NK Cell-Derived IFN-{gamma} Differentially Regulates Innate Resistance and Neutrophil Response in T Cell-Deficient Hosts Infected with Mycobacterium tuberculosis.

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Although it is known that IFN-gamma-secreting T cells are critical for control of Mycobacterium tuberculosis infection, the contribution of IFN-gamma produced by NK cells to host resistance to the pathogen is less well understood. By using T cell-deficient RAG(-/-) mice, we showed that M. tuberculosis stimulates NK cell-dependent IFN-gamma production in naive splenic cultures and in lungs of infected animals. More importantly, common cytokine receptor gamma-chain(-/-)RAG(-/-) animals deficient in NK cells, p40(-/-)RAG(-/-), or anti-IFN-gamma mAb-treated RAG(-/-) mice displayed significantly increased susceptibility to M. tuberculosis infection compared with untreated NK-sufficient RAG(-/-) controls. Studies comparing IL-12 p40- and p35-deficient RAG(-/-) mice indicated that IL-12 plays a more critical role in the induction of IFN-gamma-mediated antimycobacterial effector functions than IL-23 or other p40-containing IL-12 family members. The increased susceptibility of IL-12-deficient or anti-IFN-gamma mAb-treated RAG(-/-) mice was associated not only with elevated bacterial loads, but also with the development of granulocyte-enriched foci in lungs. This tissue response correlated with increased expression of the granulocyte chemotactic chemokines KC and MIP-2 in NK as well as other leukocyte populations. Interestingly, depletion of granulocytes further increased bacterial burdens and exacerbated pulmonary pathology in these animals, revealing a compensatory function for neutrophils in the absence of IFN-gamma. The above observations indicate that NK cell-derived IFN-gamma differentially regulates T-independent resistance and granulocyte function in M. tuberculosis infection and suggest that this response could serve as an important barrier in AIDS patients or other individuals with compromised CD4(+) T cell function.

Antiretroviral therapy in AIDS patients with tuberculosis.

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Tuberculosis associated with HIV infection continues to be an important problem throughout the world. Since the advent of HAART, the medication of HIV-infected patients who have to receive concomitant treatment for tuberculosis has become a difficult task. The two main problems faced by clinicians include the significant pharmacokinetic interactions between rifamycins, a cornerstone in antituberculosis therapy, and protease inhibitors and nonnucleoside reverse transcriptase inhibitors, which are essential components of antiretroviral combination regimens, as well as the best moment to initiate antiretroviral therapy in patients with tuberculosis. The therapy of choice for patients with no previous antiretroviral experience includes an antituberculous regimen with rifampin and an efavirenz-based antiretroviral regimen. No dose adjustments of these drugs seem

to be necessary. Nevirapine can be an alternative to efavirenz in this situation. For patients who cannot take efavirenz, either due to resistance or intolerance, rifabutin and a boosted protease inhibitor can be coadministered, with the necessary dose adjustments. No definite recommendations can be given regarding the optimal timing of antiretroviral therapy, but a delay of two months after initiation of antituberculosis therapy would be advisable and seems to be safe in most patients.

Antituberculosis drugs and hepatotoxicity.

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Isoniazid, pyrazinamide and rifampicin have hepatotoxic potential, and can lead to such reactions during antituberculosis chemotherapy. Most of the hepatotoxic reactions are dose-related; some are, however, caused by drug hypersensitivity. The immunogenetics of antituberculosis drug-induced hepatotoxicity, especially inclusive of acetylaor phenotype polymorphism, have been increasingly unravelled. Other principal clinical risk factors for hepatotoxicity are old age, malnutrition, alcoholism, HIV infection, as well as chronic hepatitis B and C infections. Drug-induced hepatic dysfunction usually occurs within the initial few weeks of the intensive phase of antituberculosis chemotherapy. Vigilant clinical (including patient education on symptoms of hepatitis) and biochemical monitoring are mandatory to improve the outcomes of patients with drug-induced hepatotoxicity during antituberculosis chemotherapy. Some fluoroquinolones like ofloxacin/levofloxacin may have a role in constituting non-hepatotoxic drug regimens for management of tuberculosis (TB) in the presence of hepatic dysfunction. Isoniazid administration is currently the standard therapy for latent TB infection. Rifamycins like rifampicin or rifapentine, alone or in combination with isoniazid, may also be considered as alternatives, pending accumulation of further clinical data. During treatment of latent TB infection, regular follow up is essential to ensure adherence to therapy and facilitate clinical monitoring for hepatic dysfunction. Monitoring of liver chemistry is also required for those patients at risk of drug-induced hepatotoxicity.

Bacterial pneumonia, HIV therapy, and disease progression among HIV-infected women in the HIV epidemiologic research (HER) study.

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BACKGROUND: To determine the rate and predictors of community-acquired bacterial pneumonia and its effect on human immunodeficiency virus (HIV) disease progression in HIV-infected women, we performed a multiple-site, prospective study of HIV-infected women in 4 cities in the United States. METHODS: During the period of 1993-2000, we observed 885 HIV-infected and 425 HIV-uninfected women with a history of injection drug use or high-risk sexual behavior. Participants underwent semiannual interviews, and CD4+ lymphocyte count and viral load were assessed in HIV-infected subjects. Data regarding episodes of bacterial pneumonia were ascertained from medical record reviews. RESULTS: The rate of bacterial pneumonia among 885 HIV-infected women was 8.5 cases per 100 person-years, compared with 0.7 cases per 100 person-years in 425 HIV-uninfected women ($P < .001$). In analyses limited to follow-up after 1 January 1996, highly active

antiretroviral therapy (HAART) and trimethoprim-sulfamethoxazole (TMP-SMX) use were associated with a decreased risk of bacterial pneumonia. Among women who had used TMP-SMX for 12 months, each month of HAART decreased bacterial pneumonia risk by 8% (adjusted hazard ratio [HR(adj)], 0.92; 95% confidence interval [CI], 0.89-0.95). Increments of 50 CD4+ cells/mm3 decreased the risk (HR(adj), 0.88; 95% CI, 0.84-0.93), and smoking doubled the risk (HR(adj), 2.12; 95% CI, 1.26-3.55). Bacterial pneumonia increased mortality risk (HR(adj), 5.02; 95% CI, 2.12-11.87), with adjustment for CD4+ lymphocyte count and duration of HAART and TMP-SMX use. CONCLUSIONS: High rates of bacterial pneumonia persist among HIV-infected women. Although HAART and TMP-SMX treatment decreased the risk, bacterial pneumonia was associated with an accelerated progression to death. Interventions that improve HAART utilization and promote smoking cessation among HIV-infected women are warranted.

PMID: 16758423 [PubMed - indexed for MEDLINE]

[Human herpesvirus 6 encephalitis in trimethoprim-sulfamethoxazole-induced hypersensitivity syndrome]

[Article in French]

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INTRODUCTION: Human herpesvirus 6 (HHV-6), the causative agent of the common exanthem subitum, is a known cause of central nervous system infection in immunocompromised patients. It has been suggested that HHV-6 participate in the development of drug-induced hypersensitivity syndrome. CASE REPORT: We reported a case of HHV-6 encephalitis associated with hypersensitivity syndrome induced by trimethoprim-sulfamethoxazole in a 72-year-old HIV-negative woman. DISCUSSION: Our case confirmed that reactivation of HHV-6 infection may contribute to the development of the hypersensitivity syndrome.

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Trimethoprim-sulfamethoxazole-induced hypersensitivity syndrome associated with reactivation of human herpesvirus-6.

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A 27-year-old man who had a history of bronchial asthma, eosinophilic enteritis, and eosinophilic pneumonia presented with fever, skin eruptions, cervical lymphadenopathy, hepatosplenomegaly, atypical lymphocytosis, and eosinophilia two weeks after receiving trimethoprim (TMP)-sulfamethoxazole (SMX) treatment. After the withdrawal of TMP-SMX and the administration of high-dose steroid, these systemic symptoms gradually resolved. During the disease course, the patient showed a transient increase in anti-human herpesvirus (HHV)-6 antibody titers and HHV-6 DNA in the peripheral blood, indicating the reactivation of a latent HHV-6 infection. This is the first case of TMP-SMX-induced hypersensitivity syndrome associated with the reactivation of a latent viral infection.

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Combination exposure to zidovudine plus sulfamethoxazole-trimethoprim diminishes B-lymphocyte immune responses to Pneumocystis murina infection in healthy mice.

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We have previously shown that zidovudine plus sulfamethoxazole-trimethoprim exposure decreases immune cell populations in the bone marrow of healthy mice by inducing apoptosis. The hypothesis of the current work was that this toxicity would have an adverse impact on the immune response. To determine this, BALB/c mice were treated with zidovudine, sulfamethoxazole-trimethoprim, the combination of both drugs, or vehicle only (control) via oral gavage for 21 days. On day 4 after dosing completion, the mice were infected intratracheally with 1x10(7) Pneumocystis murina organisms. Immune cell populations (in lung digest, bronchoalveolar lavage fluid, tracheobronchial lymph node, and bone marrow samples), the lung Pneumocystis burden, and serum Pneumocystis-specific antibody titers were determined at days 6, 10, and 20 postinfection. While total bone marrow cellularity was recovered by day 6 postinfection in the combination exposure group, B-cell numbers did not recover until 10 days postinfection, primarily due to the persistent depletion of the late pre-B-cell phenotype. The numbers of CD4+ and CD8+ T cells, as well as the numbers of total B cells and activated B cells in tracheobronchial lymph nodes, were decreased at days 10 and 20 as a result of zidovudine plus sulfamethoxazole-trimethoprim exposure compared to the numbers in the control group. No significant differences in lung lavage or lung digest cell populations were observed. There was a trend of a delay in Pneumocystis clearance in the combination treatment group, and Pneumocystis-specific serum immunoglobulin G titers were reduced at day 20 postinfection. Together, these data indicate that the combination of zidovudine and sulfamethoxazole-trimethoprim adversely affects the humoral immune response to Pneumocystis.

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Trimethoprim-sulfamethoxazole-induced aseptic meningitis.

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We present a 46-year-old African-American man with AIDS who was admitted on two different occasions within three weeks for signs and symptoms of meningitis after using trimethoprim/sulfamethoxazole (TMP/SMX). TMP/SMX is primarily used for the treatment of pneumocystis carinii pneumonia prophylaxis in AIDS patients. Drug-induced aseptic meningitis (DIAM) is commonly seen with nonsteroidal anti-inflammatory drugs (NSAIDS), antibiotics (with TMP/SMX being the most frequently implicated), intravenous immunoglobulins and OKT3 antibodies. However, the implication of TMP/SMX inducing aseptic meningitis has been underreported to FDA/MEDWATCH program. This might be due to the fact that it has also been used to treat bacterial meningitis from organisms like Listeria monocytogenes, which is a common pathogen in the elderly and in infants. We reviewed the literature in an attempt to characterize the pattern and predictors of TMP/SMX-induced aseptic meningitis.

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Transient psychosis in an immune-competent patient after oral trimethoprim-sulfamethoxazole administration.

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We describe a rare adverse reaction to trimethoprim-sulfamethoxazole (TMP-SMX; Septra, Bactrim) in an immune-competent female adolescent. She was prescribed TMP-SMX for a urinary tract infection, which she had developed while being treated in the hospital for an extensive leg cellulitis. Shortly after receiving her third dose of TMP-SMX, she developed an

acute altered mental status with agitation as well as vivid visual and auditory hallucinations. After prompt discontinuation of TMP-SMX, the patient slowly began to improve and was able to return to her baseline mental status within 10 days. No residual mental status changes were present. Despite the recent emergence of multidrug-resistant bacterial pathogens, TMP-SMX, one of the first-generation broad-spectrum antibiotics, continues to be widely prescribed, in part because of its low cost and its easy availability. It is generally well tolerated and is associated with relatively few adverse effects. More common toxicities associated with TMP-SMX include hypersensitivity reactions, bone marrow suppression, and gastrointestinal side effects. Central nervous system toxicity is very rare; when reported, it has been in an immune-compromised or an elderly patient.

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Reconsidering empirical cotrimoxazole prophylaxis for infants exposed to HIV infection.

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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.

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Adverse reactions of nitrofurantoin, trimethoprim and sulfamethoxazole in children.

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PURPOSE: Many children with urological disease require long-term treatment with antibiotics. In many cases the choice of medical instead of surgical management hinges on the implied safety of certain drugs. Recently some groups have advocated subureteral injection procedures to avoid long-term antibiotics for low grade reflux. We present a concise and relevant review on the use and adverse reactions of nitrofurantoin, trimethoprim and sulfamethoxazole in children. MATERIALS AND METHODS: We reviewed the literature regarding the safety and toxicity of these drugs. Information regarding absorption, excretion and dosing was also gathered to explain better the mechanisms of toxicity. RESULTS: Adverse reactions in children reported in the literature related to nitrofurantoin are gastrointestinal disturbance (4.4/100 person-years at risk), cutaneous reactions (2% to 3%), pulmonary toxicity (9 patients), hepatoxicity (12 patients and 3 deaths), hematological toxicity (12 patients), neurotoxicity and an increased rate of sister chromatid exchanges. Adverse reactions in children related to trimethoprim/sulfamethoxazole are almost exclusively due to the sulfamethoxazole component, including cutaneous reactions (1.4 to 7.4 events per 100 person-years at risk), hematological toxicity (0% to 72% of patients) and hepatotoxicity (5 patients). The majority of adverse reactions were found in children on full dose therapy and not prophylaxis. CONCLUSIONS: The use of nitrofurantoin, trimethoprim and sulfamethoxazole is safe in children for long-term prophylactic therapy. The antibiotic safety issue should not be misconstrued as an argument for surgical therapy, whether minimally invasive or not. Adverse reactions exist to these medicines but they are less common than seen in adults,

presumably because of the lower dose used for therapy, and the lack of significant comorbidities and drug interactions in children. Serious side effects are extremely rare and most are reversible by discontinuing therapy. The extremely low potential for significant adverse reactions should be discussed with parents.

PMID: 15247700 [PubMed - indexed for MEDLINE]

A case of pneumocystis carinii pneumonia associated with low dose methotrexate treatment for rheumatoid arthritis and trimethoprim-sulphamethoxazole induced pancytopenia]

[Article in Japanese]

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A 64-year-old man was admitted to our hospital complaining of dyspnea and fever. He had been treated with low-dose methotrexate for rheumatoid arthritis. Chest radiography showed diffuse ground-glass attenuation in both lung fields, and hypoxia was detected. Pneumosystis carinii pneumonia was demonstrated on transbronchial lung biopsy, and the serum beta-D glucan level was high. We started treatment with trimethoprim-sulphamethoxazole, but respiratory failure worsened, and drug-induced pancytopenia occurred. Although trimethoprim-sulphamethoxazole was stopped, pancytopenia persisted and the patient required ventilatory support. After we changed the medication from trimethoprim-sulphamethoxazole to pentamidine, respiratory failure improved. It was thought that pneumocystis carinii pneumonia was associated with low-dose methotrexate and that trimethoprim-sulphamethoxazole interacted with methotrexate to induce severe pancytopenia.

PMID: 15247519 [PubMed - indexed for MEDLINE]

Trimethoprim-sulfamethoxazole--induced methemoglobinemia in an HIV-infected patient.

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PMID: 15182104 [PubMed - indexed for MEDLINE]

Trimethoprim-sulfamethoxazole-associated hepatotoxicity - part of a hypersensitivity syndrome.

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Trimethoprim-sulfamethoxazole is a commonly used medication. Side effects are numerous and include drug hypersensitivity syndrome. The case of a 24-year-old woman with severe liver failure is presented. Erythema multiforme and thrombocytopenia developed after the acute onset of hepatotoxicity and after all medications had been stopped. Clinical resolution of all features occurred over weeks but laboratory abnormalities persisted up to eight months later. A causal link with sulfamethoxazole was supported by timing, liver biopsy and lymphocyte toxicity test. This case illustrates one presentation and the possible severity of the drug hypersensitivity syndrome associated with trimethoprim-sulfamethoxazole.

PMID: 14712321 [PubMed - indexed for MEDLINE]

Adverse reactions to trimethoprim/sulfamethoxazole in AIDS.

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OBJECTIVE: To report the case of a woman with AIDS who developed tremor, acute pancreatitis, and elevated serum creatinine levels while receiving trimethoprim/sulfamethoxazole (TMP/SMX).CASE SUMMARY: A 37-year-old Puerto Rican woman with AIDS, HIV nephropathy, and a recent history of disseminated histoplasmosis presented with fever, nonproductive cough, pancytopenia, and elevated transaminase and alkaline phosphatase levels. Serum creatinine was near her baseline level of 2.9 mg/dL. Treatment was started with amphotericin B lipid complex for histoplasmosis and intravenous TMP/SMX for presumed Pneumocystis carinii pneumonia. Two days later, the patient developed a high-frequency tremor and severe abdominal pain, and serum creatinine increased to 5.6 mg/dL. TMP/SMX was discontinued, after which the patient's symptoms resolved within 72 hours and serum creatinine returned to baseline levels.DISCUSSION: A high incidence of adverse reactions to TMP/SMX has been reported among HIV-infected persons. Toxic sulfamethoxazole metabolites may elicit hypersensitivity reactions. Trimethoprim can inhibit renal creatinine secretion, leading to high serum creatinine levels. Trimethoprim also inhibits dihydrofolate reductase, causing decreased dopamine production, which may lead to parkinsonian symptoms. Use of the Naranjo probability scale indicated a probable relationship between the adverse effect and TMP/SMX.CONCLUSIONS: The high frequency and wide range of potential adverse effects associated with the use of TMP/SMX in HIV-infected persons require that clinicians consider drug toxicity as a cause of new symptoms in patients receiving this medication.

PMID: 14632594 [PubMed - indexed for MEDLINE]

Recurrence of Pneumocystis carinii pneumonia in an HIV-infected patient: apparent selective immune reconstitution after initiation of antiretroviral therapy.

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Although several studies have reported that it is safe to discontinue secondary Pneumocystis carinii pneumonia (PCP) prophylaxis in patients infected with HIV who experience a sustained immune response as a result of antiretroviral therapy, we describe a patient who developed recurrent PCP <3 months after discontinuing trimethoprim-sulfamethoxazole prophylaxis. He developed disease despite a sustained CD4 T-cell count above 200 cells/microL for more than 3 years while on antiretroviral therapy, as well as an apparent immune reconstitution against disseminated Mycobacterium avium complex (MAC) and Histoplasma capsulatum, for which he also discontinued therapy but without adverse effects. Thus, although increasing evidence continues to indicate that HIV-infected patients receiving combinations of antiretroviral therapies may regain specific immunity against opportunistic infections, our patient's experience suggests that this immune recovery may be selective and incomplete.

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Hyponatremia and/or hyperkalemia in patients treated with the standard dose of trimethoprim-sulfamethoxazole.

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OBJECTIVE: High-dose trimethoprim-sulfamethoxazole (TMP-SMX) is known to cause hyperkalemia by blocking amiloride-sensitive sodium (Na) channels in distal nephrons. The purpose of this study was to establish whether the standard dose of TMP-SMX could cause electrolyte disorders. METHODS AND PATIENTS: Serum Na, potassium (K) and creatinine (Cr) levels were examined retrospectively in 53 of 77 patients prescribed TMP-SMX, before and after taking the antibiotic combination. RESULTS: Electrolyte disorders (Na < 135 mEq/l and/or K > 5.0 mEq/l) were found in 14 of the 53 patients (26.4%) during TMP-SMX treatment. The average dose was 145.7 +/- 24.9 mg/day. The dose of TMP was significantly larger in patients with electrolyte disorders (267.7 +/- 84.2 mg vs. 101.9 +/- 9.38 mg, p = 0.0024). Electrolyte disorders were also seen in 9.1% and 22.2% of patients given the low dose (TMP < 80 mg) or standard dose (TMP 80-120 mg) of TMP-SMX, respectively. Electrolyte disorders were seen in 85.7% of patients with renal dysfunction (Cr > 1.2 mg/dl), compared with 17.5% of patients with normal renal function (p = 0.0008). Logistic regression analysis showed that the dose of TMP and the presence of renal dysfunction increased the incidence of electrolyte disorders with an odds ratio of 2.35 and 80.29, respectively. CONCLUSION: Electrolyte disorders, particularly hyperkalemia and hyponatremia can be detected in patients given TMP-SMX. These disorders are more frequent in patients given high doses, but can also be detected after low-dose administration. Renal dysfunction accelerates the incidence of electrolyte disorders induced by TMP-SMX.

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Trimethoprim-sulfamethoxazole (TMP/SMX) potentiates indinavir nephrotoxicity.

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OBJECTIVES: Indinavir is a widely prescribed protease inhibitor in the treatment of HIV infection. It has been associated with nephrolithiasis, crystalluria and tubulointerstitial nephritis. Nelfinavir is another protease inhibitor used successfully in AIDS treatment. The objective of this study was to evaluate the effect of both indinavir and nelfinavir individually, and in association with trimethoprim-sulfamethoxazole (TMP/SMX), on renal function in Wistar rats. METHODS: Doses of indinavir (80 mg/kg body weight [BW] daily), nelfinavir (75 mg/kg BW daily) and TMP/SMX (100 mg TMP/kg BW daily) were given by gavage for 15 days. Seven groups were studied: control, vehicle, TMP/SMX, indinavir, indinavir+TMP/SMX, nelfinavir, and nelfinavir+TMP/SMX. RESULTS: No changes were observed in body weight, urine volume and blood pressure. The vehicle group did not differ from the control group. TMP/SMX induced a small decrease in inulin clearance with no tubular alterations. Indinavir decreased inulin clearance (indinavir: 0.48 +0.03 vs control: 0.93 +/- 0.08, P < 0.001) and renal blood flow (indinavir: 6.2 +/- 0.2 vs control: 8.0 +/- 0.3, P < 0.05). These effects were potentiated by TMP/SMX, which produced high vasoconstriction associated with alterations in tubular functions, characterised by increased fractional excretion of sodium (indinavir+TMP/SMX: 1.14 +/- 0.16 vs control: 0.39 +/- 0.07, P < 0.01). Nelfinavir either alone or in combination with TMP/SMX did not change the renal function of the rats. CONCLUSION: These results suggest that indinavir nephrotoxicity in rats is potentiated by TMP/SMX and that nelfinavir alone or in combination with TMP/SMX is not nephrotoxic.

PMID: 12487385 [PubMed - indexed for MEDLINE]

Study finds NAC fails to prevent Bactrim/Septra hypersensitivity.

[Article in English, French]
[No authors listed]

AIDS: Bactrim/Septra is a drug used for treating and preventing PCP (Pneumocystis carinii pneumonia) and toxoplasmosis. However, people with HIV are more likely to develop hypersensitivity reactions to Bactrim/Septra. NAC (N-acetyl-cysteine) is being studied to determine if its detoxifying properties could reduce the risk of hypersensitivity to

Bactrim/Septra. However, a Canadian study found no statistically significant difference in the rates of hypersensitivity among the nearly 200 subjects.

PMID: 11366023 [PubMed - indexed for MEDLINE]

Incidence and determinants of Pseudomonas aeruginosa infection among persons with HIV: association with hospital exposure.

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BACKGROUND: Little information exists on risk factors for Pseudomonas aeruginosa infection in persons with HIV. We assessed the incidence and factors associated with P aeruginosa among persons with HIV enrolled in a large observational cohort study in Los Angeles. METHODS: Data were analyzed from 4825 persons aged > or =13 years with HIV infection enrolled from 4 outpatient facilities from 1990 to 1998. The association between P aeruginosa infection and demographic, risk behavior, and clinical factors was assessed. RESULTS: P aeruginosa was diagnosed in 72 (1.5%) patients representing a crude incidence rate of 0.74 per 100 person-years. The most frequent site of infection was pulmonary (47%). In multivariate analysis, prior hospitalization (adjusted rate ratio = 7.9, 95% CI, 3.8-16.2), and both dapsone (adjusted rate ratio = 4.0, 95% CI, 2.2-7.4) and trimethoprim-sulfamethoxazole (adjusted rate ratio = 2.5, 95% CI, 1.2-5.3) use were independently associated with higher rates of infection. Increasing days of inpatient stay (P <.01) and decreasing CD4(+) counts (P <.01) were strongly associated with P aeruginosa. Azithromycin use decreased the risk of infection by nearly 70%. CONCLUSION: Although the overall observed incidence of P aeruginosa was low, hospital exposure, declining CD4(+) levels, and the use of dapsone or trimethoprim-sulfamethoxazole increased the risk of P aeruginosa disease, and azithromycin use was protective in this population. These findings may assist in the early recognition and diagnosis of persons likely to be at increased risk of P aeruginosa infection.

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Clinical implications of stenotrophomonas maltophilia resistant to trimethoprim-sulfamethoxazole: a study of 69 patients at 2 university hospitals.

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We conducted a retrospective case study at 2 tertiary care centers to determine the clinical implications of trimethoprim-sulfamethoxazole resistant Stenotrophomonas maltophilia (TSRSM). Of 69 reviewed cases (mean age, 57 y; male gender, 70%), 40 (58%) were classified as infections associated with TSRSM (respiratory tract, 14; soft tissue, 11; bloodstream, 8; other sites, 7). Severe underlying comorbidities (86%) and previous antibiotic exposure (99%) were common. Cefotetan (susceptibility, 55%), chloramphenicol (49%) and ticarcillin-clavulanate (45%) showed the highest in vitro activity against TSRSM, but were seldom used for therapy (7%). Among the 40 infected cases, 8 developed sepsis disorders and 8 died. Only 1 death could be directly attributed to autopsy-proven TSRSM infection (pneumonia). McCabe score (p = 0.03) and organ dysfunction (p = 0.006) were associated with an increased risk of death in infected patients; exposure to appropriate therapy tended to be protective against death (p = 0.08). 22 infected patients were treated medically; an additional procedure was necessary to clear the infection in 18 cases (surgery, 13; catheter removal, 5). Isolation precautions were rarely exercised, even in the presence of panresistant isolates. In summary, TSRSM-related infections occurred in severely ill patients with extensive exposure to the health-care system, and often required invasive procedures for cure. Infections were directly associated with severe morbidity, and tended to have an indirect rather than a direct impact on mortality.

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Association analysis of drug metabolizing enzyme gene polymorphisms in HIV-positive patients with co-trimoxazole hypersensitivity.

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The use of co-trimoxazole in HIV-positive patients has been associated with a high frequency (40-80%) of hypersensitivity reactions. This has been attributed to the bioactivation of the sulphonamide component, sulphamethoxazole (SMX), to its toxic hydroxylamine and nitroso metabolites. The aim of this study was to determine whether functionally significant polymorphisms in the genes coding for enzymes involved in SMX metabolism influence susceptibility to SMX hypersensitivity. HIV-positive patients with (n = 56) and without (n = 89) SMX hypersensitivity were genotyped for allelic variants in CYP2C9, GSTM1, GSTT1, GSTP1 and NAT2 using polymerase chain reaction (PCR) and/or PCR-restriction fragment length polymorphism analysis. The CYP2C9*2/*3 genotype and CYP2C9*3 allele frequencies were nine- and 2.5-fold higher in the hypersensitive group compared to non-sensitive patients, respectively, although they were not statistically significant when corrected for multiple testing. There were no differences in the frequencies of the GSTM1 and GSTT1 null genotypes, and the slow acetylator genotype, between hypersensitive and non-sensitive patients, while GSTP1 frequency was lower (although non-significant) in the hypersensitive group [21% versus 32%, odds ratio (OR) = 0.5, Pc = 0.24]. Comparison of the genotype frequencies in HIV-positive and -negative patients showed that the NAT2 slow acetylator genotype frequency in the HIV-positive patients (74%) was significantly (Pc = 0.0003, OR = 2.3) higher than in control subjects (56%). Our results show that genetic polymorphisms in drug metabolizing enzymes are unlikely to be major predisposing factors in determining individual susceptibility to co-trimoxazole hypersensitivity in HIV-positive patients.

PMID: 11186133 [PubMed - indexed for MEDLINE]

Antibiotics, acne, and upper respiratory tract infections.

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About two million people per year in the U.S. have acne severe enough to require treatment with antibiotics. Treatment frequently lasts for more than six months, prompting concerns about antibiotic resistance and other possible consequences of long-term antibiotic use, such as increased susceptibility to infections. This Issue Brief summarizes a large study that evaluates the risk for upper respiratory and urinary tract infections among adolescents and young adults treated with antibiotics for acne.

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Haematological changes in adults receiving a zidovudine-containing HAART regimen in combination with cotrimoxazole in Cote d'Ivoire.

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OBJECTIVE: Neutropenia is the most frequent side effect of cotrimoxazole in sub-Saharan Africa. We estimated the incidence of haematological disorders during the first 6 months of a zidovudine-containing highly active antiretroviral therapy (HAART) regimen in sub-Saharan African adults receiving cotrimoxazole. METHODS: Prospective cohort study in Abidjan, with blood cell count measurement at baseline (HAART initiation), month 1, month 3 and month 6. RESULTS: A total of 498 adults [baseline: 80% currently on cotrimoxazole prophylaxis; median CD4 count 237/mm3 [interquartile range (IQR) 181;316]; median neutrophil count 1647/mm3 (IQR 1221;2256); median haemoglobin 113 g/l (IQR 102;122)] started zidovudine (AZT)/lamivudine/efavirenz. During follow-up, 118 patients had a grade 3-4 neutropenia [(56.3/100 person-years (PY)], 23 had a grade 3-4 anaemia (9.6/100 PY) and no cases of grade 3-4 thrombocytopenia. Of the 118 patients with grade 3-4 neutropenia, 86 (73%) had to stop cotrimoxazole because neutropenia persisted, and one (<1%) had to stop AZT because of persistent neutropenia after cotrimoxazole was stopped (neutropenia-related HAART modification: 0.4/100 PY). Of the 23 patients with grade 3-4 anaemia, 11 had to stop AZT (anaemia-related HAART modification: 4.4/100 PY). In patients who stopped cotrimoxazole but not AZT, the median gain in neutrophils at 1 month was +540/mm3 (IQR +150;+896). CONCLUSIONS: At baseline, most patients had a normal neutrophil count and 80% of them were already receiving cotrimoxazole. An unexpectedly high rate of grade 3-4 neutropenia occurred shortly after introduction of AZT. Almost all of the persistent severe neutropenia disappeared after cotrimoxazole was stopped. This suggests an accentuated drug interaction between the two drugs in these sub-Saharan African individuals. Grade 3-4 anaemia was much less frequent, but remained the first cause of AZT discontinuation.

PMID: 16152755 [PubMed - indexed for MEDLINE]

Trimethoprim/sulfamethoxazole for treatment of severe Staphylococcus aureus infections.

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OBJECTIVE: To evaluate the role of trimethoprim/sulfamethoxazole (TMP/SMX) as an alternative to vancomycin for the treatment of severe Staphylococcus aureus infections. DATA SOURCES: Clinical literature was accessed through MEDLINE (1966-February 2003) and EMBASE (1980-February 2003). Key search terms included trimethoprim/sulfamethoxazole combination and Staphylococcus aureus. DATA SYNTHESIS: An evaluation of case reports, case series, and clinical studies focusing on the use of TMP/SMX for treatment of severe S. aureus infections was conducted. The majority of the reports indicate that TMP/SMX may be effective for the treatment of infections due to low bacterial burdens of susceptible strains of S. aureus. CONCLUSIONS: In select infections, TMP/SMX may be a useful alternative to vancomycin for treatment of severe S. aureus infections. Additional randomized studies should be conducted comparing this agent with vancomycin and linezolid.

PMID: 14742775 [PubMed - indexed for MEDLINE]

Severe thrombocytopenia possibly associated with TMP/SMX therapy.

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OBJECTIVE: To report a case of possible severe, life-threatening thrombocytopenia associated with trimethoprim/sulfamethoxazole (TMP/SMX) therapy. CASE SUMMARY: A 54-year-old white woman received a 10-day course of TMP/SMX for treatment of chronic sinusitis. One day after finishing the course of TMP/SMX therapy, the presented to the emergency department because of the development of scattered petechiae on both hands and blood blisters in her mouth. On admission, her complete blood cell count results revealed a severely low platelet count of 2 x 10(3)/mm3. Other laboratory test results were normal, except for elevated blood glucose (nonfasting blood glucose). TMP/SMX was believed to be the most likely cause of thrombocytopenia. She was treated successfully with a transfusion of 2 units of platelets and oral prednisone. Her platelet count increased to 110 x 10(3)/mm3 4 days after discontinuation of TMP/SMX. She was discharged on hospital day 5. On follow-up (2 wk after hospital discharge), her platelet count was normal (351 x 10(3)/mm3). DISCUSSION: TMP/SMX has been implicated as a cause of thrombocytopenia, which is defined as platelet count < 150 x 10(3)/mm3. Although it is uncommon, spontaneous severe bleeding may occur when platelet count decreases to < or = 10 x 10(3)/mm3. Thrombocytopenia associated with TMP/SMX appears to be an immune-mediated process resulting in platelet destruction by drug-dependent platelet antibodies. Treatment of thrombocytopenia associated with TMP/SMX therapy includes discontinuation of the offending drug and the use of corticosteroids. Platelet transfusion and intravenous immunoglobulin may be required in some patients. CONCLUSIONS: Thrombocytopenia associated with TMP/SMX therapy can be serious or life threatening because it may result in significant bleeding complications. This hematologic adverse effect of TMP/SMX may occur even with the usual recommended dosage and duration of therapy. Careful monitoring of complete blood cell count, including platelet count, before and during TMP/SMX therapy is suggested.

PMID: 11816265 [PubMed - indexed for MEDLINE]

The teratogenic risk of trimethoprim-sulfonamides: a population based case-control study.

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OBJECTIVE: To study human teratogenic potential of two trimethoprim-sulfonamide combinations: trimethoprim-sulfamethoxazole (cotrimoxazole) and trimethoprim-sulfamethazine during pregnancy. These agents have antifolate effects and other

antifolate agents can induce multiple congenital abnormalities, neural-tube defects, cardiovascular, and other malformations in animal experiments and in humans. DESIGN: Pair analysis of cases with congenital abnormalities and matched healthy controls in the large population-based data set of the Hungarian Case-Control Surveillance of Congenital Abnormalities between 1980 and 1996. PARTICIPANTS: 38,151 pregnant women who had newborn infants without any congenital abnormalities (control group) and 22,865 case pregnant women who had newborns or fetuses with congenital abnormalities. MAIN OUTCOME: Prevalence of drug use in matched case-control pairs to study the possible association with congenital abnormalities. RESULTS: In the case group 351 (1.5%) and in the control group 443 (1.2%) pregnant women were treated with cotrimoxazole (crude OR 1.3 with 95% CI 1.1-1.5). In addition 45 (0.2%) case and 39 (0.1%) control pregnant women had trimethoprim-sulfamethazine treatment (crude OR 1.9 with 95% CI 1.3-3.0). A higher rate of multiple congenital abnormalities (including mainly urinary tract and cardiovascular abnormalities) was found in case infants born to mothers with cotrimoxazole treatment during the second-third months of pregnancy. In addition, a higher rate of cardiovascular malformations occurred in cases born to mothers with cotrimoxazole treatment and trimethoprim-sulfamethazine treatment during the second-third months of pregnancy, respectively. CONCLUSION: Treatment with cotrimoxazole during pregnancy may increase the risk of cardiovascular malformations, and particularly multiple congenital abnormalities including defects of the urinary tract and cardiovascular system. A higher rate of cardiovascular malformations was also found after treatment with trimethoprim-sulfamethazine in the second-third months of pregnancy.

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Spinal malformations in the fetuses of HIV infected women receiving combination antiretroviral therapy and co-trimoxazole.

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HIV positive women of reproductive age are increasingly treated with a combination of antiretroviral agents, with effects on the developing human fetus that are largely unknown. We report two cases of severe spinal malformations in the fetuses of women treated with combination antiretroviral therapy and co-trimoxazole.

PMID: 11074147 [PubMed - indexed for MEDLINE]

Incidence of bacterial pneumonia in HIV-positive patients treated with preventive co-trimoxazole or pentamidine]

[Article in German]
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BACKGROUND: Besides Pneumocystis carinii bacterial pathogens represent the most common aetiology of pulmonary infections in HIV-positive patients. However, the impact of PCP prophylaxis on the incidence of bacterial pneumonia in HIV-positive patients using pentamidine or co-trimoxazole is still unknown. PATIENTS AND METHODS: We analysed retrospectively the data of 80 consecutive HIV-positive patients with a CD4-cell count < 300/microliter. The total observation period was 1993 patient months. Type and duration of chemoprophylaxis, frequency of bacterial pneumonia, PCP, extrapulmonary bacterial infections and cerebral toxoplasmosis were documented in a standardised manner. For statistical analysis we used the Kaplan-Meier test for the time to a recurrence of the various infections under both prophylaxis regimens and the Odds ratio for determination of the relative risk. RESULTS: We followed up 47 patients inhaling 300 mg pentamidine monthly for a total of 1133 months and 33 patients taking 480 mg co-trimoxazole per day p.o. for a total of 860 months. There were no statistically significant differences between the two groups in respect of demographic parameters, stage and therapy of HIV infection and distribution of risk groups. We found seven bacterial pneumonias in the co-trimoxazole group and 13 in the pentamidine group (not significant); the most common causative organisms were S. pneumoniae (n = 4), S. aureus (n = 3) and H. influenzae (n = 3). Furthermore, in the pentamidine group 12 PCP and nine cases of toxoplasma encephalitis were observed, whereas none of these infections occurred in the co-trimoxazole group ($p < 0.05$). Two of the patients taking co-trimoxazole and 15 of those inhaling pentamidine had extrapulmonary bacterial infections ($p < 0.05$), the most frequently identified pathogen being S. aureus (n = 7). The two prophylaxis groups did not differ significantly with regard to laboratory data, course and therapy of the bacterial pneumonias. CONCLUSION: There was no significant influence of chemoprophylaxis on the incidence of bacterial pneumonia in patients with advanced HIV-disease in our study. Since S. pneumoniae represents the most common causative agent, we suggest immunisation with a polyvalent pneumococcal vaccine at an early stage of HIV-infection.

PMID: 9885511 [PubMed - indexed for MEDLINE]

Epidemiology of resistance to antibiotics. Links between animals and humans.

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An inevitable side effect of the use of antibiotics is the emergence and dissemination of resistant bacteria. Most retrospective and prospective studies show that after the introduction of an antibiotic not only the level of resistance of pathogenic bacteria, but also of commensal bacteria increases. Commensal bacteria constitute a reservior of resistance genes for (potentially) pathogenic bacteria. Their level of resistance is considered to be a good indicator for selection pressure by antibiotic use and for resistance problems to be expected in pathogens. Resistant commensal bacteria of food animals might contaminate, like zoonotic bacteria, meat (products) and so reach the intestinal tract of humans. Monitoring the prevalence of resistance in indicator bacteria such as faecal Escherichia coli and enterococci in different populations, animals, patients and healthy humans, makes it feasible to compare the prevalence of resistance and to detect transfer of resistant bacteria or resistance genes from animals to humans and vice versa. Only in countries that use or used avoparcin (a glycopeptide antibiotic, like vancomycin) as antimicrobial growth promoter (AMGP), is vancomycin resistance common in intestinal enterococci, not only in

exposed animals, but also in the human population outside hospitals. Resistance genes against antibiotics, that are or have only been used in animals, i.e. nourseothricin, apramycin etc. were found soon after their introduction, not only in animal bacteria but also in the commensal flora of humans, in zoonotic pathogens like salmonellae, but also in strictly human pathogens, like shigellae. This makes it clear that not only clonal spread of resistant strains occurs, but also transfer of resistance genes between human and animal bacteria. Moreover, since the EU ban of avoparcin, a significant decrease has been observed in several European countries in the prevalence of vancomycin resistant enterococci in meat (products), in faecal samples of food animals and healthy humans, which underlines the role of antimicrobial usage in food animals in the selection of bacterial resistance and the transport of these resistances via the food chain to humans. To safeguard public health, the selection and dissemination of resistant bacteria from animals should be controlled. This can only be achieved by reducing the amounts of antibiotics used in animals. Discontinuing the practice of routinely adding AMGP to animal feeds would reduce the amounts of antibiotics used for animals in the EU by a minimum of 30% and in some member states even by 50%.

PMID: 10794955 [PubMed - indexed for MEDLINE]

Occurrence and relatedness of vancomycin-resistant enterococci in animals, humans, and the environment in different European regions.

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Vancomycin-resistant enterococci (VRE) in Europe are thought to have emerged partly due to the use of the glycopeptide avoparcin in animal husbandry. We compared the occurrence of VRE in geographical regions of Europe in which until 1997 large amounts of avoparcin were used (Spain, United Kingdom, and Denmark) with the occurrence of VRE in Sweden, where avoparcin was banned in 1986. We also studied the relatedness between VRE strains from different regions and habitats. In total, 2,580 samples were collected from humans, animals, and the environment (soil, sewage, recipient water). VRE resistant to 20 microg/ml vancomycin were identified in 8.2% of the samples and were found most frequently in raw and treated urban sewage samples (means, 71% and 36% of the samples, respectively), pig manure (17%), and hospital sewage (16%). The proportions of VRE-positive sewage samples were similar in Sweden, Spain, and the United Kingdom, whereas pig feces and manure were more often positive in Spain than in Sweden (30% versus 1%). Most VRE were Enterococcus faecium carrying vanA, and computerized biochemical phenotyping of the isolates of different ecological origins showed a high degree of polyclonality. In conclusion, it seems that animal-associated VRE probably reflect the former use of avoparcin in animal production, whereas VRE in human-associated samples may be a result of antibiotic use in hospitals. Since there seems to be a reservoir of the resistance genes in all countries studied, precautions must be taken to limit the use of antibiotics and antibiotic-like feed additives.

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Persistence of vancomycin-resistant enterococci in New Zealand broilers after discontinuation of avoparcin use.

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Large amounts of tylosin, zinc-bacitracin, and avilamycin are currently used as prophylactics in New Zealand broiler production. Avoparcin was also used from 1977 to 2000. A total of 382 enterococci were isolated from 213 fecal samples (147 individual poultry farms) using enrichment broths plated on m-Enterococcus agar lacking antimicrobials. These isolates were then examined to determine the prevalence of antimicrobial resistance. Of the 382 isolates, 5.8% (22 isolates) were resistant to vancomycin, and 64.7% were resistant to erythromycin. The bacitracin MIC was > or =256 microg/ml for 98.7% of isolates, and the avilamycin MIC was > or =8 microg/ml for 14.9% of isolates. No resistance to ampicillin or gentamicin was detected. Of the 22 vancomycin-resistant enterococci (VRE) isolates, 18 (81.8%) were Enterococcus faecalis, 3 were Enterococcus faecium, and 1 was Enterococcus durans. However, when the 213 fecal enrichment broths were plated on m-Enterococcus agar containing vancomycin, 86 VRE were recovered; 66% of these isolates were E. faecium and the remainder were E. faecalis. Vancomycin-resistant E. faecium isolates were found to have heterogenous pulsed-field gel electrophoresis (PFGE) patterns of SmaI-digested DNA, whereas the PFGE patterns of vancomycin-resistant E. faecalis isolates were identical or closely related, suggesting that this VRE clone is widespread throughout New Zealand. These data demonstrate that vancomycin-resistant E. faecalis persists in the absence and presence of vancomycin-selective pressure, thus explaining the dominance of this VRE clone even in the absence of avoparcin.

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High prevalence of vancomycin-resistant enterococci in Swedish sewage.

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In Europe the use of the growth promoter avoparcin is considered to have selected for vancomycin-resistant enterococci (VRE). Sweden ceased using avoparcin in 1986, and only occasional cases of VRE from hospitals have been reported since 1995. Within the framework of a European study, samples from urban raw sewage, treated sewage, surface water, and hospital sewage in Sweden (n = 118) were screened for VRE. Surprisingly, VRE were isolated from 21 of 35 untreated sewage samples (60%), from 5 of 14 hospital sewage samples (36%), from 6 of 32 treated sewage samples (19%), and from 1 of 37 surface water samples. Thirty-five isolates from 33 samples were further characterized by geno- and phenotyping, MIC determination, and PCR

analysis. Most isolates (30 of 35) carried the vanA gene, and the majority (24 of 35) of the isolates were Enterococcus faecium. Most of the VRE were multiresistant. The typing revealed high diversity of the isolates. However, one major cluster with seven identical or similar isolates was found. These isolates came from three different sewage treatment plants and were collected at different occasions during 1 year. All VRE from hospital sewage originated from one of the two hospitals studied. That hospital also had vancomycin consumption that was 10-fold that of the other. We conclude that VRE were commonly found in sewage samples in Sweden. The origin might be both healthy individuals and individuals in hospitals. Possibly, antimicrobial drugs or chemicals released into the sewage system may sustain VRE in the system.

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Epidemiology of resistance to antibiotics. Links between animals and humans.

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An inevitable side effect of the use of antibiotics is the emergence and dissemination of resistant bacteria. Most retrospective and prospective studies show that after the introduction of an antibiotic not only the level of resistance of pathogenic bacteria, but also of commensal bacteria increases. Commensal bacteria constitute a reservior of resistance genes for (potentially) pathogenic bacteria. Their level of resistance is considered to be a good indicator for selection pressure by antibiotic use and for resistance problems to be expected in pathogens. Resistant commensal bacteria of food animals might contaminate, like zoonotic bacteria, meat (products) and so reach the intestinal tract of humans. Monitoring the prevalence of resistance in indicator bacteria such as faecal Escherichia coli and enterococci in different populations, animals, patients and healthy humans, makes it feasible to compare the prevalence of resistance and to detect transfer of resistant bacteria or resistance genes from animals to humans and vice versa. Only in countries that use or used avoparcin (a glycopeptide antibiotic, like vancomycin) as antimicrobial growth promoter (AMGP), is vancomycin resistance common in intestinal enterococci, not only in exposed animals, but also in the human population outside hospitals. Resistance genes against antibiotics, that are or have only been used in animals, i.e. nourseothricin, apramycin etc. were found soon after their introduction, not only in animal bacteria but also in the commensal flora of humans, in zoonotic pathogens like salmonellae, but also in strictly human pathogens, like shigellae. This makes it clear that not only clonal spread of resistant strains occurs, but also transfer of resistance genes between human and animal bacteria. Moreover, since the EU ban of avoparcin, a significant decrease has been observed in several European countries in the prevalence of vancomycin resistant enterococci in meat (products), in faecal samples of food animals and healthy humans, which underlines the role of antimicrobial usage in food animals in the selection of bacterial resistance and the transport of these resistances via the food chain to humans. To safeguard public health, the selection and dissemination of resistant bacteria from animals should be controlled. This can only be achieved by reducing the amounts of

antibiotics used in animals. Discontinuing the practice of routinely adding AMGP to animal feeds would reduce the amounts of antibiotics used for animals in the EU by a minimum of 30% and in some member states even by 50%.

PMID: 10794955 [PubMed - indexed for MEDLINE]

Geoffrey Cannon: Superbugs, Nature's Revenge

Virgin Publishing Ltd., London 1995

Part Four: Apocalypse Now: How Antibiotics Breed Disease

Chapter 15: Nature's Most Malicious Trick?
Reasons to be careful- Immunosuppression - a link with AIDS? -Increasing risk of colon cancer.

Reasons to be careful

Once you know, that you need the resident bacteria in your gut to protect your health, and that antibiotics especially when overused may eventually not only devaste these friendly flora but also may strip away the outer immune defences in your gut, it is easy to see that prolonged course of antibiotics can in time lay you open to all sorts of infections and also non-infectious diseases.
Many diseases, some serious, have evidently become more common in countries like UK and the USA in the last 50 years. They may in part be caused by medical treatment. Infants and children are vulnerable to repeated ear, nose and throat infections. Girls and women are vulnerable to repeated cysteitis and to fungal superinfection, which can become invasive. Antibiotics are certainly one cause of this diseases and may be one cause of a variety of bowel diseases and some forms of arthritis. And the serious general malaise known as chronic fatique syndrome may be in part a complication of invasive fungal infection. Young children and old people are especially at risk, as are the chronically ill. This in addition to the known immediate or acurate ill-effects of antibiotics already described.
Once again, these are not reasons to always avoid antibiotics. To repeat, they are a presicous resource: in case of reliably diagnosed serious invasive bacterial infetions their benefits far outweight their risks. But risks there are: and many of the ill-effects of antibiotics are insidious, quite likely not to be linked with the drug either by victims or their doctors.

Immunosuppression

Our resident gut flora have another vital function not mentioned so far. They stimulate the production of immunoglobulins, proteins in the blood integral to the body's inner immune defences. Experiments show that animals with all their gut flora removed, make only about one-fiftieth as much immunoglobuline as normal animals. Commenting on this finding, the standard textbook 'Immunology' states: "If the commensal organisms of the gut are removed by antibiotics, pathogenic organisms can readily gain a foothold", and emphasises the importance of not disturbing the relationship between the host and its indigenous flora.
Does this mean that antibiotics are immunosuppressant drugs? This is an explosive question. Drugs generally classified as immunosuppressants are very dangerous. They are used only on people with cancer, and also after organ-transplants. They greatly increase the risk of serious bacterial and viral infection, and also of cancer, and are used only when patients are otherwise likely to die.

In ordinary circumstances, antibiotics are nothing like as dangerous as these drugs. As already stated, one course of antibiotics destroys the bacteria in the gut but not utterly, and a healthy balance of resident bacteria is usually restored soon after antibiotic therapy.
The only class of antibiotic that is commonly identified as immunosuppressive is tetracycline, because of its profound destruction of so many species of resident gut flora. And in a sense allergic reactions are reassuring because as mentioned, they show, that the body's inner immune defences are beeing irritated, and therefore obviously in working order. Basically healthy people are very unlikely to disrupt their inner immune defences by taking just one course of antibiotics.
Nevertheless, antibiotics do have a suppressive effect on our defences against infection. Given that our outer defences, including resident bacteria and the mucosal lining of the body's inner passages, are an integral part of our immune system, it follows inescapably that all antibiotics are by their nature immunosuppressants -mildly so, no doubt, compared with the drugs used on cancer and organtransplant patients, but immunosuppressive none the less.
How much this matters depends on the general state of the health of the individual, the type of antibiotic and the strength and length of the course. As ever, babies and little children, old people, hospital patients and anybody else who is generally weak or ill are at greatest risk, and this includes many, if not most people on the antibiotic treadmill, taking more and more courses for recurrent infections.
Most vulneralbe of all are people who are already immunosuppressed. But which came first; immunosuppression or antibiotics?
Here ist the view of Professor Sandy Raeburn, head of the departement of clinical genetics at Nottingham University, a specialist in disease of young children. In 1972 he wrote a paper for the Lancet, on "Antibiotics and Immunodeficiency":

"Immunological-deficiency syndromes were not observed before 1952. A possible explanation is that some of these conditions are produced by administration of antibiotics to certain individuals at a critical point in the development of immune responses."

Dr Raeburn gave examples of immunodeficiency diseases suffered mostly by babies and young children. Combined immunodeficiency (DIC) lays infants open to diarrhoea, thrush, pneumonia and other infections, and may increase the chance of cancer. Chronic granulomatous disease (CGD) also makes babies more vulnerable to bacterial infections.
"This diseases were not described before the antibiotic era" said Dr. Raeburn, "and the usual view is that modern therapy has enabled affected patients to survive longer. An alternative explanation, however, is that antibiotics have actually led to immunodeficiency states -diseases which did not previously exist".
He supports this proposal by three lines of argument. First, since one of the main purposes of the immune system (including the bacteria that have evolved with us) is to protect the body against invading micro-organisms, 'removal of bacteria by other means, such as rapidly effective antibacterial therapy, could have profound effects -for exaple, in infancy, during immunological development.' Later in life, antibiotics might provoke bacteria, even the friendly flora, into producing poisons that the immune system cannot handle. "The rarest clinical effects will emerge sooner or later because antibiotics are so widely used".

Second -and here Dr. Raeburn draws on his own clinical experience -while antibiotics work well for previous healthy people with an acute infection, they usually don't work for patients who are immunodeficient.

"Failures of antibiotic therapy are often excused by an assumption that host resistance was impaired. Could it be that infection persisted because the antibiotics interfered with host

resistance in a susceptible patient? I have seen several patients whose infections progressed while they were receiving seeminly appropriate antibiotics.

Third, he cited the laboratory evidence showing that antibiotics make experimental animals more vulneralbe to infections by suppressing their immune responses -some very much mor than others. Those at greatest risk of immunodeficiency diseases caused by antibiotics will include: those born vulnerable; babies and young children; people who are suffering from other diseases; and anybody taking regular heavy doses of antibiotics. He concluded: "If this theory is substantiated, it follows that antibiotics shoud be reserved for life-threatening infections, until the risk of immunotoxicity ist excluded in each patient".
I wrote to Dr. Raeburn asking him if, in the twenty years since he had published tha Lancet paper, he had changed his view. He wrote back saying: "Since I published that paper, there has been a vast amount of work on the interaction between antibiotics and the immune system. Much of it bears my own original hypothesis...
When a patient receives antibiotic treatment, the beneficial effects due to antibacterial activity could be reduced or even negated by deleterious effects on the immune system". Overall, he said, antibiotics are beneficial, "but in my special area of medical genetics, we might well see patients in which the balance is set differently -for exaple in cystic fibrosis".
In 1984, a dozen years after Dr. Raeburn's Lancet paper., Dr William Hauser of the Bosten University Medical Center and Dr. Jack Remington of the Palo Alto Medical Foundation, both specialists in infectious disease, published a review of the scientific literature on the "Effect of Antimicrobial Agents on the Immune Response" in the textbook Antimicrobial Therapy. Antibiotics listed as having ill-effects on the human immune response include: some aminoglycosides (gentamicin, tobramycin); a cephalosoprin (cephalotin); chloramphenicol; a lincosamide (clindamycin), ;various sulphonamides, and co-trimoxazole; various tetracyclines; sodium fusidate; and a number of anti-fungal and ant-tubercular drugs. Penicillins are not included, and evidently do not have ill-effects on the body's inner immune defences.

Hauser and Remington comment:
There is clearly a need for a better understanding of the potentail beneficial and deleterious effects of antibiotic therapy on the host's immune defences, especially in the immunosuppressed patient.
Indeed there is. But when antibiotics suppress our immune defences against disease, as evidently they may do, then people given constant courses of antibiotics to drive out infection will be not so much on a drug treadmill as caught in vortes pulling them down deeper into disease.
Here is an appalling prospekt. A child suffers middle-ear inflammation, treated with antibiotics, which then recurs because of antibiotics. A woman suffers cystitis, which is cleared up with antibiotics, but which then recurs in a more invasive form because of antibiotics. These infections occured in the first place because of antibiotics taken in infancy and childhood. Then people of all ages and both sexes suffer a cascade of diseases of the gut, each stage accelerated by antibiotics, which eventually cause irreversible infections carried by bacteria and by viruses that easily break thrugh weakened immune defences. At some stage in this cascade, the victims become chronically immunosuppressed, vulneralbe to invasion by any infectious agend around..
The idea that medicine can cure illness immediately and yet cause illness later may seem strange. But in other areas of life we know that gain now can mean loss later -this, after all, is one of the tenets of the Christian religion. Or, to take two familiar analogies, we knwo we can drive to destinations faster by breaking the speed limit, and we know we can spend our way out of immediate trouble by running up and overdraft. We also know we are running the risk

of wrecking our car or our finances. A friendly garage mechanic or bank manager will advise us to be careful.

A link with AIDS

When Professor Raeburn wrote his paper, chronic fatigue syndrome was obscure, and AIDS was unknown. When Drs Hauser and Remington wrote their review, neither disease was common. While AIDS kills and CFS does not, the two diseases are in some ways rather similar. Both are new, epidemic, afflict young people, have no known cure, take many clinical forms and cause profound debility. In the case of AIDS it is generally but not universally agreed that the infectious agent ist the HIV retrovirus. In the case of CFS there is a growing belief, that an enterovirus is involved.

As Professor James Mowbray has said of CFS, why has the immunity of people who suffer AIDS broken down?What is it that some people who are exposed to the disease remain untouched while other become infected with HIV? Why is it that some pople who test HIV positive remain in good health for many years, perhaps never suffering full blown AIDS, while others die rapidly?
Because AIDS is a new disease, is deadly and is an accelerating epidemic with in 1990 alone an estimated one million new cases of people worldwide infected with the HIV virus, other sexually transmitted diseases seem less important now. But at the end of 1990, the World Health Organisation announced that more than 250 million new cases of sexually transmitted diseases are reported every year. According to WHO Director-General Dr. Hiroshi Nakajima, "they have reached epidemic proportion globally, and if sexual behaviour is not modified and effectiv new prevention programmes are not implemented immediately the resulting disease and mortality rates will be even more staggering".
In 1990, 25 million new cases of gonorrhoea and 3,5 million new cases of syphilis were reported worldwide. Gonorrhoea is now often very resistant to penicillin, the original durg of choice, in which case, treatment is either with massive doses of penicillin, or other antibiotics including aminoglycosides, sulphonamides or co-trimoxazole. Penicillin usually still works on symphilis; an alteernative drug is tetracycline. In the last half-century, other sexually transmitted diseases have become more common. These include genital ulcers, treated with sulphonamides or tetracyclines; chlamydia, with tetracyclines, chancroid, with co-trimoxazole, trichomoniasis, with metronidazole; and genital herpes, a viral disease.
More than any other community, people whose lifestyle involves very many sexual partners are almost certain to suffer combinations and permutations of sexuelly transmitted diseases, which when bacterial are treated with constant courses of antibiotics, often broad-spectrum and/or cocktails. Such treatment over time provokes superinfection and drug-resistant superbugs -so more antibiotics are used, often more toxic in their effect. On such a drug treadmill, people who have constantly quenched their sexually transmitted diseaes with antimicrobial drugs are more vulneralbe to any infection, whether bacterial, fungal or viral, and once infected, are more likely to be overwhelmed.

In his book "The Plague Maker, Dr. Jeffrey Fisher states that Dr. Luc Montagnier of the Pasteur Institute in Paris, co-discoverer of HIV, believes that gross overuse of antibitocs may be a co-factor with HIV development of full-blown AIDS. This theory, sensation only because AIDS is the great deadly plague of our time, is also believed by some homoeopaths. Can it be true?
It makes microbiological sense: there is some experimental evidence suggesting that tetracycline has a side-effect of mutating mycoplasmas, including M. pirium and M. fermetans, into virus-type micro-organisms that can invade T-lymphocyte cells, whose

function is crucial to the body's inner immunity against infectious diseases. The Theory goes on to propose that if these cells are also already invaded by HIV, the mutated mycoplasmas effectively feed the HIV, activating them and enabling them to destroy T-lymphocyte function, thus laying the victim open to a great range of infections identified as full-blown AIDS.

On a separate point, Dr. Fisher quotes other research scientists who confirm the findings of Drs. Hauser and Remington, and who state that various antimicrobial drugs, including sulphonamides, cephalosporins, antifungals and antiparastics are directly immunosuppressive in different ways and, when overused, themselves increase vulnerability to infectious diseases.

If the mycoplasma theory is ture, it would follow that pople who test positive for presence of the HIV virus in their bodies, but whose lifestyles have not led them to gross overuse of antibiotics, will be less likely to develop full-blown AIDS. And indeed, haemophiliacs and others frequently show no signs of illness for ten or fifteen years after beeing accidentally treated or transfused with clotting factors or blood infected with HIV.

If the mycoplasma theory turns out not to be supported by evidence from other researchers, it remains true that destruction of gut flora and damge to the body's immunological defences by continual courses of antibiotics lays the body open to all sorts of bacterial, fungal and viral infections, including those most commonly associated with AIDS.

For men, the dream of sexual liberation began in the 1940ies. American Gis believed that because of penicillin they could go on the rampage with European and Asian women during World War II, and then during the Korean and Vietnam wars, without risk to themselves. The result is multi drug-resitant gonorrhoea. But antibiotics retained their reputation as magic bullets throughout the 1970s and 1980s, enabling incresingly wild liefestyles. In the USA and other rich countries, this is the context of AIDS. It can be said, that AIDS is a disease that was waiting to happen.