapidly induced DNA lesions in human AGS cells. The level of DNA lesions attained a maximum at about 1h, and then declined steadily and reached almost the basal level at 6h following the drug treatment. Similar induction pattern of DNA lesions was found with amoxicillin-related antibiotics such as ampicillin but not with the unrelated antibiotics such as kanamycin. For studying the repair kinetics, the cells were treated with amoxicillin for only 1h and continued culture in the absence of the drug for a certain period of time before subsequent analysis. Repair of the amoxicillin-induced DNA lesions was essentially completed within 4h. Such repair may not involve nucleotide excision repair (NER) pathway because the repair was completed with similar kinetics in both NER proficient Chinese hamster CHO-K1 cells and its isogenic NER deficient UV24 cells. Instead, the repair may involve base excision repair (BER) pathway because immunodepletion of OGG1/2, glycosylases involved in BER rendered the nuclear extract unable to excise DNA lesions induced by amoxicillin in the modified comet assay. Furthermore, amoxicillin induced intracellular reactive oxygen species (ROS) at

the tempo similar to that of DNA lesions induction. Thus, we hypothesize that amoxicillin causes oxidative DNA damage in mammalian cells via ROS.

: Cleft Palate Craniofac J. 2007 Mar;44(2):194-202. Links

Drug treatment during pregnancy and isolated orofacial clefts in hungary.

Puhó EH, **Szunyogh M**, **Métneki J**, **Czeizel AE**.

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OBJECTIVE: To evaluate the possible association between all kinds of drug treatments during pregnancy and isolated cleft lip with or without cleft palate (CL/P) and posterior cleft palate (PCP) in the offspring. SETTING: The dataset of the large population-based Hungarian Case-Control Surveillance of Congenital Abnormalities, 1980-1996, was evaluated. PARTICIPANTS: One thousand three hundred seventy-four cases with isolated CL/P and 601 with PCP, plus 38,151 population controls (without birth defects) and 20,868 malformed controls with other defects. Intervention: In this observation case-control study the data collection was based on prospective medical records particularly prenatal logbook, retrospective maternal data via a self-reported questionnaire, and home visits of nonresponding mothers. MAIN OUTCOME MEASURES: Isolated CL/P and PCP associated with drug treatments during pregnancy. RESULTS: An increased risk for isolated CL/P was found in cases born to mothers treated with amoxicillin, phenytoin, oxprenolol, and thiethylperazine during the second and third month of pregnancy, i.e., the critical period of isolated CL/P. Risk of isolated PCP was increased in mothers with oxytetracycline and carbamazepine treatment during the third and fourth month of pregnancy, i.e., the critical period of PCP. CONCLUSIONS: This study confirmed the orofacial cleft (OFC) inducing effect of phenytoin, carbamazepine, oxytetracycline, and thiethylperazine and suggested a possible association between OFCs and oxprenolol and amoxicillin. However, drugs may have only a limited role in the origin of isolated OFCs.

1: Eur J Gastroenterol Hepatol. 2007 Jan;19(1):15-20. Wolters Kluwer | Lippincott Williams & Wilkins Links

Antibiotic therapy: a major cause of drug-induced jaundice in southwest England.

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OBJECTIVE: To determine the incidence and causes of drug-induced jaundice in a rural community. METHODS: A retrospective analysis of 800 patients presenting to a

single-centre jaundice referral system serving a community of 400 000 over a period of 66 months (1998-2004). Standard criteria for drug-induced liver injury were applied to patients with a putative diagnosis of drug-induced jaundice. The incidence rates per prescription of drug-induced jaundice caused by co-amoxiclav and flucloxacillin were derived from local and national annual prescription rates. RESULTS: The incidence of drug-induced jaundice was 1.27 (confidence limits 0.85-1.8) per 100 000 per annum in a total of 28 patients (17 men, mean age 69 years). Antibiotics were the commonest cause of jaundice (n=21). Of these, co-amoxiclav (n=9) and flucloxacillin (n=7) caused the majority with an incidence rate per 100 000 prescriptions of 9.91 (4.6-18.0) and 3.60 (1.5-7.2), respectively. Co-amoxiclav-induced jaundice was observed more commonly in elderly males (age 65 years, M : F 7 : 2). In those patients with flucloxacillin or co-amoxiclav-induced jaundice, bilirubin ranged from 54 to 599 mumol/l (267 mumol/l) with a resolution of jaundice between 30 and 90 days. Counselling with regard to potential drug-induced liver injury and reporting of the adverse reaction had been performed in 1/28 patients. CONCLUSIONS: 8.1% patients with no biliary obstruction and jaundice had a drug-induced and predominantly antibiotic-related aetiology particularly affecting an elderly population. We recommend that all patients receiving co-amoxiclav and flucloxacillin should be counselled before the therapy regarding the potential risk of jaundice and that an alternative antibiotic to co-amoxiclav is used if possible in men over the age of 60 years.

1: Antimicrob Agents Chemother. 2005 Nov;49(11):4658-66.

Safety and efficacy of tigecycline in treatment of skin and skin structure infections: results of a double-blind phase 3 comparison study with vancomycin-aztreonam.

Breedt J, **Teras J**, **Gardovskis J**, **Maritz FJ**, **Vaasna T**, **Ross DP**, **Gioud-Paquet M**, **Dartois N**, **Ellis-Grosse EJ**, **Loh E**; **Tigecycline 305 cSSSI Study Group**.

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In a randomized, double-blind, controlled trial, 546 patients with complicated skin and skin structure infections received tigecycline 100 mg/day (a 100-mg initial dose and then 50 mg intravenously twice daily) or the combination of vancomycin 2 g/day (1 g intravenously twice daily) and aztreonam 4 g/day (2 g intravenously twice daily) for up to 14 days. The primary end point was the clinical response in the clinical modified intent-to-treat (c-mITT) and clinically evaluable (CE) populations at the test-of-cure visit 12 to 92 days after the last dose. The microbiologic response at the test-of-cure visit was also assessed. Safety was assessed by physical examination, laboratory results, and adverse event reporting. Five hundred twenty patients were included in the c-mITT population (tigecycline group, n = 261; combination group, n = 259), and 436 were clinically evaluable (tigecycline group, n = 223; combination group, n = 213).

The clinical responses in the tigecycline and the combination vancomycin and aztreonam groups were similar in the c-mITT population (84.3% versus 86.9%; difference, -2.6% [95% confidence interval, -9.0, 3.8]; P = 0.4755) and the CE population (89.7% versus 94.4%; difference, -4.7% [95% confidence interval, -10.2, 0.8]; P = 0.1015). Microbiologic eradication (documented or presumed) occurred in 84.8% of the patients receiving tigecycline and 93.2% of the patients receiving vancomycin and aztreonam (difference, -8.5 [95% confidence interval, -16.0, -1.0]; P = 0.0243). The numbers of patients reporting adverse events were similar in the two groups, with increased nausea and vomiting rates in the tigecycline group and an increased incidence of rash and increases in alanine aminotransferase and aspartate aminotransferase levels in the combination vancomycin and aztreonam group. Tigecycline was shown to be safe and effective for the treatment of complicated skin and skin structure infections.

Drug Saf. 1995 May;12(5):305-13. Links

Adverse effects of monobactams and carbapenems.

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Monobactams and carbapenems are 2 classes of beta-lactam antibiotics that were introduced in the 1980s. This review considers the monobactam aztreonam and the carbapenems imipenem and meropenem. Imipenem is administered together with cilastatin, which inhibits the enzymatic breakdown of imipenem in the kidney. The antibacterial activities of these drugs are quite different from older beta-lactams. Aztreonam is directed towards aerobic Gram-negative bacteria, especially Pseudomonas aeruginosa, while imipenem and meropenem are active against both aerobic and anaerobic Gram-positive and Gram-negative bacteria. Thus, these drugs should be reserved for patients who have a special need for them. They are also structurally different from older beta-lactams and possess different adverse drug reaction profiles. It was initially suggested that aztreonam would be less immunogenic than previous beta-lactams because reactive breakdown products acting as haptens are less likely to be formed. Clinical reports now support this assumption, and, in particular, cross hypersensitivity between aztreonam and other beta-lactams seems to be rare which makes the drug a useful therapeutic alternative. However, hypersensitivity to aztreonam does occur. The predominant concern in terms of adverse reactions to imipenem/cilastatin is the increased tendency to cause seizures compared with other beta-lactams. The risk of producing a seizure is highly associated with inadequate dose adjustment in relation to kidney function. If appropriate care is taken, seizures occur in less than 1% of patients treated. However, it is possible that concomitant administration of other drugs with neurotoxic profiles (e.g. theophylline and cyclosporin) given in overdose, may increase the risk of seizures.(ABSTRACT TRUNCATED AT 250 WORDS)

Clin Infect Dis. 2009 Jan 1;48(1):65-71. The University of Chicago Press Links

Severity of gentamicin's nephrotoxic effect on patients with infective endocarditis: a prospective observational cohort study of 373 patients.

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BACKGROUND: Gentamicin is often used to treat infective endocarditis (IE). Gentamicin is highly effective, but its applicability is reduced by its nephrotoxic effect. The aim of this study was to quantify the nephrotoxic effect of gentamicin and the association between the nephrotoxic effect and mortality in patients with IE. METHODS: A prospective observational cohort study was performed at 2 tertiary university hospitals in Copenhagen from October 2002 through October 2007; 373 consecutive patients with IE were included. A total of 287 (77%) of the patients received gentamicin treatment (median duration, 14 days); dosage was adjusted according to daily serum creatinine and trough serum gentamicin levels. Kidney function was determined by estimated endogenous creatinine clearance (EECC). Statistical correlation between gentamicin and EECC change was analyzed, and the association between mortality and nephrotoxicity was investigated. RESULTS: The primary bacteriological etiologies were as follows: Streptococcus species (37.1%), Staphylococcus aureus (18.2%), and Enterococcus species (16.1%). In the gentamicin group, the mean EECC change was an 8.6% decrease, but in the no-gentamicin group, the mean change was an increase of 2.3% (P = .05). The decrease in EECC was significantly correlated with the duration of gentamicin treatment: a 0.5% EECC decrease per day of gentamicin treatment (P = .002). The decrease in EECC during hospitalization was not related to postdischarge mortality. The mean duration of follow-up was 562 days. CONCLUSIONS: The nephrotoxic effect of gentamicin is directly related to treatment duration, with a decrease in EECC of 0.5% per day of gentamicin treatment. In patients treated with gentamicin, the in-hospital decrease in EECC was not related to postdischarge mortality. Consequently, this study does not support abolishment of gentamicin in treatment of IE.

1: Dtsch Med Wochenschr. 2008 Mar;133(11):511-5. Thieme connect Links

[Antibiotic therapy in pregnancy]

[Article in German]

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Apart from pregnancy-related ascending and hematogenous infections, non-pregnancy-associated may be a potential thread for pregnant women as well as for their unborn children. Infections are one of the causes of abortion during the first trimester, whereas during second and third trimester, they represent the primary cause

of preterm birth. Both pregnant women and their physicians may feel profoundly uncertain with regards to appropriate treatment. If antimicrobial agents are indicated, beta-lactam antibiotics are generally safe and effective. With respect to penicillins, an approximately 10 per cent maternal allergy rate should be taken into consideration, and first-generation cephalosporins may be a suitable alternative. Among the macrolide antibiotics, erythromycin should be preferred. Clindamycin, metronidazole, sulfonamides and chloramphenicol may be used as second-line agents, however, sulfonamides and chloramphenicol should be avoided during the prepartal period. Glycopeptide and aminoglycoside antibiotics should be reserved for life-threatening maternal infections refractory to other antibiotics. Tetracyclins may only be used before the 12 (th) week of gestation. Quinolones should be strictly avoided due to potential toxicity for the unborn children.

http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0074-02762007005000120&lng=en&nrm=iso&tlng=e

1: Mem Inst Oswaldo Cruz. 2007 Nov;102(7):853-9. Epub 2007 Dec 11.

Antimicrobial resistance profiles of enterococci isolated from poultry meat and pasteurized milk in Rio de Janeiro, Brazil.

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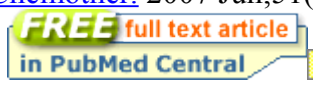
The enterococci are important nosocomial pathogens with a remarkable capacity of expressing resistance to several antimicrobial agents. Their ubiquitous nature and resistance to adverse environmental conditions take account for their ability to colonize different habitats and for their potential for easy spreading through the food chain. In the present study we evaluated the distribution of species and antimicrobial susceptibility among enterococcal isolates recovered from food obtained in retail stores in Rio de Janeiro, Brazil. The following species were identified among 167 isolates obtained from poultry meat and 127 from pasteurized milk: Enterococcus faecalis (62.6%), E. casseliflavus (17.3%), E. durans (6.5%), E. gallinarum (3.0%), E. gilvus (2.4%), E. faecium (2.0%), E. hirae (1.4%), and E. sulfureus (1.0%). The overall percentages of antimicrobial resistant isolates were: 31.2 % to tetracycline, 23.8% to erythromycin, 11.3% to streptomycin, 4.3% to chloramphenicol, 3.9% to gentamicin, 1.4% to norfloxacin, 1.1% to imipenem, 0.7% to ciprofloxacin, nitrofurantoin, and penicillin, and 0.4% to ampicillin. Intermediate resistance was detected in frequencies varying from 0.5% for linezolid to 58.2% for erythromycin. None of the isolates showed resistance to glycopeptides. High-level resistance to aminoglycosides was observed in 13.1% of the isolates. Multiresistance was observed in E. faecalis, E. casseliflavus, E. faecium, E. gallinarum, E. durans and E. gilvus.

1: Antimicrob Agents Chemother. 2007 Jun;51(6):2070-7. Epub 2007 Apr 16.



Links

Polyamine effects on antibiotic susceptibility in bacteria.

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Biogenic polyamines (e.g., spermidine and spermine) are a group of essential polycationic compounds found in all living cells. The effects of spermine and spermidine on antibiotic susceptibility were examined with gram-negative Escherichia coli and Salmonella enterica serovar Typhimurium bacteria and clinical isolates of Pseudomonas aeruginosa and with gram-positive Staphylococcus aureus bacteria, including methicillin-resistant S. aureus (MRSA). Exogenous spermine exerted a dose-dependent inhibition effect on the growth of E. coli, S. enterica serovar Typhimurium, and S. aureus but not P. aeruginosa, as depicted by MIC and growth curve measurements. While the MICs of polymyxin and ciprofloxacin were in general increased by exogenous spermine and spermidine in P. aeruginosa, this adverse effect was not observed in enteric bacteria and S. aureus. It was found that spermine and spermidine can decrease the MICs of beta-lactam antibiotics in all strains as well as other types of antibiotics in a strain-dependent manner. Significantly, the MICs of oxacillin for MRSA Mu50 and N315 were decreased more than 200-fold in the presence of spermine, and this effect of spermine was retained when assessed in the presence of divalent ions (magnesium or calcium; 3 mM) or sodium chloride (150 mM). The effect of spermine on the sensitization of P. aeruginosa and MRSA to antibiotics was further demonstrated by population analysis and time-killing assays. The results of checkerboard assays with E. coli and S. aureus indicated a strong synergistic effect of spermine in combination with beta-lactams and chloramphenicol. The decreased MICs of beta-lactams implied that the possible blockage of outer membrane porins by exogenous spermine or spermidine did not play a crucial role in most cases. In contrast, only the MIC of imipenem against P. aeruginosa was increased by exogenous spermine and spermidine, and this resistance effect was abolished in a mutant strain devoid of the outer membrane porin OprD. In E. coli, the MICs of carbenicillin, chloramphenicol, and tetracycline were decreased in two acrA mutants devoid of a major efflux pump, AcrAB. However, retention of the spermine effect on antibiotic susceptibility in two acrA mutants of E. coli suggested that the AcrAB efflux pump was not the target for a synergistic effect by spermine and antibiotics and ruled out the hypothesis of spermine serving as an efflux pump inhibitor in this organism. In summary, this interesting finding of the effect of spermine on antibiotic susceptibility provides the basis for a new potential approach against drug-resistant pathogens by use of existing beta-lactam antibiotics.

1: Saudi J Kidney Dis Transpl. 2009 Jan;20(1):131-3. 

Links

Granulomatous interstitial nephritis after prolonged use of phenytoin.

Ram R, Swarnalatha G, Prasad N, Prayaga A, Dakshina Murthy KV.

1: Toxicol Sci. 2006 Nov;94(1):206-16. Epub 2006 Aug 17.  Links

Hepatic gene expression profiling and lipid homeostasis in mice exposed to steatogenic drug, tetracycline.

Yin HQ, Kim M, Kim JH, Kong G, Lee MO, Kang KS, Yoon BI, Kim HL, Lee BH.

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Tetracycline is one of a group of drugs known to induce microvesicular steatosis. In the present study, we investigated the effects of tetracycline on gene expression in mouse liver, using Applied Biosystems Mouse Genome Survey Microarrays. A single oral dose of 0.1 or 1 g/kg tetracycline was administered to male ICR mice, and liver samples were obtained after 6, 24, or 72 h. Histopathological evaluation showed microvesicular steatosis in the high-dose group at 24 h. In total, 96 genes were identified as tetracycline responsive. Their level of expression differed significantly from controls (two-way analysis of variance; $p < 0.05$), after adjustment by the Benjamini-Hochberg multiple testing correction, and displayed a twofold or greater induction or repression. The largest groups of gene products affected by tetracycline exposure were those involved in signal transduction, nucleic acid metabolism, developmental processes, and protein metabolism. The expression of genes known to be involved in lipid metabolism was examined, using two-sample Student's t-test for each treatment group versus a corresponding control group. The overall net effects on expression of lipid metabolism genes indicated an increase in cholesterol and triglyceride biosynthesis and a decrease in beta-oxidation of fatty acids. Our data support a proposed mechanism for tetracycline-induced steatogenic hepatotoxicity that involves these processes. Moreover, we demonstrated global changes in hepatic gene expression following tetracycline exposure; many of these genes have the potential to be used as biomarkers of exposure to steatogenic hepatotoxic agents.

1: Eur J Med Chem. 2009 Jan;44(1):345-58. Epub 2008 Mar 7.  Links

Synthesis and antimycobacterial activities of novel 6-nitroquinolone-3-carboxylic acids.

Senthilkumar P, Dinakaran M, Yogeeswari P, Sriram D, China A, Nagaraja V.

Medicinal Chemistry Research Laboratory, Pharmacy group, Birla Institute of Technology and Science, Pilani 333031, India.

Various 1-(substituted)-1,4-dihydro-6-nitro-4-oxo-7-(sub-secondary amino)-quinoline-3-carboxylic acids were synthesized from 2,4-dichlorobenzoic acid by six step synthesis. The compounds were evaluated for antimycobacterial in vitro and in vivo against Mycobacterium tuberculosis H37Rv (MTB), multi-drug resistant Mycobacterium tuberculosis (MDR-TB) and Mycobacterium smegmatis (MC(2)) and also tested for the ability to inhibit the supercoiling activity of DNA gyrase from M. smegmatis. Among the 48 synthesized compounds, 7-(4-((benzo[d][1,3]dioxol-5-yl)methyl)piperazin-1-yl)-1-cyclopropyl-1,4-dihydro-6-nitro-4-oxoquinoline-3-carboxylic acid (8c) was found to be the most active compound in vitro with MIC of 0.08 and 0.16 microM against MTB and MDR-TB, respectively. In the in vivo animal model 8c decreased the bacterial load in lung and spleen tissues with 2.78 and 4.15-log10 protections, respectively, at the dose of 50 mg/kg body weight.

: J Clin Gastroenterol. 2005 Sep;39(8):709-16. Wolters Kluwer | Lippincott Williams & Wilkins Links

Drug-induced pancreatitis: an update.

Trivedi CD, **Pitchumoni CS**.

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BACKGROUND AND AIMS: Many frequently prescribed drugs are suspected to cause acute pancreatitis (AP). The goal of this paper is to bring to light the often occult but real problem of drug-induced pancreatitis (DIP). METHODS: We searched the National Library of Medicine/Pubmed for reported cases of DIP from 1966 to April 30, 2004. Medications implicated in AP are classified based on the strength of evidence into one of three classes of drugs associated with pancreatitis. We reviewed the top 100 prescription medications in the United States for their association with AP. RESULTS: Class I medications (medications implicated in greater than 20 reported cases of acute pancreatitis with at least one documented case following reexposure): didanosine, asparaginase, azathioprine, valproic acid, pentavalent antimonials, pentamidine, mercaptopurine, mesalamine, estrogen preparations, opiates, tetracycline, cytarabine, steroids, trimethoprim/sulfamethoxazole, sulfasalazine, furosemide, and sulindac. Class II medications (medications implicated in more than 10 cases of acute pancreatitis): rifampin, lamivudine, octreotide, carbamazepine, acetaminophen, phenformin, interferon alfa-2b, enalapril, hydrochlorothiazide, cisplatin, erythromycin, and cyclopenthiazide. Class III medications (all medications reported to be associated with pancreatitis). Of the top 100 most frequently prescribed medications in the United States, 44 have been implicated in AP, 14 of them fall into either Class I or II of medications associated with AP. CONCLUSIONS: Among adverse drug reactions, pancreatitis is often-ignored because of the difficulty in implicating a drug as its cause. The physician should have a high index of suspicion for DIP, especially in specific subpopulations such as geriatric patients who may be on

multiple medications, HIV+ patients, cancer patients, and patients receiving immunomodulating agents.

1: Indian Pediatr. 2007 Apr;44(4):311-2. Links

Acute lymphoblastic leukemia in association with long term exposure to trimethoprim-sulfomethaxozole.

Hudaoglu O, **Tokgöz Y**.

1: Ann Intern Med. 1981 Jun;94(6):780-1. Links

Acute megaloblastic anemia induced by high-dose trimethoprim-sulfamethoxazole.

Kobrinsky NL, **Ramsay NK**.

1: J Paediatr Child Health. 1997 Apr;33(2):166-7. Links

Megaloblastic anaemia and pancytopenia secondary to prophylactic cotrimoxazole therapy.

Tapp H, **Savarirayan R**.

Haematology/Oncology Unit, Women's and Children's Hospital, North Adelaide, Australia.

1: Pediatr Blood Cancer. 2005 Jan;44(1):55-62. Links

Methemoglobinemia in children with acute lymphoblastic leukemia (ALL) receiving dapsone for pneumocystis carinii pneumonia (PCP) prophylaxis: a correlation with cytochrome b5 reductase (Cb5R) enzyme levels.

Williams S, **MacDonald P**, **Hoyer JD**, **Barr RD**, **Athale UH**.

Division of Hematology/Oncology, Department of Pediatrics, McMaster University, McMaster Children's Hospital, Hamilton Health Sciences Corporation, Hamilton, Ontario, Canada.

BACKGROUND: Dapsone is commonly used for pneumocystis carinii pneumonia (PCP) prophylaxis in immunocompromised patients. Methemoglobinemia is a known complication of dapsone, but its true frequency and pathogenesis in childhood cancer patients are unknown. Additionally, practice guidelines for evaluation and management of dapsone-induced methemoglobinemia are not available. PROCEDURE: We studied 15 children with acute lymphoblastic leukemia (ALL) receiving dapsone for PCP prophylaxis to determine the frequency of methemoglobinemia, and correlate its occurrence with cytochrome b5 reductase (Cb5R) enzyme levels. Ten children with ALL receiving trimethoprim-sulfamethaxazole (TMP-SMX) were studied as controls. All patients underwent physical examination, pulse oximetry, and methemoglobin (metHb) estimation. Commercially available assay was used to measure Cb5R levels. RESULTS: Three (20%) patients receiving dapsone developed symptomatic methemoglobinemia. Average duration of dapsone prophylaxis prior to diagnosis was 6.6 weeks (range 3.5-10 weeks). Mean metHb level in symptomatic patients was 11.67%; 95% confidence interval (CI) 0-25.79 (range 7-18%), and 1.37%; 95% CI 0.6-2.14 (range 0.02-3%) in asymptomatic patients (P = 0.09), whereas the mean metHb level in the control group was 0.54%; 95% CI 0.35-0.73 (range 0.1-0.8%) (asymptomatic vs control P < 0.0001). Mean Cb5R level in symptomatic patients was 8.6 IU/g Hb; 95% CI 3.4-13.7 (range 6.9-10.9) compared to 12.5 IU/g Hb; 95% CI 11.1-13.9 (range 10.8-14.6) in asymptomatic patients (P = 0.06). Two symptomatic patients had Cb5R levels at or below 50% of normal, consistent with heterozygosity. Parental studies for Cb5R levels were suggestive of a carrier state in one of each patient's parents. CONCLUSIONS: Heterozygosity for Cb5R deficiency may pre-dispose to methemoglobinemia even on a thrice-weekly regimen of dapsone. Such individuals should avoid subsequent exposure to oxidant agents, if possible. Children with ALL tend to be symptomatic at low levels of metHb and may have delayed detection of methemoglobinemia. Hence, frequent monitoring of patients receiving dapsone is recommended. Monitoring guidelines for dapsone prophylaxis are proposed. (c) 2004 Wiley-Liss, Inc.

1: Int J Dermatol. 2000 Aug;39(8):621-3.

Toxic epidermal necrolysis following combination of methotrexate and trimethoprim-sulfamethoxazole.

Yang CH, **Yang LJ**, **Jaing TH**, **Chan HL**.

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A 15-year-old boy with T-cell acute lymphoblastic leukemia (ALL) (FAB L1), diagnosed in 1995, received combination chemotherapy consisting of 6 weeks of induction (vincristine, epirubicin, L-asparaginase, prednisolone) and 2 weeks of consolidation (cytosine arabinosides, etoposide). After achieving remission, for further maintenance of remission, he was treated with 14 cycles of intensive chemotherapy consisting of 6-MP, 10 mg/kg orally on the first 4 days, and cyclophosphamide, 1200 mg/m2, vincristine, 1.5 mg/m2, epirubicin, 15 mg/m2, and cytosine arabinoside, 40 mg/m2, intravenously on days 4, 11, 39, and 40, respectively. On day 18 of each

cycle, he received intravenous methotrexate (MTX) infusion in a total dose of 150 mg/m2 plus oral leucovorin (30 mg/m2) rescue 36 h after starting MTX therapy. In addition, oral trimethoprim-sulfamethoxazole was given regularly to prevent Pneumocystis carinii infection. The patient achieved remission during the first course of treatment, but 8 months later the disease relapsed. He then received four doses of MTX (800 mg intravenously) plus leucovorin rescue in the following 4 months. During the last MTX therapy, small hemorrhagic bullae were found on the lateral side of the right ankle, but subsided after a few days. Due to partial remission of the disease, he was admitted again in January 1999 for high-dose MTX therapy. An initial hemogram on admission revealed hemoglobin 7.2 g/dL, white cell count 15,200/mm3, platelet count 153/mm3, blood creatinine 0.5 mg/dL, and alanine leucine aminotransferase (ALT) 20 U/L. He received 8500 mg of MTX (5000 mg/m2) as a continuous intravenous infusion for 24 h. Thirty-six hours after the start of MTX infusion, leucovorin (30 mg, intravenous) rescue was initiated every 6 h for 3 days. Another preventive measure to cover MTX toxicity included aggressive intravenous fluid replacement (4 L/m2 /day) and the addition of 25 meq/L sodium bicarbonate to the intravenous fluid to alkalinize the urine. Concurrent medication included 6-MP (50 mg) once daily and trimethoprim-sulfamethoxazole (120 mg, 600 mg) twice daily every other day. Plasma MTX levels were 52.36 micromol/L 24 h after MTX infusion, 1.87 micromol/L after 48 h, 0.57 micromol/L after 72 h, and 0.41 micromol/L after 96 h. These indicated delayed MTX plasma clearance. The blood creatinine level was mildly elevated from 0.5 mg/dL to 0.7 mg/dL. Thirty-six hours after the administration of MTX, the patient developed an erythematous painful swelling on the right middle finger. The erythema, with subsequent large bulla formation, progressed to all the fingers, toes, palms, and the soles of the feet. Some erythematous to hemorrhagic papules also appeared on the bilateral elbows. Subsequently, diffuse tender erythema with extensive erosions and focal tiny pustules developed on the back, abdomen, proximal extremities, and face (Fig. 1a,b). A positive Nikolsky's sign was also present. A biopsy specimen of the right dorsal hand lesion revealed parakeratosis, detached acanthotic epidermis with scattered necrotic keratinocytes, dyskeratotic cells and nuclear atypia, neutrophilic exocytosis, and many neutrophils in the papillary dermis (Fig. 2). The skin condition deteriorated rapidly. Toxic epidermal necrolysis-like lesions involved 90% of the total body surface on the fifth day after MTX infusion. Mucositis, diarrhea, involuntary tremor, fever, and chills were noted. The patient was then sent to the burn unit for intensive skin care. Ten days after MTX therapy, profound agranulocytosis and thrombocytopenia (white cell count 100/mm3, platelets 14,000/mm3, and hemoglobin 5.6 g/dL) were found. The patient was then started on granulocyte colony stimulation factor (G-CSF, 5 microg/kg/day), but his general condition deteriorated rapidly and he died 6 days later due to septic shock and multiple organ failure.

1: Haematologia (Budap). 1993;25(2):137-41. Links

Hyperkalaemia with renal tubular dysfunction by sulfamethoxazole-trimethoprim for Pneumocystis carinii pneumonia in patients with lymphoid malignancy.

Funai N, Shimamoto Y, Matsuzaki M, Watanabe M, Tokioka T, Sueoka E, Suga K, Ono K, Sano M, Yamaguchi M.

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Hyperkalaemia with renal tubular dysfunction by oral therapy of sulfamethoxazole-trimethoprim (co-trimoxazole) is described in 2 elderly Japanese patients with lymphoid malignancy, who developed Pneumocystis carinii pneumonia and improved. A high dose of cotrimoxazole induced hyperkalaemia with the elevation of serum creatinine and blood urea, and increased urinary N-acetyl glucosaminase after several days of the drug administration in these patients; one patient became unconscious. Discontinuation of co-trimoxazole normalized serum potassium level and symptoms. A repeated low dose of the drug induced hyperkalaemia. Before the treatment of co-trixomazole, their serum levels of creatinine showed upper limits of normal ranges. In the present study, our cases suggested that patients receiving a high dose of co-trimoxazole should be evaluated for these potential complications during a course of treatment, particularly in elderly patients with preexisting renal dysfunction.

1: Chest. 1991 Jan;99(1):143-6. Full Text FREE Chest Links

Pulmonary complications of combination therapy with cyclophosphamide and prednisone.

Sen RP, Walsh TE, Fisher W, Brock N.

Department of Internal Medicine, National Naval Medical Center, Bethesda, Md.

Oral cyclophosphamide and prednisone are standard treatment for some neoplasms and necrotizing systemic vasculitis and are advocated with increasing frequency for idiopathic interstitial lung disease. During a 15-month period, we observed four cases of acute respiratory failure from Pneumocystis carinii pneumonia (PCP) in patients treated with oral cyclophosphamide and prednisone. One patient each had polyarteritis nodosa, Wegener's granulomatosis, bronchiolitis obliterans with organizing pneumonia, and chronic lymphocytic leukemia with red blood cell aplasia. Hypoalbuminemia (serum albumin level less than 3.0 g/dl) and daily therapy were associated with increased risk for development of PCP (p less than 0.05). None of the patients had leukopenia (less than 3,500/cu mm) or neutropenia (less than 1,000/cumm) at diagnosis. All were negative for the human immunodeficiency virus. Patients receiving oral cyclophosphamide and prednisone may be at higher or increasing risk for PCP. A high index of suspicion and aggressive evaluation for opportunistic infection are needed in these patients; consideration for trimethoprim-sulfamethoxazole prophylaxis and development of more quantitative measures of immunosuppression are needed.

1: Arch Dis Child. 1987 Jan;62(1):85-7. FREE full text article in PubMed Central Links

Co-trimoxazole red cell aplasia in leukaemia.

Unter CE, Abbott GD.

A 4 year old boy with acute lymphoblastic leukaemia developed a pure red cell aplasia 13 months after entering remission and while on maintenance chemotherapy. Co-trimoxazole was also being administered for prophylaxis against Pneumocystis carinii infection. When co-trimoxazole was stopped the red cell aplasia resolved.

High risk of neutropenia in HIV-infected children following treatment with artesunate plus amodiaquine for uncomplicated malaria in Uganda.

Gasasira AF, Kamya MR, Achan J, Mebrahtu T, Kalyango JN, Ruel T, Charlebois E, Staedke SG, Kekitiinwa A, Rosenthal PJ, Havlir D, Dorsey G.

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BACKGROUND: Artemisinin-based combination therapies are rapidly being adopted for the treatment of malaria in Africa; however, there are limited data on their safety and efficacy among human immunodeficiency virus (HIV)-infected populations. METHODS: We compared malaria treatment outcomes between cohorts of HIV-infected and HIV-uninfected children in Uganda who were observed for 18 and 29 months, respectively. Malaria was treated with artesunate plus amodiaquine, and outcomes were assessed using standardized guidelines. HIV-infected children received trimethoprim-sulfamethoxazole prophylaxis and antiretroviral therapy in accordance with current guidelines. RESULTS: Twenty-six HIV-infected participants experiencing 35 episodes of malaria and 134 HIV-uninfected children experiencing 258 episodes of malaria were included in the study. Twelve HIV-infected children were receiving antiretroviral therapy, 11 of whom were receiving zidovudine. Malaria treatment was highly efficacious in both the HIV-infected and HIV-uninfected cohorts (28-day risk of recrudescence, 0% and 3.6%, respectively); however, there was a trend towards increased risk of recurrent malaria among the HIV-uninfected children (2.9% vs. 13.2%; p = .08). Importantly, the risk of neutropenia 14 days after initiation of treatment with artesunate plus amodiaquine was higher among HIV-infected children than among HIV-uninfected children (45% vs. 6%; p < .001). The severity of all episodes of neutropenia in HIV-uninfected children was mild to moderate, and 16% of episodes of neutropenia in the HIV-infected cohort were severe or life-threatening (neutrophil count, <750 cells/mm(3)). In the HIV-infected cohort, the risk of neutropenia was significantly higher among children who received antiretroviral therapy than among those who did not receive antiretroviral therapy (75% vs. 26%; p < .001). CONCLUSIONS: Artesunate plus amodiaquine was highly efficacious for malaria treatment in HIV-infected children but was associated with a high risk of neutropenia, especially in the context of concurrent antiretroviral use. Our findings highlight an urgent need for evaluation of alternative antimalarial therapies for HIV-infected individuals.

1: Rev Med Liege. 2004;59 Suppl 1:118-23. Links

[Neurotoxic effects of medications: an update]

[Article in French]

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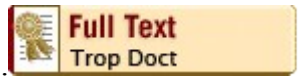
Peripheral neuropathy is a common neurotoxic effect of medications. Antineoplastic agents and antiretroviral medications are most often involved: platinum compounds, vinca alkaloids, taxols and nucleoside reverse transcriptase inhibitors. These agents cause a dose-related axonal polyneuropathy. Symptoms are indicative of a predominantly sensory or sensory-motor neuropathy which in some cases is accompanied by dysfunction of autonomic nervous system. Depending on dosage and agent used symptoms resolve completely or not. Neurotoxic effect can appear immediately during or shortly after administration of the drug but sometimes after cessation of chemotherapy. In all cases the neuropathy alters the quality of life. A general predisposition for developing a neuropathy has been observed in nerves previously damaged by diabetes mellitus, alcohol or in inherited neuropathy. Within the past five years, some cases of neuropathy caused by alpha-interferon, statins or tacrolimus have been reported. Although rare, these aetiologies should be considered by physicians and the drugs removed when others causes of neuropathy have been excluded. Few cases of peripheral neuropathy have been recently reported with metronidazole, dapsone, nitrofurantoin or colchicin. Thalidomide induces a dose-dependant sensori-motor length-dependent axonal neuropathy. It should be judiciously used with close neurologic monitorin. Little is known about the mechanisms responsible for the development of neuropathy. Up to now, no drug is available to prevent or cure drug-induced neuropathies.

1: Trop Doct. 2006 Apr;36(2):79-82. 

Links

Cotrimoxazole prophylaxis for HIV-positive TB patients in developing countries.

Zachariah R, **Massaquoi M**.

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Despite provisional recommendations from the World Health Organization and UNAIDS that cotrimoxazole (CTX) prophylaxis be offered to all individuals living with AIDS, including HIV-positive patients with TB, its routine use in developing countries particularly Africa has been minimal. Concerns were expressed regarding its effectiveness in areas of high bacterial resistance, that its widespread use might substantially increase bacterial cross-resistance in the community and that this intervention might promote resistance of malaria parasites to sulphadoxine-pyrimethamine. We review the current evidence on the above concerns and highlight

the main operational considerations related to implementing CTX prophylaxis as a basic component of care for HIV-positive TB patients in developing countries.

1: Trans R Soc Trop Med Hyg. 2007 Nov;101(11):1059-60. Epub 2007 Jul 26.

Co-trimoxazole prophylaxis in tropical countries in the era of highly active antiretroviral therapy: do we know enough?

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Co-trimoxazole prophylaxis in HIV-infected persons is beyond doubt one of the cheapest and most important interventions, next to antiretroviral therapy (ART), to improve survival. However, many questions, ranging from programme coverage and public health impact to individual tolerance and compliance, remain unanswered. Together with the need for more research to identify optimal ART regimens for resource-poor settings, research regarding optimal chemoprophylaxis against opportunistic infections should also remain high on the agenda.

Reconsidering empirical cotrimoxazole prophylaxis for infants exposed to HIV infection.

Gill CJ, **Sabin LL**, **Tham J**, **Hamer DH**.

Department of International Health, Center for International Health and Development, Boston University School of Public Health, Boston, MA, USA. cgill@bu.edu

Infants with HIV infection are vulnerable to Pneumocystis carinii pneumonia (PCP) during their first year of life. WHO and the Joint United Nations Programme on HIV/AIDS now recommend that all children of HIV-positive mothers receive prophylactic cotrimoxazole against PCP from six weeks of age and continue this therapy until exposure through breast milk ceases-and the infant is confirmed to be HIV-negative (rarely before one year of age). Empirical prophylaxis invokes a trade-off between possible benefit to the infant versus the risk of resistance to antibiotics and antimalarials. From a critical analysis of the literature, we offer a conceptual model demonstrating how, under certain circumstances, a policy of mass cotrimoxazole prophylaxis may be counterproductive.

PMID: 17253490 [PubMed - indexed for MEDLINE] **1:** Antimicrob Agents Chemother. 2002 Feb;46(2):594-7.

Impact of trimethoprim-sulfamethoxazole prophylaxis on etiology and susceptibilities of pathogens causing human immunodeficiency virus-associated bacteremia.

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The impact of chronic prophylactic administration of trimethoprim-sulfamethoxazole (SXT) on the ecology and the antimicrobial susceptibilities of bloodstream pathogens in human immunodeficiency virus (HIV)-infected patients was studied using a retrospective chart review. Eighty-nine patients with advanced HIV infection developed 124 episodes of bacteremia with 156 pathogenic isolates. Staphylococcus aureus and Enterobacteriaceae tended to be less common among patients receiving SXT. Isolates from patients receiving SXT were likelier (75%) to be resistant to 20 microg of SXT/ml than those from patients not receiving SXT (33%) ($P < 0.001$).

1: Trans R Soc Trop Med Hyg. 2002 Mar-Apr;96(2):202-4. Links

Changes in Escherichia coli resistance to co-trimoxazole in tuberculosis patients and in relation to co-trimoxazole prophylaxis in Thyolo, Malawi.

Zachariah R, **Harries AD**, **Spielmann MP**, **Arendt V**, **Nchingula D**, **Mwenda R**, **Courtielle O**, **Kirpach P**, **Mwale B**, **Salaniponi FM**.

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In Thyolo district, Malawi, an operational research study is being conducted on the efficacy and feasibility of co-trimoxazole prophylaxis in preventing deaths in HIV-positive patients with tuberculosis (TB). A series of cross-sectional studies were carried out in 1999 and 2001 to determine (i) whether faecal Escherichia coli resistance to co-trimoxazole in TB patients changed with time, and (ii) whether the resistance pattern was different in HIV-positive TB patients who were taking co-trimoxazole prophylaxis. Co-trimoxazole resistance among E. coli isolates in TB patients at the time of registration was 60% in 1999 and 77% in 2001 ($P < 0.01$). Resistance was 89% among HIV-infected TB patients (receiving cotrimoxazole), while in HIV-negative patients (receiving anti-TB therapy alone) it was 62% ($P < 0.001$). The study shows a significant increase of E. coli resistance to co-trimoxazole in TB patients which is particularly prominent in HIV-infected patients on co-trimoxazole prophylaxis. Since a high degree of plasmid-mediated transfer of resistance exists between E. coli and the Salmonella species, these findings could herald limitations on the short- and long-term benefits to be expected from the use of

co-trimoxazole prophylaxis in preventing non-typhoid Salmonella bacteraemia and enteritis in HIV-infected TB patients in Malawi.

: Trop Doct. 2006 Apr;36(2):79-82.  Links

Cotrimoxazole prophylaxis for HIV-positive TB patients in developing countries.

Zachariah R, **Massaquoi M**.

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Despite provisional recommendations from the World Health Organization and UNAIDS that cotrimoxazole (CTX) prophylaxis be offered to all individuals living with AIDS, including HIV-positive patients with TB, its routine use in developing countries particularly Africa has been minimal. Concerns were expressed regarding its effectiveness in areas of high bacterial resistance, that its widespread use might substantially increase bacterial cross-resistance in the community and that this intervention might promote resistance of malaria parasites to sulphadoxine-pyrimethamine. We review the current evidence on the above concerns and highlight the main operational considerations related to implementing CTX prophylaxis as a basic component of care for HIV-positive TB patients in developing countries.

LETTER

Hyperkalemia and Trimethoprim-Sulfamethoxazole

Igor Ougorets, MD; Deborah Asnis, S., MD; and Alex Melchert, MS

1 November 1996 | Volume 125 Issue 9 | Page 779

TO THE EDITOR:

Trimethoprim-sulfamethoxazole has been used since 1968 and has been associated with major adverse reactions, including skin lesions, thrombocytopenia and leukopenia, and gastrointestinal dysfunction. In the past decade, hyperkalemia has been increasingly recognized as a side effect of this drug combination.

Allapan and colleagues [1] described 80 patients treated with standard-dose therapy (trimethoprim, <320 mg/d; sulfamethoxazole, <1600 mg/d) for various infections other than *Pneumocystis carinii* pneumonia. They found that hyperkalemia developed and serum creatinine levels increased 4 to 5 days after the start of therapy in many patients. No other electrolyte abnormalities were noted. Trimethoprim-sulfamethoxazole was believed to inhibit distal tubule sodium reabsorption and potassium secretion.

Velazquez and associates [2] and Greenberg and coworkers [3] observed hyperkalemia, hyponatremia, and increased creatinine levels in patients with human immunodeficiency virus infection (HIV) who received high-dose therapy (trimethoprim, 20 mg/kg of body weight per day; sulfamethoxazole, 100 mg/kg per day). These side effects peaked on day 5 [2] or between days 7 and 10 [3]. All patients had normal plasma renin activity and aldosterone levels.

We recently treated a 49-year-old HIV-positive patient (CD4 count, 34 cells/mm^3) for *P. carinii* pneumonia using trimethoprim-sulfamethoxazole (20 mg/kg per day). On admission, his potassium level was 3.8 mmol/L, his sodium level was 136 mmol/L, his blood urea nitrogen level was 8 mg/dL, and his creatinine level was 0.9 mg/dL. On day 12, his potassium level was 6.0 mmol/L, his sodium level was 131 mmol/L, his blood urea nitrogen level was 22 mg/dL, and his creatinine level was 1.0 mg/dL. The patient showed no evidence of acidosis or dehydration. His aldosterone level was 2 µg/dL, and his renin was 1.4 µg/mL per hour after intravenous therapy with furosemide (40 mg). His baseline cortisol level was 7.8 mg/dL. One hour after cosyntropin (0.25 mg) was given intravenously, the cortisol level increased to 10.3 mg/dL. Despite therapy with corticosteroids, electrolyte abnormalities persisted. On day 14, trimethoprim-sulfamethoxazole therapy was discontinued, and pentamidine was started. Two days later, the patient's potassium level was 4.0 mmol/L, and his sodium level was 136 mmol/L.

Seney and colleagues [4] described several electrolyte disorders in HIV-positive patients that were caused by adrenal or pituitary dysfunction, hyporeninemic hypoaldosteronism, or renal sodium wasting. The adrenal and pituitary defects may be subtle and may explain the high incidence (20% to 50%) of electrolyte abnormalities seen in HIV-positive patients [5]. Trimethoprim-sulfamethoxazole may unmask or exacerbate preexisting defects. Patients with HIV infection may also be susceptible to hyperkalemia during trimethoprim-sulfamethoxazole therapy because of an unrecognized defect in the renal or adrenal axis [2]. We believe that if hyperkalemia occurs, an endocrinologic evaluation should be done to predict future overt adrenal insufficiency.

Hamel MJ, **Greene C**, **Chiller T**, **Ouma P**, **Polyak C**, **Otieno K**, **Williamson J**, **Shi YP**, **Feikin DR**, **Marston B**, **Brooks JT**, **Poe A**, **Zhou Z**, **Ochieng B**, **Mintz E**, **Slutsker L**.

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We assessed the effect of daily cotrimoxazole, essential for HIV care, on development of antifolate-resistant Plasmodium falciparum, naso-pharyngeal Streptococcus pneumoniae (pneumococcus), and commensal Escherichia coli. HIV-positive subjects with CD4 cell count < 350 cells/muL (lower-CD4; N = 692) received cotrimoxazole; HIV-positive with CD4 cell count > or = 350 cells/muL (higher-CD4; N = 336) and HIV-negative subjects (N = 132) received multivitamins. Specimens were collected at baseline, 2 weeks, monthly, and at sick visits during 6 months of follow-up to compare changes in resistance, with higher-CD4 as referent. P. falciparum parasitemia incidence density was 16 and 156/100 person-years in lower-CD4 and higher-CD4, respectively (adjusted rate ratio [ARR] = 0.11; 95% confidence interval [CI] = 0.06-0.15; P < 0.001) and 97/100 person-years in HIV-negative subjects (ARR = 0.62; 95% CI = 0.44-0.86; P = 005). Incidence density of triple and quintuple dihydrofolate-reductase/dihydropteroate-synthetase mutations was 90% reduced in lower-CD4 compared with referent. Overall, cotrimoxazole non-susceptibility was high among isolated pneumococcus (92%) and E. coli (76%) and increased significantly in lower-CD4 subjects by Week 2 (P < 0.005). Daily cotrimoxazole prevented malaria and reduced incidence of antifolate-resistant P. falciparum but contributed to increased pneumococcus and commensal Escherichia coli resistance.

Trans R Soc Trop Med Hyg. 2006 Aug;100(8):785-90. Epub 2006 Feb 3.
Links

Incidence of neutropenia in HIV-infected African adults receiving co-trimoxazole prophylaxis: a 6-year cohort study in Abidjan, Côte d'Ivoire.

Toure S, **Gabillard D**, **Inwoley A**, **Seyler C**, **Gourvellec G**, **Anglaret X**.

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In a placebo-controlled trial of co-trimoxazole prophylaxis in Côte d'Ivoire, neutropenia was the most frequent short-term side effect. The long-term incidence of neutropenia in sub-Saharan African adults receiving co-trimoxazole has never been reported. We followed a prospective cohort of HIV-infected adults receiving co-trimoxazole (sulphamethoxazole 800 mg/trimethoprim 160 mg daily) in Abidjan. Grades of neutropenia were successively defined as at least one absolute neutrophil count (ANC) of: <1500/mm(3) (severity grade >/=1), <1000/mm(3) (grade >/=2), <750/mm(3) (grade >/=3) or <500/mm(3) (grade 4). In total, 533 adults were followed-up during 1450 person-years, with a total of 3154 ANCs. The probability of

remaining free of neutropenia at 48 months was 0.29 (95% CI 0.23-0.34) for grade >/=1, 0.64 (95% CI 0.60-0.71) for grade >/=2, 0.82 (95% CI 0.77-0.86) for grade >/=3 and 0.96 (95% CI 0.93-0.99) for grade 4. The only factor significantly associated with a higher rate of all grades of neutropenia was a low baseline CD4 count. There was no association between any grade of neutropenia and the global risk of serious morbidity during the study period. In adults receiving co-trimoxazole in Abidjan, mild neutropenia is a common observation with no evidence of negative clinical consequences. The consequences of associating co-trimoxazole with other haematotoxic drugs should be carefully assessed.

Rapid disease progression in human immunodeficiency virus type 1-infected individuals with adverse reactions to trimethoprim-sulfamethoxazole prophylaxis.

Veenstra J, Veugelers PJ, Keet IP, van der Ven AJ, Miedema F, Lange JM, Coutinho RA.

Municipal Health Service, Department of Public Health, Nijmegen, The Netherlands.

We studied the relation between the occurrence of adverse reactions to trimethoprim-sulfamethoxazole (TMP-SMZ) prophylaxis and the subsequent course of human immunodeficiency virus (HIV) infection in a cohort of homosexual men. Adverse reactions to TMP-SMZ were associated with a more rapid progression to AIDS (P < .001) and death (P < .001) and with a more rapid decline in CD4+ cell counts (P = .001). The median time to progression to AIDS was 14.9 months in subjects with adverse reactions to TMP-SMZ and 32.5 months in those without adverse reactions. After exclusion of Pneumocystis carinii pneumonia (PCP) and toxoplasmosis from the case definition of AIDS, the differences in the rate of progression to AIDS between subjects with and without adverse reactions to TMP-SMZ were still highly significant (P = .004). A low CD4+ cell count at baseline and the use of antiretroviral agents before the start of prophylaxis were predictors of adverse reactions to TMP-SMZ but did not account for the difference in progression to AIDS between subjects with and without adverse reactions to TMP-SMZ. In a univariate analysis, the relative hazard of adverse reactions to TMP-SMZ for progression to AIDS was 2.54 (95% confidence interval [CI], 1.50-4.28); in a multivariate analysis, it was 2.21 (95% CI, 1.29-3.81). The relative hazards of adverse reactions to TMP-SMZ for progression to AIDS with the exclusion of PCP and toxoplasmosis, CD4+ cell counts of <50/mm3, and death were 2.16 (95% CI, 1.25-3.72), 2.37 (95% CI, 1.36-4.12), and 3.21 (95% CI, 1.80-5.72), respectively. It is unclear whether adverse reactions to TMP-SMZ induce or merely predict progression of HIV disease.

1: Can Fam Physician. 2003 Sep;49:1085-6.

Trimethoprim-sulfonamide combination therapy in early pregnancy.

Sivojelezova A, **Einarson A**, **Shuhaiber S**, **Koren G**; **Motherisk Team**.

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QUESTION: One of my patients presented with bacteriuria early in her pregnancy. Urine culture was positive for Escherichia coli. I would like to prescribe a trimethoprim-sulfamethoxazole combination because it worked well for her in the past. What is known about the safety of this medication during early pregnancy? ANSWER: Evidence-based studies report an association between trimethoprim-sulfonamide combinations in early pregnancy and several major malformations, such as neural tube defects and cardiovascular defects. If clinically possible, physicians are advised to use alternative antimicrobial medications for treatment of urinary tract infections during early pregnancy.

1: J Antimicrob Chemother. 1996 May;37 Suppl B:55-60. Links

Adverse reactions to co-trimoxazole in HIV infection: a reappraisal of the glutathione-hydroxylamine hypothesis.

van der Ven AJ, **Vree TB**, **Koopmans PP**, **van der Meer JW**.

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It is postulated that the unstable hydroxylamine metabolite of sulphamethoxazole is responsible for the adverse reactions to co-trimoxazole and in HIV infection systemic glutathione deficiency leads to a reduced capacity to counteract the hydroxylamine toxicity. This hypothesis has been investigated by studying the metabolism of sulphamethoxazole and assessing glutathione status in HIV infection in order to explore the modification of treatment. It is concluded that the toxicity of plasma sulphamethoxazole hydroxylamine is counteracted by normal glutathione concentrations as is the case in HIV-seropositive patients, but that increased oxidation within certain cells in HIV infected individuals may possibly give rise to increased concentrations of reactive intermediates of sulphamethoxazole. Sulphametrole and sulphamethoxazole have similar half-lives but are metabolized differently: in vivo no oxidised metabolites of sulphametrole could be detected. In a retrospective study the rate of adverse reactions to trimethoprim-sulphametrole appeared to be in the lower range of those reported for trimethoprim-sulphamethoxazole indicating that the combination of trimethoprim-sulphametrole may be more favourable. The ratio of trimethoprim:sulphonamide is 1:5, but in-vitro studies with Toxoplasma gondii indicate that because of the synergic effect of both agents the dose of sulphonamide is possibly unnecessarily high.

failure to show a deficiency. *AIDS*. 1996;10:501-507. **1:** Indian Pediatr. 2007 Apr;44(4):311-2.
Indian Pediatrics Links

Acute lymphoblastic leukemia in association with long term exposure to trimethoprim-sulfomethaxozole.

Hudaoglu O, **Tokgöz Y**.

1: Emerg Med J. 2003 May;20(3):E3.   Links

Co-trimoxazole induced acute thrombocytopenic purpura.

Papaioannides D, **Bouropoulos C**, **Korantzopoulos P**.

Department of Medicine, Arta General Hospital, Arta, Greece.
gnnartas@art.forthnet.gr

1: Nephron Clin Pract. 2008;110(1):c55-7. Epub 2008 Aug 25.  
Links

Urinary infections due to multi-drug-resistant Escherichia coli among persons with HIV disease at a tertiary AIDS care centre in South India.

Vignesh R, **Shankar EM**, **Murugavel KG**, **Kumarasamy N**, **Sekar R**, **Irene P**, **Solomon S**, **Balakrishnan P**.

YRG Centre for AIDS Research and Education, VHS Campus, Rajiv Gandhi Salai, Taramani, Chennai, India.

BACKGROUND: While the spectrum of opportunistic infections due to HIV infection has been widely discussed, there are very limited data available in south India on certain incident infections especially urinary tract infections (UTI) in HIV-infected subjects. METHODS: Bacterial aetiology of 350 symptomatic UTI in HIV-infected subjects and the drug resistance pattern of the Escherichia coli isolates tested between June 2005 and July 2007 at the YRG Centre for AIDS Research and Education, a tertiary HIV Referral Centre in Chennai has been described here. RESULTS: E. coli was the most common etiological agent of UTI in HIV patients, followed by Staphylococcus aureus, Klebsiella pneumoniae, Enterococcus faecalis, Pseudomonas aeruginosa, Proteus spp. and Staphylococcus epidermidis. Twenty-nine E. coli isolates were multi-drug-resistant and 83.3% of the isolates were resistant to sulfamethoxazole-trimethoprim. CONCLUSIONS: Urinary pathogens in HIV-infected patients demonstrate high antimicrobial resistance and with majority of therapy for UTIs being empiric, constant updates of the aetiological agents and their drug susceptibility pattern would largely be beneficial to clinicians in choosing the right drug.

Pediatrics. 2008 Nov;122(5):1064-71. PEDIATRICS FINAL VERSION Links

Prophylaxis after first febrile urinary tract infection in children? A multicenter, randomized, controlled, noninferiority trial.

Montini G, Rigon L, Zucchetta P, Fregonese F, Toffolo A, Gobber D, Cecchin D, Pavanello L, Molinari PP, Maschio F, Zanchetta S, Cassar W, Casadio L, Crivellaro C, Fortunati P, Corsini A, Calderan A, Comacchio S, Tommasi L, Hewitt IK, Da Dalt L, Zacchello G, Dall'Amico R; IRIS Group.

Department of Pediatric Nephrology, Azienda Ospedaliera-University of Padua, Italy. montini@pediatria.unipd.it

OBJECTIVES: Febrile urinary tract infections are common in children and associated with the risk for renal scarring and long-term complications. Antimicrobial prophylaxis has been used to reduce the risk for recurrence. We performed a study to determine whether no prophylaxis is similar to antimicrobial prophylaxis for 12 months in reducing the recurrence of febrile urinary tract infections in children after a first febrile urinary tract infection. METHODS: The study was a controlled, randomized, open-label, 2-armed, noninferiority trial comparing no prophylaxis with prophylaxis (co-trimoxazole 15 mg/kg per day or co-amoxiclav 15 mg/kg per day) for 12 months. A total of 338 children who were aged 2 months to <7 years and had a first episode of febrile urinary tract infection were enrolled: 309 with a confirmed pyelonephritis on a technetium 99m dimercaptosuccinic acid scan with or without reflux and 27 with a clinical pyelonephritis and reflux. The primary end point was recurrence rate of febrile urinary tract infections during 12 months. Secondary end point was the rate of renal scarring produced by recurrent urinary tract infections on technetium 99m dimercaptosuccinic acid scan after 12 months. RESULTS: Intention-to-treat analysis showed no significant differences in the primary outcome between no prophylaxis and prophylaxis: 12 (9.45%) of 127 vs 15 (7.11%) of 211. In the subgroup of children with reflux, the recurrence of febrile urinary tract infections was 9 (19.6%) of 46 on no prophylaxis and 10 (12.1%) of 82 on prophylaxis. No significant difference was found in the secondary outcome: 2 (1.9%) of 108 on no prophylaxis versus 2 (1.1%) of 187 on prophylaxis. Bivariate analysis and Cox proportional hazard model showed that grade III reflux was a risk factor for recurrent febrile urinary tract infections. Whereas increasing age was protective, use of no prophylaxis was not a risk factor. CONCLUSIONS: For children with or without primary nonsevere reflux, prophylaxis does not reduce the rate of recurrent febrile urinary tract infections after the first episode.

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1: PLoS ONE. 2008 Sep 24;3(9):e3260. Open access to full text on PLoS one FREE full text article in PubMed Central
Links

Bacterial disease and antimicrobial susceptibility patterns in HIV-infected, hospitalized children: a retrospective cohort study.

Jaspan HB, **Huang LC**, **Cotton MF**, **Whitelaw A**, **Myer L**.

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BACKGROUND: Serious bacterial infections are a major source of morbidity and mortality in HIV-infected children. The spectrum of disease is wide, and responsible organisms vary according to setting. The use of antibiotic prophylaxis and the emergence of multi-drug resistant bacteria necessitate examination of responsible organisms and their antibiotic susceptibility. METHODOLOGY/PRINCIPAL FINDINGS: A retrospective cohort study of all HIV-positive pediatric admissions at an urban public sector hospital in Cape Town between January 2002 and June 2006 was conducted. Children between the ages of one month and nine years with laboratory confirmed HIV status, serious bacterial infection, and a hospital length of stay of 5 days or more, were eligible for inclusion. Organisms isolated from blood, urine, and cerebral spinal fluid cultures and their antimicrobial susceptibility were examined, and compared according to timing of isolation to distinguish nosocomial versus community-acquired. One hundred and forty-one children were identified (median age 1.2 years), 39% of whom were on antiretrovirals started before or during this hospitalization. Bacterial infections involved all organ systems, however pneumonia was most common (67%). S. pneumoniae and S. aureus were the most common gram positive and K. pneumoniae was the most common gram negative organism. K pneumoniae isolates were resistant to many first and second line antibiotics, and were all considered nosocomial. All S. aureus isolates were methicillin resistant, some of which were community-acquired.
CONCLUSIONS/SIGNIFICANCE: Bacterial infections are an important source of co-morbidity in HIV-infected children in resource-limited settings. Clinicians should have a low threshold to initiate antibiotics in children requiring hospitalization. Broad-spectrum antibiotics should be used judiciously. Clinicians caring for HIV-infected children should be cognizant of the most common organisms affecting such children, and of their local antimicrobial susceptibilities, when treating empirically for serious bacterial infections.

Hudaoglu O, **Tokgöz Y**.

1: Kansenshogaku Zasshi. 1990 Apr;64(4):455-66. Links

[Morphological changes in Pneumocystis carinii in the alveolar space due to treatment with co-trimoxazole--comparison of clinical cases and experimental rats]

[Article in Japanese]

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In this study, transmission electron microscopy was employed to observe the morphological changes in Pneumocystis carinii (P. carinii) in the alveolar space of patients and experimental rats treated with co-trimoxazole. Experimentally, P. carinii pneumonia was induced in Wistar rats by peritoneal injection of prednisolone and then treated with co-trimoxazole. The animals were divided into an untreated group and groups treated with co-trimoxazole for 3-9 days. In the untreated group, various forms of P. carinii were seen to be filling up the alveolar space. There were few morphological changes (shape, size and intracellular substances) in the P. carinii in the alveolar space of the animals in the 3-day and 5-day treated groups. However, in the 7-day treated group, important intracellular components such as mitochondria were not seen, and after 7 or more days of treatment there were no crescent-shaped P. carinii, which are characteristically observed in the proliferative stage. In the 9-day treated group, the cell membranes of thick-walled cysts were ruptured, and there was intracellular vacuolization. In addition, untreated patients complicated with P. carinii pneumonia (2 cases), patients treated for 3-5 days (4 cases) and a patients treated for 1 month (1 case) were studied. The morphology of P. carinii in the alveoli of those clinical cases was similar to that seen in the rats, and the changes in shape, intracellular components and cell membranes after treatment were the same except in case 5. In case 5, lamellar-body-like substances such as seen in alveolar proteinosis filled up the alveoli, and the cell membranes of P. carinii were ruptured. Electron microscopic studies revealed no changes in the cell membranes during the early period of treatment. We surmise that co-trimoxazole is taken into P. carinii cells and then interferes with the cellular metabolism. On the basis of the results of this study, the critical period determining whether a patients with P. carinii pneumonia can be cured or not is around the 9th day of treatment with co-trimoxazole. Therefore, it is necessary to make an early diagnosis, begin treatment with co-trimoxazole as soon as possible and continue the treatment for 9 or more days.

1: Int J Pediatr Otorhinolaryngol. 2007 Nov;71(11):1797-802. Epub 2007 Sep 17.


Links

Vestibular system in infants after systemic aminoglycoside therapy.

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OBJECTIVES: The ototoxic action of systemic therapy with aminoglycoside antibiotics leading to the loss of inner ear hair cells is well recognized. The mitochondria-mediated pathway of apoptosis may play a role in inducing the apoptosis of vestibular hair cells due to aminoglycoside toxicity. Aminoglycosides are, nevertheless, routinely used for treatment of vital infections in neonatologic departments. Although there is a strong supposition that aminoglycosides can influence the vestibular function in infants, the routine examination of the infants' inner ear does not include vestibular tests. The purpose of the present study was to evaluate vestibular function in a group of infants prior to and after administration of

systemic aminoglycosides, using caloric tests and vestibular-evoked myogenic potentials (VEMPs). METHODS: VEMPs and auditory brainstem responses were recorded and caloric stimulation was performed in 68 infants aged 2.5-3.5 months: 40 healthy controls and 28 infants after therapy with amikacin, 15mg/(kgday) in three doses. The therapy duration varied from 10 to 14 days. In 18 infants antibiotic therapy was administered for a respiratory infection, and in 10 for sepsis. Infants with other risk factors of inner ear damage and treated with more than one ototoxic drug were excluded from the study. The tests were performed on the day of admission to hospital and repeated on the day of discharge. RESULTS: The results of all tests were normal on admission. On the day of discharge, no reaction to caloric stimulation was elicited in six patients and no VEMPs were recorded in four subjects. Hearing thresholds were normal in all the individuals during both examinations. CONCLUSIONS: The vestibular organ in infants after systemic therapy with amikacin may be damaged more frequently than the cochlear organ. The horizontal canal is more vulnerable to aminoglycosides, as compared to the saccule. The vestibular organ should be routinely examined in infants after systemic treatment with aminoglycosides.

11: AIDS. 2006 Jun 12;20(9):1343-5. Wolters Kluwer | Lippincott Williams & Wilkins Links

HIV therapy, hepatitis C virus infection, antibiotics and obesity, a mitochondria killer mix?

Côté HC, **Brumme ZL**, **Chan JW**, **Guillemi S**, **Montaner JS**, **Harrigan PR**.

: J Antimicrob Chemother. 1984 Sep;14(3):231-41. FULL FINAL TEXT OXFORD JOURNALS Links

Inhibition of mammalian microsomal protein synthesis by aminoglycoside antibiotics.

Buss WC, **Piatt MK**, **Kauten R**.

The aminoglycoside antibiotics gentamicin, kanamycin and netilmicin produce a dose-dependent inhibition of amino acid incorporation in microsomes isolated from human liver and rat brain, kidney and liver. Inhibitory effects on microsomal protein synthesis occur at concentrations that have been shown to accumulate in rodent and human renal cortex and perilymph following therapeutic administration. Inhibition of translation in those tissues which specifically accumulate aminoglycoside antibiotics may, in part, explain toxicities observed following exposure to aminoglycosides.

1: Biochemistry. 1978 Oct 31;17(22):4825-32. Links

Stimulation of eukaryotic transcription by glycerol and polyhydroxylic compounds.

Buss WC, **Stalter K**.

: Biochem Pharmacol. 1978;27(17):2139-45. Links

Effects of rifampicin on RNA and protein synthesis in isolated rat liver mitochondria.

Buss WC, **Kun E**.

: Arch Biochem Biophys. 1970 Jan;136(1):54-64. Links

Biogenesis of mitochondria. 12. The effects of aminoglycoside antibiotics on the mitochondrial and cytoplasmic protein-synthesizing systems of Saccharomyces cerevisiae.

Davey PJ, **Haslam JM**, **Linnane AW**.

Curr Top Med Chem. 2003;3(9):1021-42. Links

Oxazolidinone antibacterial agents: a critical review.

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This review covers recent developments in several important aspects of research on oxazolidinone antibacterial agents. Structure-activity relationships are first discussed, emphasizing bioisosteric replacements for the both the oxazolidinone ring and the N-acetylaminomethyl group at C-5. The oxazolidinones have a mechanism of action that is distinct from other antibacterial agents, whereby protein synthesis is inhibited prior to initiation. Studies aimed at determining how the oxazolidinones bind to the bacterial ribosome and interfere with peptidyl transferase activity are described in detail, and are then related to the nature of the changes in the ribosomal RNA leading to resistance. Toxicity of the oxazolidinones remains a critical issue, in that early lead compounds exhibited lethal toxicity in animal studies. Preclinical and clinical safety studies of both eperezolid and linezolid are summarized, giving emphasis to histopathological effects observed in early animal studies. These studies are then related to thrombocytopenia and pancytopenia observed in patients treated with linezolid for extended time periods. Finally, studies to determine the nature and potential severity of drug-drug interactions in patients undergoing linezolid therapy are discussed.

Toxicol Appl Pharmacol. 1999 Apr 15;156(2):129-40. Links

Interactions of macrolide antibiotics (Erythromycin A, roxithromycin, erythromycylamine [Dirithromycin], and azithromycin) with phospholipids: computer-aided conformational analysis and studies on acellular and cell culture models.

Montenez JP, **Van Bambeke F**, **Piret J**, **Brasseur R**, **Tulkens PM**, **Mingeot-Leclercq MP**.

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The potential of 14/15 membered macrolides to cause phospholipidosis has been prospectively assessed, and structure-effects examined, using combined experimental and conformational approaches. Biochemical studies demonstrated drug binding to phosphatidylinositol-containing liposomes and inhibition of the activity of lysosomal phospholipase A1 toward phosphatidylcholine included in the bilayer, in close correlation with the number of cationic groups carried by the drugs (erythromycin A </= roxithromycin < erythromycylamine </= azithromycin). In cultured cells (fibroblasts), phospholipidosis (affecting all major phospholipids except sphingomyelin) was observed after 3 days with the following ranking: erythromycin A </= roxithromycin < erythromycylamine < azithromycin (roxithromycin could, however, not be studied in detail due to intrinsic toxicity). The difference between erythromycylamine and azithromycin was accounted for by the lower cellular accumulation of erythromycylamine. In parallel, based on a methodology developed and validated to study drug-membrane interactions, the conformational analyses revealed that erythromycin A, roxithromycin, erythromycylamine, and azithromycin penetrate into the hydrophobic domain of a phosphatidylinositol monolayer through their desosamine and cladinose moieties, whereas their macrocycle is found close to the interface. This position allows the aminogroups carried by the macrocycle of the diaminated macrolides (erythromycylamine and azithromycin) to come into close contact with the negatively charged phosphogroup of phosphatidylinositol, whereas the amine located on the C-3 of the desosamine, common to all four drugs, is located at a greater distance from this phosphogroup. Our study suggests that all macrolides have the potential to cause phospholipidosis but that this effect is modulated by toxicodynamic and toxicokinetic parameters related to the drug structure and mainly to their cationic character. Copyright 1999 Academic Press.

1J Antimicrob Chemother. 2008 Jul;62(1):196-204. Epub 2008 Apr 9.

Antibiotic use in 26 departments of internal medicine in 6 general hospitals in Israel: variability and contributing factors.

Shalit I, **Low M**, **Levy E**, **Chowers M**, **Zimhony O**, **Riesenberg K**, **Bishara J**, **Raz R**.

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OBJECTIVES: Increased antibiotic consumption is associated with increased bacterial resistance worldwide. We aimed to analyse antibiotic consumption and potential contributory factors in internal medicine departments in Israel. METHODS: Data (2003-04) from 26 departments in 6 hospitals were retrieved. Defined daily doses (DDD)/100 bed-days were calculated for total antibiotic use and by antibiotic class. Patterns identified were correlated with 15 patients' and departmental variables by univariate and multivariate analyses. RESULTS: Total antibiotic consumption differed by a factor of 2.3 (115 DDD/100 bed-days to 49.1 DDD/100 bed-days) between the highest and lowest consuming departments. Antibiotic classes differed by a factor of 22.8 for macrolides, a factor of 20 for piperacillin/tazobactam, a factor of 17 for carbapenems, a factor of 13.3 for quinolones, a factor of 9 for vancomycin, a factor of 6.8 for amoxicillin/clavulanate, a factor of 6.6 for aminoglycosides, a factor of 5.3 for penicillins and a factor of 2.8 for cephalosporins. Even among departments within hospitals, there was a difference of up to 1.5-fold for total use and antibiotic class differences ranged between 2.5- and 7.2-fold for third- and fourth-generation cephalosporins, despite similar Charlson scores and other patient variables. In the multivariate analysis, hospital affiliation and rate of 1 day hospitalization were the only significant variables predicting total antibiotic use, contributing 43% and 7.3%, respectively, to the variance. By antibiotic class, controlling for hospital affiliation, patients with neutropenia, lower respiratory tract infections and assisted ventilation were the most common significant contributors, ranging from 3.5% for quinolones to 7.7% for piperacillin/tazobactam. CONCLUSIONS: Patterns of antibiotic use vary widely among internal medicine departments in Israel, which cannot be explained by objective parameters related either to patients or wards. Ongoing monitoring and guideline formulation are needed to regulate antibiotic prescription.

Lancet Infect Dis. 2003 Jun;3(6):359-71.  Links

Immunomodulatory effects of quinolones.

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We review data on the in-vitro, ex-vivo, in-vivo, and clinical effects of fluoroquinolones on the synthesis of cytokines and their mechanisms of immunomodulation. In general, most fluoroquinolone derivatives superinduce in-vitro interleukin 2 synthesis but inhibit synthesis of interleukin 1 and tumour necrosis factor (TNF)alpha; furthermore, they enhance significantly the synthesis of colony-stimulating factors (CSF). Fluoroquinolones affect in-vivo cellular and humoral immunity by attenuating cytokine responses. Interleukins 10 and 12 have an important role in the functional differentiation of immunocompetent cells and trigger the initiation of the acquired immune response. In addition, certain fluoroquinolones were

seen to enhance haematopoiesis by increasing the concentrations of CSF in the lung as well as in the bone marrow and shaft. Those fluoroquinolones exerting significant effects on haematopoiesis were those with a cyclopropyl moiety at position N1 of their quinolone core structure. Mechanisms that could explain the various immunomodulatory effects of fluoroquinolones include: (1) an effect on intracellular cyclic adenosine-3',5'-monophosphate and phosphodiesterases; (2) an effect on transcription factors such as nuclear factor (NF)kappaB, activator protein 1, NF-interleukin-6 and nuclear factor of activated T cells; and (3) a triggering effect on the eukaryotic equivalent of bacterial SOS response with its ensuing intracellular events. Further studies are required, especially in the clinical setting to exploit fully the potential of the immunomodulatory effect of fluoroquinolones during, for example, immunosuppression, chronic airway inflammatory diseases, and sinusitis.

1: Antimicrob Agents Chemother. 1989 Apr;33(4):593-4. 

Links

Widespread quinolone resistance among methicillin-resistant Staphylococcus aureus isolates in a general hospital.

Shalit I, **Berger SA**, **Gorea A**, **Frimerman H**.

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Ofloxacin and ciprofloxacin resistance (MIC, greater than 4 micrograms/ml) was encountered in 45 of 50 clinical isolates of methicillin-resistant Staphylococcus aureus. None of 20 methicillin-susceptible strains was resistant to the quinolones (P less than 10(-6). Quinolone-susceptible and -resistant isolates did not differ with respect to culture source or bacteriophage type. The future usefulness of quinolones for S. aureus infection may be limited.

1: Lymphokine Res. 1989 Spring;8(1):35-46. Links

Enhancement of interleukin-2 production in human lymphocytes by two new quinolone derivatives.

Zehavi-Willner T, **Shalit I**.

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The effect of two quinolone derivatives, ciprofloxacin and ofloxacin, on the production of interleukin-2 (IL-2) was studied in human peripheral blood lymphocytes (PBL) and in a T-cell leukemia cell line (Jurkat) following phytohemagglutinin (PHA) stimulation. Both antimicrobial agents markedly increased IL-2 production in PHA-stimulated PBL cultures. No such effect was observed without PHA stimulation. The

effect of the two quinolones on IL-2 production was both time and concentration dependent, reaching a 3-5 fold increase at a drug concentration of 50-100 micrograms/ml, following 24 h incubation. IL-2 synthesized in response to ciprofloxacin or ofloxacin stimulation, exhibited identical chromatographic properties and molecular weight to IL-2 synthesized at standard IL-2 inducing conditions. Only ciprofloxacin enhanced IL-2 production in PHA or in PHA and phorbol myristic acetate (PMA)-stimulated Jurkat cells. The stimulatory effect observed in Jurkat cells at optimal dose concentration (10-50 micrograms/ml), was at most 50% above control levels. In contrast to the effect of ciprofloxacin as a costimulator of IL-2 production in PHA-stimulated PBL, the drug excerted a prominent inhibitory effect on the incorporation of radioactive thymidine and amino acids into these cells. Ciprofloxacin, but not ofloxacin, enhanced interferon (IFN) production in PHA-induced PBL, whereas immunoglobulin M [IgM] production in a SKW6 cell line was enhanced only by ofloxacin.

1: Proc Natl Acad Sci U S A. 2008 Dec 30;105(52):20888-93. Epub 2008 Dec 22.

Genetic analysis of interactions with eukaryotic rRNA identify the mitoribosome as target in aminoglycoside ototoxicity.

Hobbie SN, **Akshay S**, **Kalapala SK**, **Bruell CM**, **Shcherbakov D**, **Böttger EC**.

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Aminoglycoside ototoxicity has been related to a surprisingly large number of cellular structures and metabolic pathways. The finding that patients with mutations in mitochondrial rRNA are hypersusceptible to aminoglycoside-induced hearing loss has indicated a possible role for mitochondrial protein synthesis. To study the molecular interaction of aminoglycosides with eukaryotic ribosomes, we made use of the observation that the drug binding site is a distinct domain defined by the small subunit rRNA, and investigated drug susceptibility of bacterial hybrid ribosomes carrying various alleles of the eukaryotic decoding site. Compared to hybrid ribosomes with the A site of human cytosolic ribosomes, susceptibility of mitochondrial hybrid ribosomes to various aminoglycosides correlated with the relative cochleotoxicity of these drugs. Sequence alterations that correspond to the mitochondrial deafness mutations A1555G and C1494T increased drug-binding and rendered the ribosomal decoding site hypersusceptible to aminoglycoside-induced mistranslation and inhibition of protein synthesis. Our results provide experimental support for aminoglycoside-induced dysfunction of the mitochondrial ribosome. We propose a pathogenic mechanism in which interference of aminoglycosides with mitochondrial protein synthesis exacerbates the drugs' cochlear toxicity, playing a key role in sporadic dose-dependent and genetically inherited, aminoglycoside-induced deafness.

Ren Fail. 1992;14(3):351-7. Links

Drug-phospholipid interactions: role in aminoglycoside nephrotoxicity.

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Aminoglycoside antibiotics are known to be transported and accumulated within lysosomes of renal proximal tubular cells and to cause proximal tubular cell injury and necrosis. The pathogenesis of aminoglycoside nephrotoxicity is postulated to be related to the capacity of these organic polycations to interact electrostatically with membrane anionic phospholipids and to disrupt membrane structure and function. Aminoglycoside antibiotics have been shown to bind to anionic phospholipids of model membranes and to alter membrane permeability and promote membrane aggregation. In vivo these drugs induce phospholipiduria and a renal cortical phospholipidosis. The latter reflects the accumulation of phospholipid-containing myeloid bodies within the lysosomal compartment consequent to aminoglycoside-induced inhibition of lysosomal phospholipases. The mechanism of drug-induced inhibition of phospholipases has been shown to be secondary to the binding of these cationic drugs to anionic phospholipids. As the lysosomes became progressively distended with myeloid bodies, they become unstable and eventually rupture, which results in the release of acid hydrolases as well as high concentrations of aminoglycosides into the cytoplasm where they interact with and disrupt the function of other membranes and organelles including mitochondria and microsomes. It is postulated that the redistribution of drug from the lysosomal compartment to organellar membranes is the critical event which triggers the irreversible injury cascade. Polyaspartic acid is a polyanionic peptide which when administered in vitro or in vivo forms electrostatic complexes with aminoglycoside antibiotics and prevents these drugs from interacting with anionic phospholipids, from perturbing phospholipid metabolism and from causing cell injury and necrosis.

J Pharmacol Sci. 2005 May;98(1):49-57. Epub 2005 May 7.

Cephaloridine induces translocation of protein kinase C delta into mitochondria and enhances mitochondrial generation of free radicals in the kidney cortex of rats causing renal dysfunction.

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We have previously reported that the enhancement of free radical generation in mitochondria isolated from the kidney cortex of rats exposed to cephaloridine (CER) is probably mediated by the activation of protein kinase C (PKC). We examined which

isoenzymes of PKC might be involved in the development of nephrotoxicity induced by CER in rats. The CER-induced renal dysfunction observed 24 h after its injection was prevented by a potent antioxidant DPPD and well-known PKC inhibitors like H-7 and rottlerin. At 1.5 and 3.5 h after the CER injection, the free radical generation was increased markedly and this was associated with translocation of PKCdelta into the mitochondria of renal cortex tissue. Pretreatment of rats with H-7, a PKC inhibitor, significantly inhibited the CER-derived increase in mitochondrial generation of free radicals, suggesting that H-7 probably gets into the mitochondria and inhibits the activity of translocated PKC within the mitochondria. It was also shown that pretreatment of rats with rottlerin, a specific inhibitor of PKCdelta, suppressed the early translocation of PKCdelta into mitochondria and inhibited the CER-derived development of renal dysfunction. These results suggest that the CER-derived early translocation of PKCdelta into mitochondria probably leads to the enhanced production of free radicals through the mitochondrial respiratory chain during the development of the nephrotoxicity caused by CER. Understanding the role of PKCdelta in mitochondria may provide an important clue to the molecular mechanisms of mitochondrial production of reactive oxygen species and the free radical-induced renal failure in rats treated with CER.

Toxicol Appl Pharmacol. 1991 Jun 15;109(2):314-26. Links

Cephaloridine-induced biochemical changes and cytotoxicity in suspensions of rabbit isolated proximal tubules.

Rush GF, **Ponsler GD**.

Lilly Research Laboratories, Eli Lilly and Co., Greenfield, Indiana.

Cephalosporin antibiotics, such as cephaloridine (Cld), are known to be nephrotoxic in vivo and in vitro. In vivo, Cld causes proximal tubule necrosis in rabbits which is preceded by glutathione (GSH) depletion and, under certain conditions, inhibition of mitochondrial function. In vitro, Cld causes GSH depletion, lipid peroxidation, and inhibition of rat kidney slice organic ion uptake. The present investigations were designed to evaluate the temporal relationships of the biochemical "lesions" caused by Cld to the onset of lethal cell injury in suspensions of isolated rabbit proximal tubules. Cld was cytotoxic to suspensions of rabbit proximal tubules (EC50 = 1.10 +/- 0.33 mM) in the absence of amino acids (to support GSH synthesis). In this model, Cld also caused GSH and ATP depletion, lipid peroxidation (malondialdehyde formation), and inhibition of tubule respiration. Probenecid prevented Cld accumulation, tubule injury, ATP depletion, and lipid peroxidation and markedly attenuated the GSH depletion. Addition of glycine, cystine, and glutamate to the incubation buffer to support GSH synthesis decreased the tubule accumulation of Cld (due solely to the presence of glutamate) and blocked Cld-induced tubule lethality, lipid peroxidation, ATP depletion, and GSH depletion. Glycine or glutamate alone had no effect on Cld-induced cytotoxicity, whereas cystine was cytoprotective. Buthionine sulfoximine partially reversed the amino acid protection against Cld-induced tubule injury. Thus amino acid-induced protection of tubules from Cld cytotoxicity was due to the combination of a high intracellular GSH content and cytoprotection by cystine. The antioxidant N-N'-diphenyl-p-phenylenediamine (DPPD) blocked tubule injury, ATP

depletion, and lipid peroxidation but had no effect on Cld-induced GSH depletion when tubules were incubated for 3 hr. However, when incubations were allowed to run for up to 8 hr, DPPD had no effect on Cld cytotoxicity, despite continued inhibition of lipid peroxidation. These data demonstrate that Cld-induced tubule injury in short-term (3 hr) incubations in vitro occurs by a mechanism probably involving lipid peroxidation and occurs only in the absence of amino acids to support GSH synthesis. Inhibition of tubule respiration and ATP depletion could not clearly be causally linked to the onset of cell death in this model. The mechanism of the peroxidation-independent Cld toxicity in tubules incubated for 8 hr or longer is not known at this time.

: J Biol Chem. 2005 Jul 15;280(28):26193-9. Epub 2005 May 19. 


Links

Chloramphenicol-induced mitochondrial stress increases p21 expression and prevents cell apoptosis through a p21-dependent pathway.

Li CH, **Tzeng SL**, **Cheng YW**, **Kang JJ**.

Institute of Toxicology, College of Medicine, National Taiwan University, Taipei 100, Taiwan.

Pretreatment of HepG2 and H1299 cells with chloramphenicol rendered the cells resistant to mitomycin-induced apoptosis. Both mitomycin-induced caspase 3 activity and PARP activation were also inhibited. The mitochondrial DNA-encoded Cox I protein, but not nuclear-encoded proteins, was down-regulated in chloramphenicol-treated cells. Cellular levels of the p21(waf1/cip1) protein and p21(waf1/cip1) mRNA were increased through a p53-independent pathway, possibly because of the stabilization of p21(waf1/cip1) mRNA in chloramphenicol-treated cells. The p21(waf1/cip1) was redistributed from the perinuclear region to the cytoplasm and co-localized with mitochondrial marker protein. Several morphological changes and activation of the senescence-associated biomarker, SA beta-galactosidase, were observed in these cells. Both p21(waf1/cip1) antisense and small interfering RNA could restore apoptotic-associated caspase 3 activity, PARP activation, and sensitivity to mitomycin-induced apoptosis. Similar effects were seen with other antibiotics that inhibit mitochondrial translation, including minocycline, doxycycline, and clindamycin. These findings suggested that mitochondrial stress causes resistance to apoptosis through a p21-dependent pathway.

: Cancer Res. 2008 Jun 15;68(12):4875-81. 


Links

Chloramphenicol induces abnormal differentiation and inhibits apoptosis in activated T cells.

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Chloramphenicol is a broad-spectrum antibiotic used for the treatment of many infectious diseases and has become one of the major seafood contaminants. Hematologic disorders such as aplastic anemia and leukemia induced by chloramphenicol are a major concern. However, the mechanism underlying chloramphenicol-induced leukemogenesis is not known. By investigating the effects of chloramphenicol on the activation of mouse T cells stimulated with anti-CD3 antibody or staphylococcal enterotoxin B, we found that chloramphenicol induces the differentiation of activated T cells into lymphoblastic leukemia-like cells, characterized by large cell size, multiploid nuclei, and expression of CD7, a maker for immature T cells and T-cell lymphocytic leukemia, thus phenotypically indicating differentiation toward leukemogenesis. High expression of cyclin B1, but not p53, c-myc, and CDC25A, was detected in chloramphenicol-treated activated T cells, which may relate to abnormal cell differentiation. Chloramphenicol inhibited the activation-induced cell death of mouse and human T-cell receptor-activated T cells by down-regulating the expression of Fas ligand. Our findings show that abnormal cell differentiation and inhibition of apoptosis may contribute to the development of leukemia associated with clinical applications of chloramphenicol.

: Niger Postgrad Med J. 2001 Sep;8(3):112-5. Links

Bone marrow morphological features in anaemic patients with acquired immune deficiency syndrome in Nigeria.

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The morphological features of bone marrow aspiration biopsies performed at the University of Maiduguri Teaching Hospital from 1997 to 1999 (3 years) on 24 anaemic AIDS patients (Table i) were retrospectively reviewed. The marrow was normocellular in 7(29.2%) cases and hypocellular in 17(70.8%) cases. Erythropoiesis was normoblastic in 5(20.8%) cases, micronormoblastic in 8(33.3%) cases and megaloblastic in 11(45.8%) cases. All of the 8(33.3%) cases with micronormoblastic erythropoiesis had no stainable iron stores while the remaining 16(66.7%) cases with either normoblastic or megaloblastic erythropoiesis had increased stainable iron stores. Myelopoiesis was sequential in all cases studied. Megakaryocytes were adequate in all cases. Dysplasia in the form of cytoplasmic vacuolations affecting both erythroid and myeloid precursors was seen in 4(16.7%) cases. Lymphocytes counts were normal in 17(70.8%) cases and increased in 7(29.2%) cases. Plasma cells were increased in all cases. Haemophagocytosis was seen in only 1(4.2%) case. Of the 24 cases studied. 10 and 14 cases had positive and negative history of Chloramphenicol ingestion respectively and the cases with positive history of the drug ingestion had significantly higher frequency (90%) of marrow hypocellularity as compared to the lower frequency of 51.7% seen among cases with negative history of chloramphenicol

ingestion. These marrow features were thought to reflect the combined effect of malnutrition and drug (Chloramphenicol) in a background state of advanced chronic disease due to AIDS.

: Antimicrob Agents Chemother. 2001 Jan;45(1):44-7.

Clarithromycin inhibits NF-kappaB activation in human peripheral blood mononuclear cells and pulmonary epithelial cells.

Ichiyama T, **Nishikawa M**, **Yoshitomi T**, **Hasegawa S**, **Matsubara T**, **Hayashi T**, **Furukawa S**.

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Macrolide antibiotics modulate the production of proinflammatory cytokines in vivo and in vitro. Transcription of the genes for these proinflammatory cytokines is regulated by nuclear factor kappaB (NF-kappaB). We examined whether or not clarithromycin inhibits the activation of NF-kappaB induced by tumor necrosis factor alpha (TNF-alpha) or staphylococcal enterotoxin A (SEA) in human monocytic U-937 cells, a T-cell line (Jurkat), a pulmonary epithelial cell line (A549), and peripheral blood mononuclear cells (PBMC). Flow cytometry revealed that clarithromycin suppresses NF-kappaB activation induced by TNF-alpha in U-937 and Jurkat cells in a concentration-related manner. Western blot analysis also demonstrated that clarithromycin inhibits NF-kappaB activation induced by TNF-alpha in U-937, Jurkat, and A549 cells and PBMC and by SEA in PBMC. Western blot analysis of cytoplasmic extracts of A549 cells revealed that this inhibition is not linked to preservation of expression of the IkappaBalpha protein. The chloramphenicol acetyltransferase assay indicated that NF-kappaB-dependent reporter gene expression is suppressed in U-937 cells pretreated with clarithromycin. These findings are consistent with the idea that clarithromycin suppresses the production of proinflammatory cytokines via inhibition of NF-kappaB activation.

: Immunopharmacol Immunotoxicol. 1992;14(4):769-82.

Antimicrobial agents induce monocytes to release IL-1 alpha, IL-6, and TNF, and induce lymphocytes to release IL-4 and TNF tau.

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Evaluation was carried out on the action of different antibiotics on the release of cytokines. Experiments were done in vitro on monocytes and on human lymphocytes. Results show that the majority of the antibiotics tested are able to induce the release of one or more cytokines from their respective producing cells. Among the beta-lactams the most active were the cephalosporins (cephalexin, cefamandol, ceftazidin, and a sulbactam-ampicillin combination) in inducing the release of TNF, IL-1 alpha, and IL-6 from monocytes, and releasing IL-4 and IFN-tau from lymphocytes. The sulbactam-ampicillin combination and cefamandole were extremely active in the production of IFN-tau. Among the lincosamides, clindamycine notably stimulated the release of TNF and IL-6, while lincomycine induced a notable increment of IL-4 from monocytes. Teicoplanin is a very strong inducer of TNF, IL-1 alpha and IL-6.

Chem Biol Interact. 2005 Feb 28;152(1):13-24.  Links

Interaction of amoxicillin with DNA in human lymphocytes and H. pylori-infected and non-infected gastric mucosa cells.

Arabski M, **Kazmierczak P**, **Wisniewska-Jarosinska M**, **Poplawski T**, **Klupinska G**, **Chojnacki J**, **Drzewoski J**, **Blasiak J**.

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Amoxicillin is a penicillin derivative belonging to a group of beta-lactam antibiotics used in Helicobacter pylori eradication. Clinical application of amoxicillin is underlined by its antibacterial activity, but little is known about its interaction with DNA of human cells. Using the alkaline comet assay we investigated the genotoxicity of amoxicillin in human peripheral blood lymphocytes as well as in H. pylori-infected and non-infected human gastric mucosa cells. To assess the role of reactive oxygen species in the genotoxicity of amoxicillin we employed a set of antioxidant and free radical scavengers, including Vitamins C and E, melatonin and the nitrone spin trap N-tert-butyl-alpha-phenyl-nitrone (PBN). Amoxicillin-induced DNA damage was completely repaired after 60 min. The vitamins, melatonin and the spin trap decreased the extent of the damage. The cells exposed to amoxicillin and treated with endonuclease III and 3-methyladenine-DNA glycosylase II, the enzymes recognizing oxidized bases displayed greater extent of DNA damage than those not treated with these enzymes. H. pylori non-infected gastric mucosa cells exposed to hydrogen peroxide repaired their DNA in a 60 min incubation, but the infected cells were not able to do so. The action of DNA repair enzymes, the vitamins, melatonin and PBN indicated that amoxicillin-induced oxidative DNA damage. The drug did not induce DNA strand breaks in isolated pUC19 plasmid DNA. Our results suggest that amoxicillin can induce DNA damage in human lymphocytes and gastric mucosa cells and this effect may follow from the production of reactive oxygen species. Cellular activation of the drug is needed to induce DNA damage. Free radical scavengers and

antioxidants may be used to assist H. pylori eradication with amoxicillin to protect DNA of the host cells. Our results suggest also that H. pylori infection may alter gastric mucosa cells response to DNA-damaging agents and in this way contribute to initiation/promotion of cancer transformation of these cells induced by external or internal carcinogens.

Mol Pharmacol. 2002 Jun;61(6):1348-58. Final Version FREE Mol Pharmacol Links

A novel beta-lactam antibiotic activates tumor cell apoptotic program by inducing DNA damage.

Smith DM, **Kazi A**, **Smith L**, **Long TE**, **Heldreth B**, **Turos E**, **Dou QP**.

Drug Discovery Program, and the Department of Chemistry, College of Arts and Sciences, University of South Florida, Tampa, Florida 33612-9497, USA.

Many of the anticancer drugs in current use are toxic and thus limited in their efficacy. It therefore becomes essential to develop novel chemotherapeutic agents with lower levels of toxicity. The beta-lactam antibiotics have been used for many years to treat bacterial infections with limited or no toxicity. Until now, it has never been shown that beta-lactams could kill tumor cells. Here, for the first time, we have discovered and characterized the apoptosis-inducing properties of a family of novel beta-lactam antibiotics against human leukemia, breast, prostate, and head-and-neck cancer cells. We found that one particular lead compound (lactam 1) with an N-methylthio group was able to induce DNA damage and inhibit DNA replication in Jurkat T cells within a 2-h treatment. This was followed by p38 mitogen-activated protein kinase activation, S phase arrest, and apoptotic cell death. p38 was found to be a central player in beta-lactam-induced apoptosis and resided downstream of DNA damage but upstream of caspase activation. Accompanying caspase-8 activation was cleavage of the pro-apoptotic Bcl-2 family protein Bid, and release of the mitochondrial cytochrome c. This was also associated with activation of caspase-9 and -3. Analogs of lactam 1 in which the N-methylthio group was replaced with other organothio chains exhibited progressive decreased potencies to induce DNA damage, p38 kinase activation, S phase arrest, and apoptosis, demonstrating requirement of the N-methylthio group. Because of the ease of synthesis and structural manipulation, we believe these beta-lactams may have the potential to be developed into anticancer agents.

Toxicology. 2001 Feb 2;158(1-2):25-9. ELSEVIER FULL-TEXT ARTICLE Links

Th(1)/Th(2) responses to drugs.

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T lymphocytes can be characterized by their pattern of cytokine secretion and be divided into type I (Th(l)/Tc(l)) and type 2 (Th(2)/Tc(2)) subsets. The involvement of

type-1 or type 2-like responses in sensitization has been studied in the mouse, with reference contact and respiratory contact sensitizers. One interesting feature with certain drugs, such as beta-lactam antibiotics, is the diversity of clinical manifestations associated with immune-mediated hypersensitivity reactions in humans: immediate reactions such as urticaria, Quincke oedema and anaphylactic shock, and delayed hypersensitivity reactions, such as maculopapular rashes, allergic contact dermatitis and skin reactions of other types. In the mouse, Th(1) and Th(2) cytokines have been shown to regulate primary and secondary benzylpenicilloyl- (BPO-) specific antibody responses. Peripheral blood lymphocytes isolated from patients with a clear history of beta-lactam allergy were assessed for type-1 and type-2 phenotypes. Immediate reactions involved mixed Th(1), Tc(1), and Tc(2) responses, whereas allergic contact dermatitis involved Tc(1) and Th(1) cells. Other delayed hypersensitivity reactions to beta-lactams were restricted to Th(1) responses. It has been demonstrated that both CD4(+) and CD8(+)-lidocaine-specific T cell clones isolated from patients with allergic contact dermatitis produced IFN-gamma, even though CD8(+) clones only produce IFN-gamma, while IFN-gamma producing CD4(+) cells concomitantly produced IL-5 and IL-4. Together these data illustrate the heterogeneity of drug-specific T-cell responses.

Toxicol Lett. 2008 Jul 30;180(1):46-52. Epub 2008 Jun 5.   Links

Genotoxicity and cell death induced by tinidazole (TNZ).

López Nigro MM, **Carballo MA**.

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Tinidazole (TNZ), a second-generation 5-nitroimidazole compound chemically related to metronidazole (MTZ), has been widely used throughout Europe and developing countries for the treatment of amoebic and parasitic infections. Despite TNZ's increasing use in therapeutics, scarce experimental reports are available in literature on its potential genotoxicity in human cells. Therefore, the aim of the present study was to achieve a precise characterization of the cytotoxic and genotoxic activities of this nitroimidazole in cultured human lymphocytes at therapeutic concentrations (0.1, 1, 10 and 50 microg/ml of culture) and evaluate the possible cell death mechanism associated with it. The endpoints analyzed included: mitotic index (MI), replication index (RI), sister chromatid exchange (SCE) and chromosomal aberrations (CA). A significant decrease ($p<0.0001$) in MI as well as an increase in SCE ($p<0.0001$) and CA ($p<0.0001$) frequencies were observed. No modifications in RI were found. The results suggest a genotoxic and cytotoxic effect of TNZ related with cell death process. Therefore, we evaluated this mechanism by DNA fragmentation (laddering), fluorescence microscopy using acridine orange/ethidium bromide (AO/EB) staining and flow cytometry propidium iodide (PI). DNA extracts of TNZ-treated cells resulted in nucleosomal DNA ladder pattern after 48 h of cell treatment; meanwhile no differences were detected in untreated cells. This pattern correlated with the observed decrease in cellular viability ($p<0.05$), morphological evidence of apoptosis and increase in the percentage of nuclei with hypodiploid DNA content of TNZ exposed

cultures compared with control ($p<0.05$). We concluded that TNZ is genotoxic, cytotoxic and is able to modulate cell death through apoptotic mechanisms in the experimental design employed.

EMBO Rep. 2001 Apr;2(4):318-23.    Links

Structural basis for selectivity and toxicity of ribosomal antibiotics.

Böttger EC, **Springer B**, **Prammananan T**, **Kidan Y**, **Sander P**.

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Ribosomal antibiotics must discriminate between bacterial and eukaryotic ribosomes to various extents. Despite major differences in bacterial and eukaryotic ribosome structure, a single nucleotide or amino acid determines the selectivity of drugs affecting protein synthesis. Analysis of resistance mutations in bacteria allows the prediction of whether cytoplasmic or mitochondrial ribosomes in eukaryotic cells will be sensitive to the drug. This has important implications for drug specificity and toxicity. Together with recent data on the structure of ribosomal subunits these data provide the basis for development of new ribosomal antibiotics by rationale drug design.

1: J Clin Pharmacol. 2005 Mar;45(3):346-51.  Links

Differential toxicity of reactive metabolites of clindamycin and sulfonamides in HIV-infected cells: influence of HIV infection on clindamycin toxicity in vitro.

Wijsman JA, **Dekaban GA**, **Rieder MJ**.

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Hypersensitivity adverse drug reactions are much more common among patients with acquired immunodeficiency syndrome (AIDS) than in the general population. High rates of hypersensitivity reactions to clindamycin have been noted. To investigate the role of reactive metabolites in these reactions, the authors studied toxicity of clindamycin and sulphamethoxazole (SMX) and their metabolites in uninfected and human immunodeficiency virus (HIV)-infected MOLT3 cells. Infected and uninfected cells were incubated with clindamycin or sulphamethoxazole hydroxylamine in increasing concentrations; reactive metabolites were generated by coincubation of cells and drug with murine microsomes and a microsomal activating system. Over a concentration range of 0 to 400 microM SMX-HA, there was a significant concentration-dependent increase in cell death in HIV-infected compared to

uninfected cells (28%+/-3% vs 8%+/-5% at 400 microM, P < .05). In contrast, coincubation of cells with clindamycin, microsomes, and a microsomal activating system, as well as combinations of primaquine or pyrimethamine, was not associated with an increase in cell death among infected compared to uninfected cells. No concentration-toxicity was demonstrated. These data support the role of reactive metabolites in adverse drug reactions to sulfonamides during HIV infection, whereas alternate mechanism(s) may be responsible for increased rates of adverse drug reactions to clindamycin among patients with AIDS.

Antimicrob Agents Chemother. 1996 May;40(5):1294-7.


Links

In vitro and in vivo immunomodulatory effects of anti-Pneumocystis carinii drugs.

Viora M, **De Luca A**, **D'Ambrosio A**, **Antinori A**, **Ortona E**.

Department of Immunology, Istituto Superiore di Sanità, Rome, Italy.

The anti-Pneumocystis carinii drug effects on mitogen-, antigen-, and interleukin-2-induced proliferative responses and on natural killer (NK) cell-mediated activity were analyzed in vivo (rats) and in vitro (normal human peripheral blood mononuclear cells). Splenocytes derived from in vivo piritrexim- and clindamycin-treated rats showed a significant inhibition of mitogen-induced proliferative responses. In vitro exposure to clindamycin, piritrexim, and pyrimethamine caused an inhibition of human T lymphocyte proliferation in response to mitogen, antigen, and interleukin-2 stimulation. Rat NK cell-mediated cytotoxic activity was not affected by the drugs, and human NK cell activity was reduced only at the highest concentration (10 micrograms/ml) of the drugs. The potential immunotoxicity of the long-term administration of these agents in humans needs further investigation.

1: Chem Res Toxicol. 2009 May 22. [Epub ahead of print]


Links

Covalent Binding of Penicillamine to Macrophages: Implications for Penicillamine-Induced Autoimmunity.

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Idiosyncratic drug reactions (IDRs) represent a major clinical problem, and at present, the mechanisms involved are still poorly understood. One animal model that we have used for mechanistic studies of IDRs is penicillamine-induced autoimmunity in Brown

Norway (BN) rats. Previous work in our lab found that macrophage activation preceded the clinical autoimmune syndrome. It is thought that one of the interactions between T cells and macrophages involves reversible Schiff base formation between an amine on T cells and an aldehyde on macrophages, but the identity of the molecules involved is unknown. It is also known that penicillamine reacts with aldehyde groups to form a thiazolidine ring, which unlike a Schiff base, is essentially irreversible. Such binding could lead to macrophage activation. Generalized macrophage activation could lead to the observed autoimmune reaction. Hydralazine and isoniazid also react with aldehydes to form stable hydrazones, and they also cause an autoimmune lupuslike syndrome. In this study, isolated spleen cells from male BN rats were incubated with biotin-aldehyde-reactive probe (ARP, a hydroxylamine), biotin-hydrazide, or d-penicillamine. At all concentrations, ARP, hydrazide, and penicillamine preferentially "stained" macrophages relative to other spleen cells. In addition, preincubation of cells with penicillamine or hydralazine decreased ARP staining of macrophages, which further indicates that most of the ARP binding to macrophages involves binding to aldehyde groups. This provides support for the hypothesis that the interaction between aldehyde-containing signaling molecules on macrophages and penicillamine could be the initial event of penicillamine-induced autoimmunity. Several of the proteins to which ARP binds were identified, and some such as moesin are attractive candidates to mediate macrophage activation.

: Behav Brain Res. 2009 Jan 23;196(2):168-79. Epub 2008 Oct 11. ELSEVIER FULL-TEXT ARTICLE Links

Minocycline and neurodegenerative diseases.

Kim HS, **Suh YH**.

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Minocycline is a semi-synthetic, second-generation tetracycline analog which is effectively crossing the blood-brain barrier, effective against gram-positive and -negative infections. In addition to its own antimicrobacterial properties, minocycline has been reported to exert neuroprotective effects over various experimental models such as cerebral ischemia, traumatic brain injury, amyotrophic lateral sclerosis, Parkinson's disease, kainic acid treatment, Huntington' disease and multiple sclerosis. Minocycline has been focused as a neuroprotective agent over neurodegenerative disease since it has been first reported that minocycline has neuroprotective effects in animal models of ischemic injury [Yrjanheikki J, Keinanen R, Pellikka M, Hokfelt T, Koisinaho J. Tetracyclines inhibit microglial activation and are neuroprotective in global brain ischemia. Proc Natl Acad Sci USA 1998;95:15769-74; Yrjanheikki J, Tikka T, Keinanen R, Goldsteins G, Chan PH, Koistinaho J. A tetracycline derivative, minocycline, reduces inflammation and protects against focal cerebral ischemia with a wide therapeutic window. Proc Natl Acad Sci USA 1999;96:13496-500]. Recently, the effect of minocycline on Alzheimer's disease has been also reported. Although its precise primary target is not clear, the action mechanisms of minocycline for neuroprotection reported so far are; via; the inhibition of mitochondrial permeability-transition mediated cytochrome c release from mitochondria, the inhibition of caspase-1 and -3 expressions, and the suppression of microglial activation, involvement in some signaling pathways, metalloprotease activity inhibition. Because of the high

tolerance and the excellent penetration into the brain, minocycline has been clinically tried for some neurodegenerative diseases such as stroke, multiple sclerosis, spinal cord injury, amyotropic lateral sclerosis, Hungtington's disease and Parkinson's disease. This review will briefly summarize the effects and action mechanisms of minocycline on neurodegenerative diseases.

1: Microbiology. 2008 Mar;154(Pt 3):960-70.  
Links

Tetracycline alters drug susceptibility in Candida albicans and other pathogenic fungi.

Oliver BG, **Silver PM**, **Marie C**, **Hoot SJ**, **Leyde SE**, **White TC**.

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The tetracycline (TET) promoter has been used in several systems as an inducible regulator of gene expression. In control analyses, the standard Candida albicans laboratory strain SC5314 was found to have altered susceptibility to a variety of antifungal drugs in the presence of relatively high concentrations (50-200 microg ml(-1)) of TET. Altered susceptibility was most notable with exposure to amphotericin B (AMB), with a 32-fold increase in susceptibility, and terbinafine (TRB), with a 32-fold decrease in susceptibility. The TET/AMB synergy was observed in several clinical isolates of C. albicans and in the distantly related species Aspergillus fumigatus and Cryptococcus neoformans. The TET/AMB synergy is not related to efflux pump activity, as determined by FACS analyses and by analysis of a strain containing efflux pump deletions. Gene expression analyses by luciferase and by quantitative real-time reverse transcriptase PCR failed to identify significant alterations in expression of any genes associated with resistance. C. albicans grown with TET for 48 h does show a reduction in total cellular ergosterol. Analysis of growth curves suggests that the TET effect is associated with lack of a diauxic shift, which is related to a loss of mitochondrial function. MitoTracker fluorescent dye was used to demonstrate that TET has a direct effect on mitochondrial function. These results demonstrate the need for careful analysis of TET effects when using a TET-inducible promoter, especially in studies that involve antifungal drugs. This study defines some limits to the use of the TET-inducible promoter, and identifies effects on cells that are the result of TET exposure alone, not the result of expression of a targeted gene.

Inflamm Bowel Dis. 2007 May;13(5):557-65.  Links

Immunomodulatory effects of ciprofloxacin in TNBS-induced colitis in mice.

Lahat G, **Halperin D**, **Barazovsky E**, **Shalit I**, **Rabau M**, **Klausner J**, **Fabian I**.

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BACKGROUND: Crohn's exacerbation and pouchitis are commonly treated with ciprofloxacin and metronidazole. Few studies have shown an advantage of this regimen compared with other antibiotics. Most attributed the effect to its better antibacterial coverage. Others have shown an apparent anti-inflammatory effect of quinolones in several in vitro and in vivo models of inflammation other than inflammatory bowel diseases (IBD). Our objective was to test the hypothesis that ciprofloxacin may act as an anti-inflammatory agent rather than just an antibacterial drug using a model of chemical colitis. METHODS: TNBS colitis was induced in BALB/c mice. The anti-inflammatory effect of ciprofloxacin compared with ceftazidime and dexamethasone was assessed. RESULTS: Mice treated with ciprofloxacin (7.5 mg/kg or 15 mg/kg) had significant reductions in clinical signs, body weight loss, splenic and colonic weight increase compared with saline-treated and ceftazidime-treated mice. Histologic analysis showed mild inflammation in ciprofloxacin-treated mice with a mean score of 3.8 +/- 0.5 points compared with moderate colitis scored 7.8 +/- 1.3 and 9.5 +/- 0.5 points in saline and ceftazidime-treated mice, respectively. Analysis of cytokine levels in colon homogenates showed a significant decrease of IL-1beta, IL-8, and TNFalpha levels in ciprofloxacin-treated animals. Immunohistochemistry for NFkappaB showed strong positivity in saline and ceftazidime-treated mice in contrast to weak focal stain in ciprofloxacin- and dexamethasone-treated mice. CONCLUSIONS: These findings imply that ciprofloxacin has an anti-inflammatory effect, rather than just an antibacterial one, making its use favorable in IBD patients.

Eur Respir J. 2005 Feb;25(2):324-8.

Nontuberculous mycobacteria in cystic fibrosis associated with allergic bronchopulmonary aspergillosis and steroid therapy.

Mussaffi H, **Rivlin J**, **Shalit I**, **Ephros M**, **Blau H**.

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Nontuberculous mycobacterial (NTM) infection, particularly due to Mycobacterium abscessus, is an emerging disease that can be relentlessly progressive, particularly in cystic fibrosis (CF) patients. The risk factors that were associated with this increasingly symptomatic infection in a group of CF patients were investigated. A total of 139 CF patients aged 2-52 yrs were reviewed. Sputum was cultured for NTM annually or whenever clinical deterioration was unexplained. In total, 12 patients (8.6%) had positive cultures and six (4.3%) met the criteria for NTM pulmonary disease (five with M. abscessus). Five had allergic bronchopulmonary aspergillosis (ABPA) compared with one out of 133 patients without NTM disease. Five had received systemic steroids (four as a treatment for ABPA) compared with only one out of 133 without NTM lung disease. All six NTM patients deteriorated markedly following mycobacterial infection, and forced expiratory volume in one second dropped 18-46%. Despite prolonged triple antibiotic therapy, M. abscessus was not

eradicated, and four out of six did not return to baseline clinically. In conclusion, severe nontuberculous mycobacterial lung disease, particularly with Mycobacterium abscessus, is becoming a perplexing challenge in cystic fibrosis patients. Allergic bronchopulmonary aspergillosis and systemic steroids appear to be risk factors, although small patient numbers limit this to a descriptive observation. When pulmonary condition deteriorates, increased surveillance for mycobacteria would enable prompt diagnosis and treatment.

1: Antimicrob Agents Chemother. 2002 Aug;46(8):2442-9.

Immunomodulatory and protective effects of moxifloxacin against Candida albicans-induced bronchopneumonia in mice injected with cyclophosphamide.

Shalit I, **Horev-Azaria L**, **Fabian I**, **Blau H**, **Kariv N**, **Shechtman I**, **Alteraz H**, **Kletter Y**.

Schneider Children's Medical Center of Israel, Sackler School of Medicine, Tel-Aviv University, Tel Aviv 69978, Israel.

In a previous study, moxifloxacin was shown to ameliorate immunosuppression and enhance cytokine production in several tissues, including the lungs of cyclophosphamide-injected mice. We examined here the effects of moxifloxacin on Candida albicans lung infection in cyclophosphamide-injected mice. Mice were injected on day 0 with 250 mg of cyclophosphamide/kg, and on days 1 to 4 they were given moxifloxacin at 22.5 mg/kg/day compared to controls given ceftazidime at 75 mg/kg/day or saline. On day 6, C. albicans (10 7 CFU/mouse) was inoculated intratracheally, and animals were observed for the development of bronchopneumonia, weight loss, mortality, the presence of C. albicans, and lung cytokine production. Histopathology on day 10 postinoculation revealed bronchopneumonia in 50, 67, and 0% of saline-, ceftazidime-, and moxifloxacin-treated mice, respectively ($P < 0.05$). The mortality rates were 28, 17, and 5%, respectively ($P < 0.05$), and weight loss occurred at 20, 32, and 0%, respectively ($P < 0.05$). By day 15, C. albicans was eliminated from all moxifloxacin-treated mice but was still isolated from lung homogenates of 50 to 60% of the saline- and ceftazidime-treated groups. Among the cytokines tested on days 0 to 15, we found an increased production of tumor necrosis factor alpha, KC (functional interleukin-8), and gamma interferon in the lungs of ceftazidime- and saline-treated controls compared to the moxifloxacin pretreatment that abolished their secretion. In conclusion, moxifloxacin protected cyclophosphamide-injected mice from C. albicans-induced lung infection and significantly reduced pneumonia, weight loss, and mortality despite the lack of direct antifungal activity. This is most likely due to an immunomodulating activity conferred by moxifloxacin, as shown in this model and in our previous studies. Its potential protective role should be studied in patients undergoing chemotherapy and immune suppression.

1: Lymphokine Res. 1989 Spring;8(1):35-46. Links

Enhancement of interleukin-2 production in human lymphocytes by two new quinolone derivatives.

Zehavi-Willner T, **Shalit I**.

Israel Institute for Biological Research, Ness-Ziona.

The effect of two quinolone derivatives, ciprofloxacin and ofloxacin, on the production of interleukin-2 (IL-2) was studied in human peripheral blood lymphocytes (PBL) and in a T-cell leukemia cell line (Jurkat) following phytohemagglutinin (PHA) stimulation. Both antimicrobial agents markedly increased IL-2 production in PHA-stimulated PBL cultures. No such effect was observed without PHA stimulation. The effect of the two quinolones on IL-2 production was both time and concentration dependent, reaching a 3-5 fold increase at a drug concentration of 50-100 micrograms/ml, following 24 h incubation. IL-2 synthesized in response to ciprofloxacin or ofloxacin stimulation, exhibited identical chromatographic properties and molecular weight to IL-2 synthesized at standard IL-2 inducing conditions. Only ciprofloxacin enhanced IL-2 production in PHA or in PHA and phorbol myristic acetate (PMA)-stimulated Jurkat cells. The stimulatory effect observed in Jurkat cells at optimal dose concentration (10-50 micrograms/ml), was at most 50% above control levels. In contrast to the effect of ciprofloxacin as a costimulator of IL-2 production in PHA-stimulated PBL, the drug excerted a prominent inhibitory effect on the incorporation of radioactive thymidine and amino acids into these cells. Ciprofloxacin, but not ofloxacin, enhanced interferon (IFN) production in PHA-induced PBL, whereas immunoglobulin M [IgM] production in a SKW6 cell line was enhanced only by ofloxacin.

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: Eur J Pharmacol. 2008 Oct 10;594(1-3):39-43. Epub 2008 Jul 31. ELSEVIER FULL-TEXT ARTICLE Links

The inhibition of gluconeogenesis by gatifloxacin may contribute to its hypoglycaemic action.

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The action of gatifloxacin, the broad-spectrum fluoroquinolone antibiotic commonly used in the therapy of various bacterial infections, was investigated in isolated rabbit hepatocytes and kidney-cortex tubules by measuring the activity of gluconeogenesis, a process that maintains whole body glucose homeostasis. The data show that in kidney-cortex tubules, application of gatifloxacin at up to 100 microM was followed by a marked accumulation of the drug in the intracellular milieu and a decrease in the rate of glucose formation from pyruvate by 20-50%. Gatifloxacin did not affect the rate of

gluconeogenesis from either alanine + glycerol + octanoate or aspartate + glycerol + octanoate. At concentrations between 25 and 200 microM the drug decreased mitochondrial oxygen consumption by 20-45% with pyruvate + malate and ADP. As in the case of alpha-cyano-4-hydroxycinnamate, a well-established inhibitor of the mitochondrial pyruvate transporter, it diminished pyruvate uptake by both renal and hepatic mitochondria. The inhibitory action of gatifloxacin was less pronounced in hepatocytes where reduction in pyruvate-dependent glucose formation and mitochondrial respiration was by no more than 25%. The antibiotic did not influence mitochondrial oxygen consumption with glutamate + malate in either kidney-cortex or liver mitochondria. A differential substrate dependence of gatifloxacin action on gluconeogenesis and mitochondrial respiration combined with a decrease in pyruvate uptake by mitochondria suggest that the inhibitory action of this drug on gluconeogenesis might result from its impairment of pyruvate transport into mitochondria.

Acta Otolaryngol Suppl. 2004 Mar;(551):69-74. Links

Signaling pathway for apoptosis of vestibular hair cells of mice due to aminoglycosides.

Lee JE, **Nakagawa T**, **Kim TS**, **Iguchi F**, **Endo T**, **Kita T**, **Murai N**, **Naito Y**, **Lee SH**, **Ito J**.

Department of Otolaryngology--Head and Neck Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan.

Previous studies on regeneration of mammalian vestibular hair cells have indicated the potential for self-repair of damaged hair cells. The rescue of damaged hair cells from cell death may therefore increase regenerated hair cells in affected vestibular epithelia. The role of apoptosis in the degradation of vestibular hair cells following aminoglycoside treatment has been elucidated. To seek a method of protecting vestibular hair cells from aminoglycoside toxicity, we examined the apoptosis signaling pathway of vestibular hair cells due to aminoglycoside toxicity. Induction of apoptosis in hair cells of mouse ampullar cristae damaged by local application of neomycin was evaluated by the terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) method and transmission electron microscopy (TEM). Immunohistochemistry for apoptosis-related proteins was employed to determine the signaling pathway of apoptosis of hair cells. The occurrence of apoptosis in hair cells was demonstrated by TUNEL staining and TEM. In apoptotic hair cells, activation of caspase-3 and -9, and redistribution of cytochrome c was identified, while there was no expression of activated caspase-8 or apoptosis-inducing factor. In conclusion, these findings indicate that the mitochondria-mediated pathway of apoptosis may play a role in inducing the apoptosis of vestibular hair cells due to aminoglycoside toxicity. Stabilization of the mitochondrial membrane may therefore rescue vestibular hair cells from apoptosis, leading to an increase in self-repaired hair cells in affected vestibular epithelia.

Nephrol Dial Transplant. 1994;9 Suppl 4:130-4. Links

Antibiotic-related nephrotoxicity.

Kaloyanides GJ.

Department of Medicine State University of New York.

The toxicity of aminoglycosides is related to their concentrative uptake by proximal tubular cells and their capacity to interact with critical intracellular targets. Concentrative uptake is mediated by adsorptive endocytosis across the apical membrane followed by sequestration within lysosomes. The fundamental mechanism underlying the toxicity of these organic polycations is their capacity to interact electrostatically with and disrupt the metabolism of anionic phospholipids, especially the phosphoinositides. Polyaspartic acid, a polyanionic peptide, protects against aminoglycoside nephrotoxicity by forming electrostatic complexes with these drugs and inhibiting their interaction with critical intracellular targets. The selective toxicity of beta-lactams towards renal proximal tubular cells is related to their concentrative uptake via the organic anion transport system. Lipid peroxidation appears to play a major role in the toxicity of cephaloridine. Depressed mitochondrial respiration secondary to acylation of the mitochondrial transporter for succinate has been implicated in the pathogenesis of toxicity caused by other cephalosporins and carbapenems. The predilection of the kidney for amphotericin B toxicity is unclear as little drug is excreted by the kidneys. Toxicity is manifested by increased renal vascular resistance, depression of RBF and GFR, and altered tubular function that reflects the capacity of this drug to interact with cholesterol-containing membranes and increase membrane permeability to ions including potassium, hydrogen, calcium, and magnesium.

Fundam Appl Toxicol. 1992 May;18(4):532-9. Links

Nephrotoxicity of a new cephalosporin, DQ-2556, in rats.

Kato M, **Yoshida M**, **Shimada H**, **Akahane K**, **Takayama S**.

Drug Safety Research Center, Daiichi Pharmaceutical Co., Ltd.

A single intravenous administration of a new cephalosporin, DQ-2556, at 1200 mg/kg to Sprague-Dawley rats induced proximal tubular necrosis. The histological lesions were not closely correlated with renal cortical concentrations of DQ-2556. Development of renal injuries was examined histologically. The arcuate and cortical radial arteries of the kidneys were constricted immediately after the injection, but then became dilated and showed histological changes: penetration by erythrocytes, edematous thickening, and necrosis in the media. In addition to congestion in the outer medulla, the proximal convoluted and straight tubules exhibited the earliest changes 30 min after the injection, namely, enlargement and rounding of the mitochondria and swelling and irregular arrangement of the microvilli in the epithelial cells. Small necrotic foci of epithelium were observed from 4 hr. They were mainly distributed in the outer cortex and the outer stripe of the outer medulla 24 hr later. In the examination of hemodynamics, DQ-2556 significantly decreased the blood flow with increased vascular resistance in the renal artery during and after a single injection. These changes had disappeared wholly or partially 60 min after dosing commenced. Furthermore, Ca2+ channel blockers markedly inhibited increases in the serum urea

nitrogen and creatinine concentrations and development of the tubular necrosis and the lesions of the arterial walls, which were induced by DQ-2556. These results suggest a possible contribution of the constriction of renal artery to the tubular necrosis.

Food Chem Toxicol. 2002 Dec;40(12):1849-61.

Haemotoxicity of thiamphenicol in the BALB/c mouse and Wistar Hanover rat.

Turton JA, **Andrews CM**, **Havard AC**, **Robinson S**, **York M**, **Williams TC**, **Gibson FM**.

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Chloramphenicol (CAP) is haemotoxic in man, inducing two forms of toxicity. First, a commonly-occurring, dose-related, reversible bone marrow depression, which develops during treatment. Second, a rarer aplastic anaemia (AA), developing after treatment, is irreversible, and often fatal. Thiamphenicol (TAP) was developed as a replacement for CAP; however, there are no toxicological investigations in the mouse or rat on the dose-related haemotoxicity of TAP, in repeat dose gavage studies. Therefore, we have conducted a comprehensive investigation in these species, administering TAP for 7-17 days, to define haematological changes. Female BALB/c mice were gavaged with TAP, daily for 7-17 days at 400-1500 mg/kg; female Wistar Hanover rats were dosed with TAP daily at 50-375 mg/kg for 9 or 10 days. Haematological changes were studied at 1, 7 and 14 days post-dosing. In mice at day 1, TAP caused decreases in RBC, HCT and Hb; reticulocytes and platelets were reduced; changes were dose-related and reversible. Marrow cell counts were reduced; marrow was hypocellular, with erythroid depletion and progenitor cell vacuolation; the myeloid/erythroid (M:E) ratio was increased. In the rat, changes were not as clear-cut; there was anaemia with indications of reduced reticulocyte and platelet counts, and evidence of decreased neutrophils and lymphocytes. Marrow erythroid cells were decreased, precursor cells vacuolated, and the M:E ratio increased. We conclude that TAP induced haematological changes in the mouse and rat, parallelling the dose-dependent, reversible marrow depression reported in man; TAP is more haemotoxic in the rat than in the mouse.

1: Allergy. 2001 Jan;56(1):69-72.

Molecular features determining lymphocyte reactivity in allergic contact dermatitis to chloramphenicol and azidamphenicol.

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BACKGROUND: We report on two cases of allergic contact dermatitis to chloramphenicol and azidamphenicol respectively, with in vivo and in vitro lymphocyte reactivity to both compounds. The molecular features determining lymphocyte reactivity were explored because chloramphenicol, azidamphenicol, and thiamphenicol exhibit almost identical chemical structures. METHODS: With chloramphenicol, azidamphenicol, and the chemically related thiamphenicol, we performed patch tests and lymphocyte transformation tests with both patients. Furthermore, the interleukin-5 and interferon-gamma concentrations in the cultures of peripheral blood mononuclear cells of one patient were determined. RESULTS: Patch tests showed delayed hypersensitivity reactions to chloramphenicol and azidamphenicol, but not to thiamphenicol. These results were confirmed by lymphocyte transformation tests with peripheral blood mononuclear cells of the patients, showing a proliferative T-cell response to azidamphenicol and chloramphenicol. Moreover, lymphocytes from one patient secreted large amounts of interleukin-5, but not of interferon-gamma upon coculture with azidamphenicol. CONCLUSIONS: Since lymphocyte reactivity was observed to chloramphenicol and azidamphenicol, but not to thiamphenicol, the epitope(s) recognized by the allergen-reactive T cells may be formed by the nitro-group of the benzene ring shared by chloramphenicol and azidamphenicol.

J Chemother. 2006 Dec;18(6):641-7.  Links

Immunomodulatory properties of cefaclor: in vivo effect on cytokine release and lymphoproliferative response in rats.

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The proper and coordinated response of the host immune system to bacterial infections is known to play a central role in the eradication of an infection. Therefore, the impact of antibiotics on both innate and acquired host immunity may be involved in the therapeutic outcome. The aim of this study was to evaluate the effects of the widely used cephalosporin cefaclor on some parameters of the immune system in ex vivo conditions. The results demonstrated that short-term (3 to 6 days) treatment with this antibiotic induced pleiotropic modification of rat spleen cells upon ex vivo stimulation with the polyclonal mitogen PHA, entailing increased lymphoproliferative responses, augmented IFN-gamma, IL-2 and IL-10 synthesis and decreased production of IL-4 and IL-6 in comparison to spleen cells from control rats. The mononuclear spleen cells of healthy rats released larger amounts of IFN-gamma and IL-2 in culture supernatants in response to polyclonal mitogenic stimulation with PHA compared to the spleens of the control rats receiving vehicle only. Simultaneously, the treatment with cefaclor augmented PHA-induced lymphoproliferative responses and reduced the synthesis of IL-4 and IL-6. These data depict a type 1 cytokine inducing and immunostimulatory

pharmacological profile that, by activating the innate and acquired immune system, would be synergistic with cefaclor antibacterial activity.

1: Glia. 2001 Sep;35(3):180-8.  Links

Amphotericin B potentiates the activation of inducible nitric oxide synthase and causes nitric oxide-dependent mitochondrial dysfunction in cytokine-treated rodent astrocytes.

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Because the neurotoxic effects of the antifungal drug amphotericin B (AMB) closely resemble those ascribed to the highly reactive gaseous free radical nitric oxide (NO), we investigated the effect of AMB on NO production in rodent astrocytes. AMB caused a dose-dependent increase of NO generation in interferon-gamma (IFN-gamma)-stimulated rat and mouse astrocytes, as well as in IFN-gamma + tumor necrosis factor-alpha (TNF-alpha)-activated rat astrocytoma cell line C6. Treatment of rat astrocytes with AMB markedly potentiated IFN-gamma-triggered expression of mRNA for iNOS, but not for its transcription factor IRF-1. The activation of transcription factor NF-kappaB was apparently required for AMB-induced iNOS mRNA expression, as the latter was abolished by NF-kappaB inhibitors: pyrrolidine dithiocarbamate and MG132. AMB-mediated enhancement of astrocyte NO production was partly dependent on endogenous IL-1, as shown by partial inhibition of AMB effect with IL-1 receptor antagonist. IFN-gamma + AMB treatment led to reduction of astrocyte mitochondrial respiration (measured by MTT assay) that has been completely reverted by selective iNOS inhibitor aminoguanidine. AMB toxicity toward IFN-gamma-stimulated astrocytes was dependent on both AMB and NO action, since AMB and NO-releasing substance SNP synergized in inducing astrocyte mitochondrial dysfunction. These results suggest that the enhancement of cytokine-induced iNOS activation in astrocytes and the subsequent release of high amounts of NO might be at least partly responsible for AMB neurotoxicity. Copyright 2001 Wiley-Liss, Inc.

1: Int J Antimicrob Agents. 2005 Mar;25(3):216-20. Epub 2005 Jan 20.  
Links

Antibiotic-induced apoptosis in human activated peripheral lymphocytes.

Kadota J, **Mizunoe S**, **Kishi K**, **Tokimatsu I**, **Nagai H**, **Nasu M**.

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Long-term administration of macrolide antibiotics reduced the number of lymphocytes in bronchoalveolar lavage fluid in patients with chronic airway inflammatory disease. To evaluate the inflammatory activity of macrolides, their effect on apoptosis of activated lymphocytes isolated from human peripheral blood was compared with that of other antibiotics. Macrolides, including clarithromycin and azithromycin, at a final concentration of 100 microg/ml accelerated apoptosis of activated lymphocytes, while other antibiotics such as fosfomycin sodium, beta-lactams--ceftazidime, piperacillin sodium and biapenem, and a quinolone, ofloxacin, did not cause significant induction of apoptosis. Our results suggest that 14- or 15-membered ring macrolides are specifically involved in the augmentation of apoptosis of activated lymphocytes, and this may be of value therapeutically for chronic airway diseases.

J Chemother. 2001 Dec;13(6):615-20. Links

Desirable and undesirable immunotropic effects of antibiotics: immunomodulating properties of cefaclor.

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The effect exerted on complex immunoregulatory functions of the immune system is an important criterion when selecting an antibiotic. When assessing the effect of an antibiotic on the immune system, one should also take into consideration the existence of functional relationships between the immune system and the nervous and hormonal systems. Among these three systems, there are common factors that modify biological processes. This makes it possible for the antibiotic not only to interact directly with the elements of the immune system, but also to exert indirect influences on potential neurotropic and endocrinotropic effects of the drug. Besides highly effective bactericidal activity, cefaclor demonstrates the ability to exert a favorable effect on some of the specific and non-specific immune responses and immunoregulation mechanisms, which may be important from a clinical point of view. Cefaclor enhances phagocytosis and bactericidal activity of granulocytes and macrophages, and favorably modifies the cooperation of monocytes and T lymphocytes. In this way, it corrects, both in vivo and in vitro, the immunoregulatory disturbances induced and aggravated by an infection. This effect is reflected by an improvement in the impaired immunoregulating activity of T lymphocytes, and is manifest both as an increase in suppressive activity and a correction of the monokine level ratio in relation to the decrease of proinflammatory monokine IL-1 and a relative increase of antiinflammatory IL-1ra. By normalizing the disturbed immunoregulation mechanism, cefaclor enhances the protective potential of the immune reaction while it also reduces the risk of immunogenic clinical complications such as persistent inflammatory conditions and allergic and/or autoaggressive responses. Such immunomodulating properties of cefaclor may be useful in the clinical treatment of patients with immune

disorders leading to chronic inflammation and secondary allergic or autoaggressive reactions.

Arzneimittelforschung. 1977;27(6):1117-22. Links

[Effects of gentamicin and lincomycin on the ultrastructure of mitochondria and plastids of Chlamydomonas reinhardii (author's transl)]

[Article in German]

Zettel HB, **Arnold CG**.

It is known that antibiotics which have an effect on 70 S ribosomes inhibit both the bacterial and the mitochondrial protein synthesis of plants and animals. This also applies to the plastid protein synthesis of plants. On this basis the present study has examined whether the inhibition of the mitochondrial protein synthesis caused by such antibiotics, may also be recognized by structural changes in the mitochondria. The effects on the ultrastructure of plastids have been investigated comparatively. The mixotroph flagellate Chlamydomonas reinhardii was used in our study. It was found that gentamycin (0.3 to 0.6 microgram/ml) and lincomycin (200 and 300 microgram/ml) cause structural anomalies in the mitochondria and in the plastids as well. Depending on the concentrations and the periods of exposure the mitochondria exhibited the following alterations: disorientation of the cristae within the organelles, reduction in the number of cristae and considerable differences of their length. In addition, vesicles and bodies which are surrounded by circular single or doubled membranes appeared in the mitochondria under the influence of gentamycin. We were able to detect mitochondria of unusual sizes and shapes in the cross sections. We also noticed changes in the arrangement of the thylakoids in the plastids under the influence of both gentamycin and lincomycin. In addition, electron-dense thylakoids, the so-called compact membranes, appeared under the influence of gentamycin. We suspect that mitochondrial alterations under the influence of such antibiotics could be one of the causes of side-effects, which frequently occur in medical use.

Med Dosw Mikrobiol. 1999;51(3-4):413-9. Links

[The effect of selected antibacterial antibiotics on production of interferon gamma (IFN-G) by mouse T lymphocytes stimulated by Listeria monocytogenes]

[Article in Polish]

Sacha PT, **Zaremba ML**, **Jakoniuk P**.

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The aim of the study was to determine the influence of certain antibiotics on the production of IFN-gamma by mouse lymphocytes T after four days incubation with

Listeria monocytogenes. The level of mouse IFN-gamma was determined by ELISA method (Inter Test-gamma Mouse IFN-gamma Kit, Genzyme). The strongest immunosuppression effect was demonstrated using rifampicin (39 ng/ml IFN-gamma) (Control: 123 +/- 29 ng/ml IFN-gamma, $p < 0.05$). Lower immunosuppression effects were observed also with cephradine (54 ng/ml IFN-gamma), amikacin (56 ng/ml IFN-gamma) and ticarcillin (83 ng/ml). The obtained results show that all tested cephalosporins (cephamandole, cefotaxime, cephradine) and aminogllycosides (gentamicin, streptomycin, amicacin) inhibit production of IFN-gamma by mouse lymphocytes T. The influence of penicillin G and ampicillin, as well as, erythromycin and lincomycin on the production IFN-gamma was not observed. Our results suggest that rifampicin, ticarcillin, cephalosporins and aminoglycosides act as inhibitors of production IFN-gamma.

Microb Drug Resist. 2009 May 11. [Epub ahead of print]  Links

Growth Inhibitory Action of Ebselen on Fluconazole-Resistant Candida albicans: Role of the Plasma Membrane H(+)-ATPase.

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PMA1 is a yeast gene that codes for the plasma membrane H(+)-ATPase, a protein commonly referred to as Pma1p. Ebselen (2-phenyl-1,2-benzisoselenazol-3(2H)-one) is a synthetic selenium-containing compound that has recently been shown to display antimicrobial activity owing to its ability to inhibit Pma1p. Ebselen is able to block the activity of Pma1p not only in opportunistic pathogens such as Cryptococcus neoformans and Candida albicans but also in nonpathogenic yeasts such as Saccharomyces cerevisiae. A series of in vitro studies aimed at evaluating the antifungal activity of ebselen were performed. At low concentrations (<10 muM), ebselen was fungistatic against three strains of S. cerevisiae (IC(50) approximately 3 muM) and one fluconazole-resistant strain of C. albicans (IC(50) approximately 6 muM), and at a high concentration (30 muM) it was fungicidal against C. albicans. Moreover, ebselen was found to inhibit medium acidification by the fluconazole-resistant strain of C. albicans in a concentration-dependent manner. In comparison to currently used antifungal agents represented by azole (itraconazole, ketoconazole, fluconazole) and polyene (amphotericin B) compounds, ebselen was at least 10-fold more potent than fluconazole but less active than the other compounds tested. The present results suggest that the growth inhibitory activity of ebselen toward fluconazole-resistant yeast cells is due, at least in part, to inhibition of Pma1p. Ebselen may also serve as a useful agent in the treatment of infections caused by fluconazole-resistant fungi.

Drug Chem Toxicol. 1997 Aug;20(3):239-53.   Links

Use of human lymphoblastoid cells to detect the toxic effect of chloramphenicol and metabolites possibly involved in aplastic anemia in man.

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Some Chloramphenicol (CAP) metabolites are suspected to be involved in the etiology of bone marrow aplasia in man. The objective of the present study was to investigate the cytotoxicity as well as the genotoxicity of CAP and six of its metabolites on human bone marrow cells (RiBM cells) and to compare these results with those obtained on human peripheral blood lymphocytes in order to estimate the relative sensitivity of the two types of cells. Three CAP metabolites NO-CAP, DH-CAP and NPAP inhibited 3H thymidine incorporation in RiBM cells at concentrations ranging from 2.10(-5) M to 2.10(-4) M. NO-CAP appeared as the most potent cytotoxic compound. CAP itself and NAPD presented some toxic effect at high concentration (1-2.10(-3) M). CAPG and HAP did not present any cytotoxic effect. By comparison, the response of human lymphocytes to CAP and its metabolites showed a similar pattern but DH-CAP was the most inhibitory compound. Concerning the genotoxic potential, NO-CAP and DH-CAP induced DNA single strand breaks in RiBM cells at concentrations of 1 and 2.10(-4) M with a dose response relationship. CAP and other metabolites were completely devoid of genotoxicity up to 4.10(-3) M. The results clearly showed that RiBM cells were much less susceptible to the genotoxic effect of CAP metabolites than human lymphocytes.