

Journal Club ID

Through 6-13-06

3 new** highlighted

1. Garey KW, Rege M, Pai MP *et al.* **Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study.** Clin Infect Dis 2006; 43(1):25-31.

Notes: 6-13-06, Asako Doi presented, useful study

Abstract: BACKGROUND: Inadequate antimicrobial treatment is an independent determinant of hospital mortality, and fungal bloodstream infections are among the types of infection with the highest rates of inappropriate initial treatment. Because of significant potential for reducing high mortality rates, we sought to assess the impact of delayed treatment across multiple study sites. The goals our analyses were to establish the frequency and duration of delayed antifungal treatment and to evaluate the relationship between treatment delay and mortality. METHODS: We conducted a retrospective cohort study of patients with candidemia from 4 medical centers who were prescribed fluconazole. Time to initiation of fluconazole therapy was calculated by subtracting the date on which fluconazole therapy was initiated from the culture date of the first blood sample positive for yeast. RESULTS: A total of 230 patients (51% male; mean age +/- standard deviation, 56 +/- 17 years) were identified; 192 of these had not been given prior treatment with fluconazole. Patients most commonly had nonsurgical hospital admission (162 patients [70%]) with a central line catheter (193 [84%]), diabetes (68 [30%]), or cancer (54 [24%]). Candida species causing infection included *Candida albicans* (129 patients [56%]), *Candida glabrata* (38 [16%]), *Candida parapsilosis* (25 [11%]), or *Candida tropicalis* (15 [7%]). The number of days to the initiation of antifungal treatment was 0 (92 patients [40%]), 1 (38 [17%]), 2 (33 [14%]) or > or = 3 (29 [12%]). Mortality rates were lowest for patients who began therapy on day 0 (14 patients [15%]) followed by patients who began on day 1 (9 [24%]), day 2 (12 [37%]), or day > or = 3 (12 [41%]) (P = .0009 for trend). Multivariate logistic regression was used to calculate independent predictors of mortality, which include increased time until fluconazole initiation (odds ratio, 1.42; P < .05) and Acute Physiology and Chronic Health Evaluation II score (1-point increments; odds ratio, 1.13; P < .05). CONCLUSION: A delay in the initiation of fluconazole therapy in hospitalized patients with candidemia significantly impacted mortality. New methods to avoid delays in appropriate antifungal therapy, such as rapid diagnostic tests or identification of unique risk factors, are needed.

2. Harnden A, Ninis N, Thompson M *et al.* **Parenteral penicillin for children with meningococcal disease before hospital admission: case-control study.** BMJ 2006; 332(7553):1295-8.

Notes: 6-13-06 Iwabuchi presented, risks of retrospective study

Abstract: OBJECTIVE: To explore the impact on mortality and morbidity of parenteral penicillin given to children before admission to hospital with suspected meningococcal disease. DESIGN: Retrospective comparison of fatal and non-fatal cases. SETTING: England, Wales, and Northern Ireland; December 1997 to February 1999. PARTICIPANTS: 158 children aged 0-16 years (26 died, 132 survived) in whom a general practitioner had made the diagnosis of meningococcal disease before hospital admission. RESULTS: Administration of parenteral penicillin by general practitioners was associated with increased odds ratios for death (7.4, 95% confidence interval 1.5 to 37.7) and complications in survivors (5.0, 1.7 to 15.0). Children who received penicillin had more severe disease on admission (median Glasgow meningococcal septicaemia prognostic score (GMSPS) 6.5 v 4.0, P = 0.002). Severity on admission did not differ significantly with time taken to reach hospital. CONCLUSIONS: Children who were given parenteral penicillin by a general practitioner had more severe disease on reaching hospital than those who were not given penicillin before admission. The association with poor outcome may be because children who are more severely ill are being given penicillin before admission.

3. Schildgen O, Sirma H, Funk A *et al.* Variant of hepatitis B virus with primary resistance to adefovir. N Engl J Med 2006; 354(17):1807-12.

Abstract: The reverse-transcriptase inhibitor lamivudine (Zeffix, GlaxoSmithKline) is often used to treat chronic infection with hepatitis B virus (HBV) until resistance develops. Treatment may then be switched to the reverse-transcriptase inhibitor adefovir (Hepsera, Gilead), which has a lower

frequency of resistance. Here, we describe three cases of primary adefovir resistance that were sensitive to tenofovir (Viread, Gilead). All three cases involved a rare HBV variant with a valine at position 233 of the reverse-transcriptase domain instead of isoleucine (rtI233V), as in the wild-type virus. This HBV variant also displayed resistance to adefovir and sensitivity to tenofovir in vitro.

4. Centanni M, Gargano L, Canettieri G *et al.* Thyroxine in goiter, Helicobacter pylori infection, and chronic gastritis. *N Engl J Med* 2006; 354(17):1787-95.
Abstract: BACKGROUND: Malabsorption of thyroxine has been described in patients treated with drugs that modify an acidic environment. We determined whether there is an increased need for thyroxine in patients with euthyroid multinodular goiter and impaired secretion of gastric acid. METHODS: We assessed the dose of thyroxine required to obtain a low level of thyrotropin (0.05 to 0.20 mU per liter) in 248 patients with multinodular goiter. Of these 248 patients, 53 also had Helicobacter pylori-related gastritis and 60 had atrophic gastritis of the body of the stomach (31 with evidence of H. pylori infection and 29 without such evidence). The reference group comprised 135 patients with multinodular goiter and no gastric disorders. In addition, variation in the level of serum thyrotropin was prospectively studied in 11 patients treated with thyroxine before and after H. pylori infection and both before and during treatment with omeprazole in 10 patients treated with thyroxine who had gastroesophageal reflux. RESULTS: The daily requirement of thyroxine was higher (by 22 to 34 percent) in patients with H. pylori-related gastritis, atrophic gastritis, or both conditions than in the reference group. In prospective studies, the occurrence of H. pylori infection in the 11 patients treated with thyroxine led to an increase in the level of serum thyrotropin (P=0.002), an effect that was nearly reversed on eradication of H. pylori infection. In a similar way, omeprazole treatment was associated with an increase in the level of serum thyrotropin in all 10 patients treated with thyroxine, an effect that was reversed by an increase in the thyroxine dose by 37 percent. CONCLUSIONS: Patients with impaired acid secretion require an increased dose of thyroxine, suggesting that normal gastric acid secretion is necessary for effective absorption of oral thyroxine.

5. Ferrara G, Losi M, D'Amico R *et al.* Use in routine clinical practice of two commercial blood tests for diagnosis of infection with Mycobacterium tuberculosis: a prospective study. *Lancet* 2006; 367(9519):1328-34.
Abstract: BACKGROUND: Two commercial blood assays for the diagnosis of latent tuberculosis infection--T-SPOT.TB and QuantiFERON-TB Gold--have been separately compared with the tuberculin skin test. Our aim was to compare the efficacy of all three tests in the same population sample. METHODS: We did a prospective study in 393 consecutively enrolled patients who were tested simultaneously with T-SPOT.TB and QuantiFERON-TB Gold because of suspected latent or active tuberculosis. 318 patients also had results available for a tuberculin skin test. FINDINGS: Overall agreement with the skin test was similar (T-SPOT.TB kappa=0.508, QuantiFERON-TB Gold kappa=0.460), but fewer BCG-vaccinated individuals were identified as positive by the two blood assays than by the tuberculin skin test (p=0.003 for T-SPOT.TB and p<0.0001 for QuantiFERON-TB Gold). Indeterminate results were significantly more frequent with QuantiFERON-TB Gold (11%, 43 of 383) than with T-SPOT.TB (3%, 12 of 383; p<0.0001) and were associated with immunosuppressive treatments for both tests. Age younger than 5 years was significantly associated with indeterminate results with QuantiFERON-TB Gold (p=0.003), but not with T-SPOT.TB. Overall, T-SPOT.TB produced significantly more positive results (38%, n=144, vs 26%, n=100, with QuantiFERON-TB Gold; p<0.0001), and close contacts of patients with active tuberculosis were more likely to be positive with T-SPOT.TB than with QuantiFERON-TB Gold (p=0.0010). INTERPRETATION: T-SPOT.TB and QuantiFERON-TB Gold have higher specificity than the tuberculin skin test. Rates of indeterminate and positive results, however, differ between the blood tests, suggesting that they might provide different results in routine clinical practice.

6. Fisman DN, Abrutyn E, Spaude KA, Kim A, Kirchner C, Daley J . Prior Pneumococcal Vaccination Is Associated with Reduced Death, Complications, and Length of Stay among Hospitalized Adults with Community-Acquired Pneumonia. *Clin Infect Dis* 2006; 42(8):1093-101.
Notes: Reviewed by Asako Doi, April 4, 2006
Abstract: Background. Vaccination with pneumococcal polysaccharide reduces the incidence of bacteremic pneumococcal disease in adults. We investigated the impact of prior pneumococcal

vaccination on in-hospital mortality and the probability of respiratory failure among hospitalized adults with community-acquired pneumonia. Methods. Consecutive individuals hospitalized with community-acquired pneumonia (diagnosed by International Classification of Diseases, Ninth Revision, Clinical Modification codes 480.0-487.0) at 109 community and teaching hospitals in the United States were identified using the Quality and Resource Management System, a database constructed by Tenet HealthCare to improve the quality of patient care. Vaccination status, comorbidities, and outcomes were abstracted by case managers concurrently with patient care. Associations between vaccination, survival, and respiratory failure were defined using multivariable logistic regression models. Results. Of 62,918 adults hospitalized with community-acquired pneumonia between 1999 and 2003, 7390 (12%) had a record of prior pneumococcal vaccination. Vaccine recipients were less likely to die of any cause during hospitalization than were individuals with no record of vaccination (adjusted odds ratio [OR], 0.50; 95% confidence interval [CI], 0.43-0.59), even after adjustment for the presence of comorbid illnesses, age, smoking, and influenza vaccination and under varying assumptions about missing vaccination data. Vaccination also lowered the risk of respiratory failure (adjusted OR, 0.67; 95% CI, 0.59-0.76) and other complications and reduced median length of stay by 2 days, compared with nonvaccination ($P < .001$). Conclusions. Prior vaccination against pneumococcus is associated with improved survival, decreased chance of respiratory failure or other complications, and decreased length of stay among hospitalized patients with community-acquired pneumonia. These observations reinforce current efforts to improve compliance with existing pneumococcal vaccination recommendations for adults.

7. Kyaw MH, Lynfield R, Schaffner W *et al.* Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant *Streptococcus pneumoniae*. *N Engl J Med* 2006; 354(14):1455-63.

Notes: CORPORATE NAME: Active Bacterial Core Surveillance of the Emerging Infections Program Network.

Abstract: BACKGROUND: Five of seven serotypes in the pneumococcal conjugate vaccine, introduced for infants in the United States in 2000, are responsible for most penicillin-resistant infections. We examined the effect of this vaccine on invasive disease caused by resistant strains. METHODS: We used laboratory-based data from Active Bacterial Core surveillance to measure disease caused by antibiotic-nonsusceptible pneumococci from 1996 through 2004. Cases of invasive disease, defined as disease caused by pneumococci isolated from a normally sterile site, were identified in eight surveillance areas. Isolates underwent serotyping and susceptibility testing. RESULTS: Rates of invasive disease caused by penicillin-nonsusceptible strains and strains not susceptible to multiple antibiotics peaked in 1999 and decreased by 2004, from 6.3 to 2.7 cases per 100,000 (a decline of 57 percent; 95 percent confidence interval, 55 to 58 percent) and from 4.1 to 1.7 cases per 100,000 (a decline of 59 percent; 95 percent confidence interval, 58 to 60 percent), respectively. Among children under two years of age, disease caused by penicillin-nonsusceptible strains decreased from 70.3 to 13.1 cases per 100,000 (a decline of 81 percent; 95 percent confidence interval, 80 to 82 percent). Among persons 65 years of age or older, disease caused by penicillin-nonsusceptible strains decreased from 16.4 to 8.4 cases per 100,000 (a decline of 49 percent). Rates of resistant disease caused by vaccine serotypes fell 87 percent. An increase was seen in disease caused by serotype 19A, a serotype not included in the vaccine (from 2.0 to 8.3 per 100,000 among children under two years of age). CONCLUSIONS: The rate of antibiotic-resistant invasive pneumococcal infections decreased in young children and older persons after the introduction of the conjugate vaccine. There was an increase in infections caused by serotypes not included in the vaccine.

8. Park-Wyllie LY, Juurlink DN, Kopp A *et al.* Outpatient gatifloxacin therapy and dysglycemia in older adults. *N Engl J Med* 2006; 354(13):1352-61.

Notes: Reviewed by Iwabuchi, April 4, 2006

Abstract: BACKGROUND: Gatifloxacin has been associated with both hypoglycemia and hyperglycemia. We examined dysglycemia-related health outcomes associated with various antibiotics in a population of approximately 1.4 million Ontario, Canada, residents 66 years of age or older. METHODS: We conducted two population-based, nested case-control studies. In the first, case patients were persons treated in the hospital for hypoglycemia after outpatient treatment with a macrolide, a second-generation cephalosporin, or a respiratory fluoroquinolone (gatifloxacin,

levofloxacin, moxifloxacin, or ciprofloxacin). In the second, case patients were persons who received hospital care for hyperglycemia. For each case patient, we identified up to five controls matched according to age, sex, the presence or absence of diabetes, and the timing of antibiotic therapy. RESULTS: Between April 2002 and March 2004, we identified 788 patients treated for hypoglycemia within 30 days after antibiotic therapy. As compared with macrolide antibiotics, gatifloxacin was associated with an increased risk of hypoglycemia (adjusted odds ratio, 4.3; 95 percent confidence interval, 2.9 to 6.3). Levofloxacin was also associated with a slightly increased risk (adjusted odds ratio, 1.5; 95 percent confidence interval, 1.2 to 2.0), but no such risk was seen with moxifloxacin, ciprofloxacin, or cephalosporins. We then identified 470 patients treated for hyperglycemia within 30 days after antibiotic therapy. As compared with macrolides, gatifloxacin was associated with a considerably increased risk of hyperglycemia (adjusted odds ratio, 16.7; 95 percent confidence interval, 10.4 to 26.8), but no risk was noted with the other antibiotics. Risks were similar in the two studies regardless of the presence or absence of diabetes. CONCLUSIONS: As compared with the use of other broad-spectrum oral antibiotics, including other fluoroquinolones, the use of gatifloxacin among outpatients is associated with an increased risk of in-hospital treatment for both hypoglycemia and hyperglycemia.

9. Humair JP, Revaz SA, Bovier P, Stalder H. Management of acute pharyngitis in adults: reliability of rapid streptococcal tests and clinical findings. *Arch Intern Med* 2006; 166(6):640-4.
Abstract: BACKGROUND: How to use clinical score, the rapid streptococcal antigen test (RSAT), and culture results is uncertain for efficient management of acute pharyngitis in adults. METHODS: This prospective cohort study included 372 adult patients with pharyngitis treated at a Swiss university-based primary care clinic. In eligible patients with 2 to 4 clinical symptoms and signs (temperature \geq 38 degrees C, tonsillar exudate, tender cervical adenopathy, and no cough or rhinitis), we performed an RSAT and obtained a throat culture. We measured sensitivity and specificity of RSAT with culture as a gold standard and compared appropriate antibiotic use with cost per patient appropriately treated for the following 5 strategies: symptomatic treatment, systematic RSAT, selective RSAT, empirical antibiotic treatment, and systematic culture. RESULTS: RSAT had high sensitivity (91%) and specificity (95%) for the diagnosis of streptococcal pharyngitis. Systematic throat culture resulted in the highest antibiotic use, in 38% of patients with streptococcal pharyngitis. Systematic RSAT led to nearly optimal treatment (94%) and antibiotic prescription (37%), with minimal antibiotic overuse (3%) and underuse (3%). Empirical antibiotic treatment in patients with 3 or 4 clinical symptoms or signs resulted in a lower rate of appropriate therapy (59%) but higher rates of antibiotic use (60%), overuse (32%), and underuse (9%). Systematic RSAT was more cost-effective than strategies based on empirical treatment or culture: 15.00 dollars, 26.00 dollars, and 32.00 dollars, respectively, per patient appropriately treated. CONCLUSIONS: The RSAT we used is a valid test for diagnosis of pharyngitis in adults. A clinical approach combining this RSAT and clinical findings efficiently reduces inappropriate antibiotic prescription in adult patients with acute pharyngitis. Empirical therapy in patients with 3 or 4 clinical symptoms or signs results in antibiotic overuse.

10. Chang TT, Gish RG, de Man R *et al.* **A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B.** *N Engl J Med* 2006; 354(10):1001-10.
Notes: Ogii presented 6-13-06; promising new product
Abstract: BACKGROUND: Entecavir is a potent and selective guanosine analogue with significant activity against hepatitis B virus (HBV). METHODS: In this phase 3, double-blind trial, we randomly assigned 715 patients with hepatitis B e antigen (HBeAg)-positive chronic hepatitis B who had not previously received a nucleoside analogue to receive either 0.5 mg of entecavir or 100 mg of lamivudine once daily for a minimum of 52 weeks. The primary efficacy end point was histologic improvement (a decrease by at least two points in the Knodell necroinflammatory score, without worsening of fibrosis) at week 48. Secondary end points included a reduction in the serum HBV DNA level, HBeAg loss and seroconversion, and normalization of the alanine aminotransferase level. RESULTS: Histologic improvement after 48 weeks occurred in 226 of 314 patients in the entecavir group (72 percent) and 195 of 314 patients in the lamivudine group (62 percent, $P=0.009$). More patients in the entecavir group than in the lamivudine group had undetectable serum HBV DNA levels according to a polymerase-chain-reaction assay (67 percent vs. 36 percent, $P<0.001$) and

normalization of alanine aminotransferase levels (68 percent vs. 60 percent, $P=0.02$). The mean reduction in serum HBV DNA from baseline to week 48 was greater with entecavir than with lamivudine (6.9 vs. 5.4 log [on a base-10 scale] copies per milliliter, $P<0.001$). HBeAg seroconversion occurred in 21 percent of entecavir-treated patients and 18 percent of those treated with lamivudine ($P=0.33$). No viral resistance to entecavir was detected. Safety was similar in the two groups. CONCLUSIONS: Among patients with HBeAg-positive chronic hepatitis B, the rates of histologic, virologic, and biochemical improvement are significantly higher with entecavir than with lamivudine. The safety profile of the two agents is similar, and there is no evidence of viral resistance to entecavir. (ClinicalTrials.gov number, NCT00035633.).

11. Strevel EL, Kuper A, Gold WL. Severe and protracted hypoglycaemia associated with co-trimoxazole use. *Lancet Infect Dis* 2006; 6(3):178-82.
Notes: Junichiro Adachi; 14 March 06
Abstract: Co-trimoxazole (trimethoprim-sulfamethoxazole) is a commonly prescribed antimicrobial agent. Although it is well tolerated in most patients, serious adverse events related to its use have been described. Hypoglycaemia is a rare but potentially life-threatening complication of therapy. We describe a case of refractory hypoglycaemia complicated by seizure associated with co-trimoxazole for the treatment of *Pneumocystis carinii* pneumonia in a patient with AIDS. We also review 13 previously reported cases of co-trimoxazole-induced hypoglycaemia. Among this patient population, renal insufficiency was the most prevalent predisposing risk factor (93%). The mean daily dose of co-trimoxazole was 4.5 double strength (160 mg trimethoprim/800 mg sulfamethoxazole) tablets per day. Serum insulin levels were raised or inappropriately normal in 88% of cases in which they were measured, suggesting a sulfonylurea-like effect of co-trimoxazole as the mechanism of hypoglycaemia. All cases required intravenous glucose administration, and 43% experienced protracted (>12 hours) hypoglycaemia. Dosage adjustments should be made when prescribing co-trimoxazole to patients with renal dysfunction.

12. Alfageme I, Vazquez R, Reyes N *et al.* Clinical efficacy of anti-pneumococcal vaccination in patients with COPD. *Thorax* 2006; 61(3):189-95.
Notes: Reviewed by Riyosuke 24 March 2006
Abstract: BACKGROUND: A study was undertaken to evaluate the clinical efficacy of the 23-valent pneumococcal polysaccharide vaccine (PPV) in immunocompetent patients with chronic obstructive pulmonary disease (COPD). METHODS: A randomised controlled trial was carried out in 596 patients with COPD of mean (SD) age 65.8 (9.7) years, 298 of whom received PPV. The main outcome was radiographically proven community acquired pneumonia (CAP) of pneumococcal or unknown aetiology after a mean period of 979 days (range 20-1454). RESULTS: There were 58 first episodes of CAP caused by pneumococcus or of unknown aetiology, 25 in the intervention group and 33 in the non-intervention group. Kaplan-Meier survival curves for CAP did not show significant differences between the intervention and non-intervention arms (log rank test = 1.15, $p = 0.28$) in the whole group of patients. The efficacy of PPV in all patients was 24% (95% CI -24 to 54; $p = 0.333$). In the subgroup aged <65 years the efficacy of PPV was 76% (95% CI 20 to 93; $p = 0.013$), while in those with severe functional obstruction (forced expiratory volume in 1 second <40%) it was 48% (95% CI -7 to 80; $p = 0.076$). In younger patients with severe airflow obstruction the efficacy was 91% (95% CI 35 to 99; $p = 0.002$). There were only five cases of non-bacteraemic pneumococcal CAP, all in the non-intervention group (log rank test = 5.03; $p = 0.025$). Multivariate analysis gave a hazard ratio for unknown and pneumococcal CAP in the vaccinated group, adjusted for age, of 0.20 (95% CI 0.06 to 0.68; $p = 0.01$). CONCLUSIONS: PPV is effective in preventing CAP in patients with COPD aged less than 65 years and in those with severe airflow obstruction. No differences were found among the other groups of patients with COPD.

13. Thompson MJ, Ninis N, Perera R *et al.* Clinical recognition of meningococcal disease in children and adolescents. *Lancet* 2006; 367(9508):397-403.
Abstract: BACKGROUND: Meningococcal disease is a rapidly progressive childhood infection of global importance. To our knowledge, no systematic quantitative research exists into the occurrence of symptoms before admission to hospital. METHODS: Data were obtained from questionnaires answered by parents and from primary-care records for the course of illness before admission to

hospital in 448 children (103 fatal, 345 non-fatal), aged 16 years or younger, with meningococcal disease. In 373 cases, diagnosis was confirmed with microbiological techniques. The rest of the children were included because they had a purpuric rash, and either meningitis or evidence of septicaemic shock. Results were standardised to UK case-fatality rates. FINDINGS: The time-window for clinical diagnosis was narrow. Most children had only non-specific symptoms in the first 4-6 h, but were close to death by 24 h. Only 165 (51%) children were sent to hospital after the first consultation. The classic features of haemorrhagic rash, meningism, and impaired consciousness developed late (median onset 13-22 h). By contrast, 72% of children had early symptoms of sepsis (leg pains, cold hands and feet, abnormal skin colour) that first developed at a median time of 8 h, much earlier than the median time to hospital admission of 19 h. INTERPRETATION: Classic clinical features of meningococcal disease appear late in the illness. Recognising early symptoms of sepsis could increase the proportion of children identified by primary-care clinicians and shorten the time to hospital admission. The framework within which meningococcal disease is diagnosed should be changed to emphasise identification of these early symptoms by parents and clinicians.

14. Zuluaga AF, Galvis W, Saldarriaga JG, Agudelo M, Salazar BE, Vesga O. Etiologic diagnosis of chronic osteomyelitis: a prospective study. *Arch Intern Med* 2006; 166(1):95-100.

Notes: Asako Doi

Abstract: BACKGROUND: Although bone specimens were established 25 years ago as the gold standard for etiologic diagnosis of chronic osteomyelitis, recent studies suggest that nonbone specimens are as accurate as bone to identify the causative agent. We examined concordance rates between cultures from nonbone and bone specimens in 100 patients. METHODS: Prospective study conducted at Hospital Universitario San Vicente de Paul, a 750-bed university-based hospital located in Medellin, Colombia. We included patients with chronic osteomyelitis who had been free of antibiotic therapy for at least 48 hours, excluding those with diabetic foot and decubitus ulcers. At least 1 nonbone and 1 bone specimen were taken from each individual and subjected to complete microbiologic analysis. RESULTS: Bone cultures allowed agent identification in 94% of cases, including anaerobic bacteria in 14%. Cultures of nonbone and bone specimens gave identical results in 30% of patients, with slightly better concordance in chronic osteomyelitis caused by *Staphylococcus aureus* (42%) than by all other bacterial species (22%). However, statistical concordance determined by the Cohen kappa statistic was less than 0 (-0.0092+/-0.0324), indicating that the observed concordance was no better than that expected by chance alone ($P > .99$). CONCLUSIONS: Appropriate diagnosis and therapy of chronic osteomyelitis require microbiologic cultures of the infected bone. Nonbone specimens are not valid for this purpose.

15. Ruiz-Palacios GM, Perez-Schael I, Velazquez FR *et al.* Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med* 2006; 354(1):11-22.

Notes: CORPORATE NAME: Human Rotavirus Vaccine Study Group.

Abstract: BACKGROUND: The safety and efficacy of an attenuated G1P[8] human rotavirus (HRV) vaccine were tested in a randomized, double-blind, phase 3 trial. METHODS: We studied 63,225 healthy infants from 11 Latin American countries and Finland who received two oral doses of either the HRV vaccine (31,673 infants) or placebo (31,552 infants) at approximately two months and four months of age. Severe gastroenteritis episodes were identified by active surveillance. The severity of disease was graded with the use of the 20-point Vesikari scale. Vaccine efficacy was evaluated in a subgroup of 20,169 infants (10,159 vaccinees and 10,010 placebo recipients). RESULTS: The efficacy of the vaccine against severe rotavirus gastroenteritis and against rotavirus-associated hospitalization was 85 percent ($P < 0.001$ for the comparison with placebo) and reached 100 percent against more severe rotavirus gastroenteritis. Hospitalization for diarrhea of any cause was reduced by 42 percent (95 percent confidence interval, 29 to 53 percent; $P < 0.001$). During the 31-day window after each dose, six vaccine recipients and seven placebo recipients had definite intussusception (difference in risk, -0.32 per 10,000 infants; 95 percent confidence interval, -2.91 to 2.18; $P = 0.78$). CONCLUSIONS: Two oral doses of the live attenuated G1P[8] HRV vaccine were highly efficacious in protecting infants against severe rotavirus gastroenteritis, significantly reduced the rate of severe gastroenteritis from any cause, and were not associated with an increased risk of intussusception. (ClinicalTrials.gov numbers, NCT00139347 and NCT00263666.)

16. Kapetanovic MC, Saxne T, Sjöholm A, Truedsson L, Jonsson G, Geborek P. Influence of methotrexate, TNF blockers and prednisolone on antibody responses to pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis. *Rheumatology (Oxford)* 2006; 45(1):106-11.
Abstract: OBJECTIVE: To compare antibody responses to 23-valent pneumococcal vaccine (Pneumovax) in controls and patients with established rheumatoid arthritis (RA) treated with TNF blockers, methotrexate (MTX) or a combination of both. METHODS: Patients with RA (n = 149) and healthy controls (n = 47) were vaccinated. Treatment with TNF blockers (etanercept or infliximab) and MTX was given to 50 patients, and 62 patients were treated with TNF blockers alone or with other DMARDs. MTX alone was given to 37 patients. Concentrations of immunoglobulin G (IgG) antibodies against pneumococcal capsular polysaccharides 23F and 6B were measured by enzyme-linked immunoassay before and 4-6 weeks after vaccination. An immune response was defined as a twofold or higher increase in antibody concentration following vaccination. RESULTS: Prevacination antibody levels for both 23F and 6B were similar in the patient groups. Antibody concentrations after vaccination increased significantly in all groups. Patients treated with TNF blockers without MTX showed better immune responses than those treated with TNF blockers in combination with MTX (P = 0.037 for 23F and P = 0.004 for 6B) or MTX alone (P < 0.001 for both 23F and 6B). RA patients given MTX alone had the lowest immune responses. Prednisolone treatment did not influence the responses. CONCLUSIONS: Patients treated with TNF blockers and controls showed similar responses to vaccination. In contrast, patients treated with MTX had reduced responses regardless of anti-TNF treatment. The findings do not argue against the use of pneumococcal vaccination in RA patients undergoing treatment with TNF blockers.
17. Dial S, Delaney JA, Barkun AN, Suissa S. Use of gastric acid-suppressive agents and the risk of community-acquired *Clostridium difficile*-associated disease. *JAMA* 2005; 294(23):2989-95.
Abstract: CONTEXT: Recent reports suggest an increasing occurrence and severity of *Clostridium difficile*-associated disease. We assessed whether the use of gastric acid-suppressive agents is associated with an increased risk in the community. OBJECTIVE: To determine whether the use of gastric acid-suppressive agents increases the risk of *C difficile*-associated disease in a community population. DESIGN, SETTING, AND PATIENTS: We conducted 2 population-based case-control studies using the United Kingdom General Practice Research Database (GPRD). In the first study, we identified all 1672 cases of *C difficile* recorded between 1994 and 2004 among all patients registered for at least 2 years in each practice. Each case was matched to 10 controls on calendar time and the general practice. In the second study, a subset of these cases defined as community-acquired, that is, not hospitalized in the prior year, were matched on practice and age with controls also not hospitalized in the prior year. MAIN OUTCOME MEASURES: The incidence of *C difficile* and risk associated with gastric acid-suppressive agent use. RESULTS: The incidence of *C difficile* in patients diagnosed by their general practitioners in the General Practice Research Database increased from less than 1 case per 100,000 in 1994 to 22 per 100,000 in 2004. The adjusted rate ratio of *C difficile*-associated disease with current use of proton pump inhibitors was 2.9 (95% confidence interval [CI], 2.4-3.4) and with H₂-receptor antagonists the rate ratio was 2.0 (95% CI, 1.6-2.7). An elevated rate was also found with the use of nonsteroidal anti-inflammatory drugs (rate ratio, 1.3; 95% CI, 1.2-1.5). CONCLUSIONS: The use of acid-suppressive therapy, particularly proton pump inhibitors, is associated with an increased risk of community-acquired *C difficile*. The unexpected increase in risk with nonsteroidal anti-inflammatory drug use should be investigated further.
18. Marrie TJ, Huang JQ. Low-risk patients admitted with community-acquired pneumonia. *Am J Med* 2005; 118(12):1357-63.
Abstract: PURPOSE: To describe the natural history of community-acquired pneumonia in the subset of a large cohort of patients at low risk for mortality who were admitted to the hospital. METHODS: Prospective observational study of all patients at low risk for mortality (risk classes I and II) who presented to 6 hospitals and 1 emergency department in Edmonton, Alberta, Canada with a diagnosis of possible community-acquired pneumonia from November 15, 2000, to November 14, 2002. RESULTS: A total of 586/3065 (19.1%) low-risk patients (Fine criteria) were admitted, 48.4% of whom stayed more than 5 days. Multivariate analysis revealed that patients who

were admitted were more likely to be female, to have presented at Site B, which serves an inner city population, to have diminished premorbid functional status, to have comorbidities likely to be made worse by pneumonia (chronic obstructive pulmonary disease, asthma, heart disease, inflammatory bowel disease), and to suffer from substance abuse or psychiatric illness. A respiratory rate of ≥ 28 breaths per minute, and symptoms of shaking chills, shortness of breath, nausea or diarrhea were the remaining factors predicting admission. Nineteen percent of the patients suffered one or more complications, the most serious of which was progression of the pneumonia, resulting in respiratory failure necessitating mechanical ventilation in 2.4% and empyema in 1.4%. Four patients had lung cancer, and 1 had cancer of the vocal cords. Thirty-one percent of those who were admitted were still unable to eat or drink enough to maintain hydration by hospital day 5 or on discharge day. CONCLUSIONS: One in 5 patients at low risk for mortality were admitted to the hospital and half stayed more than 5 days; 19% suffered 1 or more complications. Our data emphasize the need for better rules to guide the admission decision and the importance of physician judgment in this decision.

19. Satomura K, Kitamura T, Kawamura T *et al.* Prevention of upper respiratory tract infections by gargling: a randomized trial. *Am J Prev Med* 2005; 29(4):302-7.
Notes: CORPORATE NAME: Great Cold Investigators-I.
Abstract: BACKGROUND: Gargling to wash the throat is commonly performed in Japan, and people believe that such hygienic routine, especially with gargle medicine, prevents upper respiratory tract infections (URTIs). Its effectiveness, however, has not been established by clinical trials. DESIGN: Randomized controlled trial carried out in 2002-2003 winter season and analyzed in 2003 and 2004. PARTICIPANTS: Healthy volunteers (387) aged 18 to 65 years. INTERVENTION: Participants were randomly assigned to water gargling, povidone-iodine gargling, and usual care (control). Subjects in the two gargling groups were requested to gargle with water or diluted povidone-iodine at least three times a day. Participants were followed for 60 days. MAIN OUTCOME MEASURES: The primary outcome measure was first URTI incidence. Severity of URTI symptoms among incident cases was also evaluated. Both outcomes were assessed with a self-administered symptom record. Analyses were performed on an intention-to-treat basis. RESULTS: A total of 130 participants contracted URTIs. The incidence rate of first URTI was 0.26 episodes/30 person-days among control subjects. The rate decreased to 0.17 episodes/30 person-days in the water gargling group, and 0.24 episodes/30 person-days in the povidone-iodine gargling group. Respective incidence rate ratios against controls were 0.64 (95% confidence interval [CI]=0.41-0.99) and 0.89 (95% CI=0.60-1.33). A Cox regression (proportional hazard model) revealed the efficacy of water gargling (hazard ratio=0.60, 95% CI=0.39-0.95). Even when a URTI occurred, water gargling tended to attenuate bronchial symptoms ($p=0.055$). CONCLUSIONS: Simple water gargling was effective to prevent URTIs among healthy people. This virtually cost-free modality would appreciably benefit the general population.
20. Bucaneve G, Micozzi A, Menichetti F *et al.* Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. *N Engl J Med* 2005; 353(10):977-87.
Abstract: BACKGROUND: The prophylactic use of fluoroquinolones in patients with cancer and neutropenia is controversial and is not a recommended intervention. METHODS: We randomly assigned 760 consecutive adult patients with cancer in whom chemotherapy-induced neutropenia (<1000 neutrophils per cubic millimeter) was expected to occur for more than seven days to receive either oral levofloxacin (500 mg daily) or placebo from the start of chemotherapy until the resolution of neutropenia. Patients were stratified according to their underlying disease (acute leukemia vs. solid tumor or lymphoma). RESULTS: An intention-to-treat analysis showed that fever was present for the duration of neutropenia in 65 percent of patients who received levofloxacin prophylaxis, as compared with 85 percent of those receiving placebo (243 of 375 vs. 308 of 363; relative risk, 0.76; absolute difference in risk, -20 percent; 95 percent confidence interval, -26 to -14 percent; $P=0.001$). The levofloxacin group had a lower rate of microbiologically documented infections (absolute difference in risk, -17 percent; 95 percent confidence interval, -24 to -10 percent; $P<0.001$), bacteremias (difference in risk, -16 percent; 95 percent confidence interval, -22 to -9 percent; $P<0.001$), and single-agent gram-negative bacteremias (difference in risk, -7 percent; 95 percent confidence interval, -10 to -2 percent; $P<0.01$) than did the placebo group. Mortality and tolerability

were similar in the two groups. The effects of prophylaxis were also similar between patients with acute leukemia and those with solid tumors or lymphoma. CONCLUSIONS: Prophylactic treatment with levofloxacin is an effective and well-tolerated way of preventing febrile episodes and other relevant infection-related outcomes in patients with cancer and profound and protracted neutropenia. The long-term effect of this intervention on microbial resistance in the community is not known.

21. Dondorp A, Nosten F, Stepniewska K, Day N, White N. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. *Lancet* 2005; 366(9487):717-25.
Abstract: BACKGROUND: In the treatment of severe malaria, intravenous artesunate is more rapidly acting than intravenous quinine in terms of parasite clearance, is safer, and is simpler to administer, but whether it can reduce mortality is uncertain. METHODS: We did an open-label randomised controlled trial in patients admitted to hospital with severe falciparum malaria in Bangladesh, India, Indonesia, and Myanmar. We assigned individuals intravenous artesunate 2.4 mg/kg bodyweight given as a bolus (n=730) at 0, 12, and 24 h, and then daily, or intravenous quinine (20 mg salt per kg loading dose infused over 4 h then 10 mg/kg infused over 2-8 h three times a day; n=731). Oral medication was substituted when possible to complete treatment. Our primary endpoint was death from severe malaria, and analysis was by intention to treat. FINDINGS: We assessed all patients randomised for the primary endpoint. Mortality in artesunate recipients was 15% (107 of 730) compared with 22% (164 of 731) in quinine recipients; an absolute reduction of 34.7% (95% CI 18.5-47.6%; p=0.0002). Treatment with artesunate was well tolerated, whereas quinine was associated with hypoglycaemia (relative risk 3.2, 1.3-7.8; p=0.009). INTERPRETATION: Artesunate should become the treatment of choice for severe falciparum malaria in adults.
22. Lehrman G, Hogue IB, Palmer S *et al.* Depletion of latent HIV-1 infection in vivo: a proof-of-concept study. *Lancet* 2005; 366(9485):549-55.
Abstract: BACKGROUND: Persistent infection in resting CD4+ T cells prevents eradication of HIV-1. Since the chromatin remodeling enzyme histone deacetylase 1 (HDAC1) maintains latency of integrated HIV, we tested the ability of the HDAC inhibitor valproic acid to deplete persistent, latent infection in resting CD4+ T cells. PROCEDURES: We did a proof-of-concept study in four volunteers infected with HIV and on highly-active antiretroviral therapy (HAART). After intensifying the effect of HAART with subcutaneous enfuvirtide 90 mug twice daily for 4-6 weeks to prevent the spread of HIV, we added oral valproic acid 500-750 mg twice daily to their treatment regimen for 3 months. We quantified latent infection of resting CD4+ T cells before and after augmented treatment by limiting-dilution culture of resting CD4+ T cells after ex-vivo activation. FINDINGS: The frequency of resting cell infection was stable before addition of enfuvirtide and valproic acid, but declined thereafter. This decline was significant in three of four patients (mean reduction 75%, range 68% to >84%). Patients had slight reactions to enfuvirtide at the injection site, but otherwise tolerated treatment well. INTERPRETATION: Combination therapy with an HDAC inhibitor and intensified HAART safely accelerates clearance of HIV from resting CD4+ T cells in vivo, suggesting a new and practical approach to eliminate HIV infection in this persistent reservoir. This finding, though not definitive, suggests that new approaches will allow the cure of HIV in the future.
23. Grandiere-Perez L, Jacqueline C, Lemabecque V, Patey O, Potel G, Caillon J. Eagle effect in *Corynebacterium diphtheriae*. *J Infect Dis* 2005; 191(12):2118-20.
Abstract: The in vivo relevance of the paradoxical bactericidal effect (the Eagle effect) is not evident. We found in vitro a paradoxical bactericidal effect of amoxicillin on 2 strains of nontoxicogenic *Corynebacterium diphtheriae*. Then, using an experimental rabbit model of endocarditis, we evaluated the in vivo relevance of this phenomenon. Rabbits were assigned to the following groups: no treatment (control group), continuous amoxicillin infusion simulating a dosage of 200 mg/kg/day in humans, and continuous amoxicillin infusion simulating a dosage of 20 mg/kg/day in humans. The low dosage (20 mg/kg/day) was significantly more effective than the high dosage (200 mg/kg/day) against both strains (P<.025), confirming the paradoxical bactericidal effect observed in vitro.

24. Petersen RC, Thomas RG, Grundman M *et al.* Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med* 2005; 352(23):2379-88.
Notes: CORPORATE NAME: Alzheimer's Disease Cooperative Study Group.
Abstract: BACKGROUND: Mild cognitive impairment is a transitional state between the cognitive changes of normal aging and early Alzheimer's disease. METHODS: In a double-blind study, we evaluated subjects with the amnesic subtype of mild cognitive impairment. Subjects were randomly assigned to receive 2000 IU of vitamin E daily, 10 mg of donepezil daily, or placebo for three years. The primary outcome was clinically possible or probable Alzheimer's disease; secondary outcomes were cognition and function. RESULTS: A total of 769 subjects were enrolled, and possible or probable Alzheimer's disease developed in 212. The overall rate of progression from mild cognitive impairment to Alzheimer's disease was 16 percent per year. As compared with the placebo group, there were no significant differences in the probability of progression to Alzheimer's disease in the vitamin E group (hazard ratio, 1.02; 95 percent confidence interval, 0.74 to 1.41; P=0.91) or the donepezil group (hazard ratio, 0.80; 95 percent confidence interval, 0.57 to 1.13; P=0.42) during the three years of treatment. Prespecified analyses of the treatment effects at 6-month intervals showed that as compared with the placebo group, the donepezil group had a reduced likelihood of progression to Alzheimer's disease during the first 12 months of the study (P=0.04), a finding supported by the secondary outcome measures. Among carriers of one or more apolipoprotein E epsilon4 alleles, the benefit of donepezil was evident throughout the three-year follow-up. There were no significant differences in the rate of progression to Alzheimer's disease between the vitamin E and placebo groups at any point, either among all patients or among apolipoprotein E epsilon4 carriers. CONCLUSIONS: Vitamin E had no benefit in patients with mild cognitive impairment. Although donepezil therapy was associated with a lower rate of progression to Alzheimer's disease during the first 12 months of treatment, the rate of progression to Alzheimer's disease after three years was not lower among patients treated with donepezil than among those given placebo.
25. Geng E, Kreiswirth B, Burzynski J, Schluger NW. Clinical and radiographic correlates of primary and reactivation tuberculosis: a molecular epidemiology study. *JAMA* 2005; 293(22):2740-5.
Abstract: CONTEXT: The traditional teaching that pulmonary tuberculosis characterized by lymphadenopathy, effusions, and lower or mid lung zone infiltrates on chest radiography represents "primary" disease from recently acquired infection, whereas upper lobe infiltrates and cavities represent secondary or reactivation disease acquired in the more distant past, is not based on well-established clinical evidence. Furthermore, it is not known whether the atypical radiograph common in human immunodeficiency virus (HIV)-associated tuberculosis is due to a preponderance of primary progressive disease or altered immunity. OBJECTIVE: To analyze the relationship between recently acquired and remotely acquired pulmonary tuberculosis, clinical and demographic variables, and radiographic features by using molecular fingerprinting and conventional epidemiology. DESIGN, SETTING, AND POPULATION: A retrospective, hospital-based series of 456 patients treated at a New York City medical center between 1990 and 1999. Eligible patients had to have had at least 1 positive respiratory culture for *Mycobacterium tuberculosis* and available radiographic data. MAIN OUTCOME MEASURES: Radiographic appearance as measured by the presence or absence of 6 features: upper lobe infiltrate, cavitory lesion, adenopathy, effusions, lower or mid lung zone infiltrate, and miliary pattern. Radiographs were considered typical if they had an upper lobe infiltrate or cavity whether or not other features were present. Atypical radiographs were those that had adenopathy, effusion, or mid lower lung zone infiltrates or had none of the above features. RESULTS: Human immunodeficiency virus infection was most commonly associated with an atypical radiographic appearance on chest radiograph with an odds ratio of 0.20 (95% confidence interval, 0.13-0.31). Although a clustered fingerprint, representing recently acquired disease, was associated with typical radiograph in univariate analysis (odds ratio, 0.68; 95% confidence interval, 0.47-0.99), the association was lost when adjusted for HIV status. CONCLUSIONS: Time from acquisition of infection to development of clinical disease does not reliably predict the radiographic appearance of tuberculosis. Human immunodeficiency virus status, a probable surrogate for the integrity of the host immune response, is the only independent predictor of radiographic appearance. The altered radiographic appearance of pulmonary tuberculosis in HIV is due to altered immunity rather than recent acquisition of infection and progression to active disease.

26. Vidaur L, Gualis B, Rodriguez A *et al.* Clinical resolution in patients with suspicion of ventilator-associated pneumonia: a cohort study comparing patients with and without acute respiratory distress syndrome. *Crit Care Med* 2005; 33(6):1248-53.
Abstract: OBJECTIVES: To determine the pattern of resolution of classic infectious and respiratory variables in patients with ventilator-associated pneumonia (VAP) and appropriate empirical therapy, depending on the presence of acute respiratory distress syndrome (ARDS). A secondary objective was to identify clinical variables that might be useful for monitoring response to therapy. DESIGN: Prospective, observational cohort study. SETTING: Medical-surgical intensive care unit. PATIENTS: Seventy-five episodes of VAP without ARDS were identified and compared with 20 episodes with ARDS at VAP onset. Six episodes were excluded due to in vitro resistance to the initial antibiotic choice and six due to death in the first 72 hrs. INTERVENTIONS: None. MEASUREMENTS AND MAIN RESULTS: Resolution of fever, Pao₂/Fio₂ >250 mm Hg, and white blood cell count in episodes of VAP were present in 73.3%, 74.7%, and 53.3% of patients after 3 days of therapy. Indeed, >50% of episodes with the absence of ARDS presented resolution of fever and Pao₂/Fio₂ >250 within the first day of therapy. In contrast, resolution of radiologic opacities and clearance of secretions (median of 14 and 6 days of resolution) were late events. In patients with ARDS, resolution of fever remained the earliest variable. However, similar to Pao₂/Fio₂ 250 and white blood cell count, fever showed a significantly worse pattern after 3 days of therapy: 45%, 15% and 25%, respectively. Radiologic resolution was an extremely poor indicator, being present in only 10% of ARDS patients after 15 days of follow-up. Failure to improve after 48 hrs of therapy was documented in 65% of ARDS patients and 14.7% of controls (p < .05). CONCLUSIONS: Measures of oxygenation and core temperature can help physicians to individualize and shorten the duration of antibiotic therapy in VAP episodes. ARDS patients with VAP take twice as long to resolve fever, whereas hypoxemia should be ignored in defining resolution in this subset.
27. Falguera M, Martin M, Ruiz-Gonzalez A, Pifarre R, Garcia M. Community-acquired pneumonia as the initial manifestation of serious underlying diseases. *Am J Med* 2005; 118(4):378-83.
Abstract: PURPOSE: Community-acquired pneumonia is common among patients with coexisting illnesses and it can be the initial manifestation of these comorbid diseases. The objectives of our study were to evaluate the frequency of this association and to analyze whether certain characteristics could predict the presence of unknown comorbid conditions. SUBJECTS AND METHODS: Over a 5-year period, we prospectively studied 660 consecutive patients with community-acquired pneumonia seen at our institution. In a subgroup of these patients, diagnosis of previously unknown comorbid conditions was established during follow-up. Characteristics of these patients were compared with data from the remaining sample of patients. RESULTS: Prior underlying diseases were present in 298 (45%) patients. One or more new comorbid conditions were found in 41 (6%), of which diabetes (14 cases), malignancies (12 cases), chronic obstructive pulmonary disease (8 cases), and human immunodeficiency virus (HIV) infection (5 cases) were the most common. In the comparative study, a bacterial etiology, positive blood cultures, and hospitalization were more frequently found (P < 0.05) in patients with new comorbid conditions than atypical microorganisms or viruses, negative blood cultures, or outpatient care. CONCLUSION: In the initial diagnostic workup of patients with community-acquired pneumonia, the possibility of unknown comorbid conditions should be carefully evaluated.
28. Isaacson E, Glaser CA, Forghani B *et al.* Evidence of human herpesvirus 6 infection in 4 immunocompetent patients with encephalitis. *Clin Infect Dis* 2005; 40(6):890-3.
Abstract: We describe 4 patients with encephalitis due to possible reactivation of human herpesvirus 6 (HHV-6) infection who were enrolled in the California Encephalitis Project. All were immunocompetent and had HHV-6 loads determined in cerebrospinal fluid specimens. Tests for detection of HHV-6 should be considered for individuals with encephalitis.
29. Strahilevitz J, Zeller Mayer O, Vangel MG, Yonath H, Feinberg MS, Rubinstein E. Case clustering in infective endocarditis: the role of availability bias. *Clinical Microbiology and Infection* 2005; 11(12):955-7.
Abstract: Abstract Limited data exist regarding the impact of variations in clinical practice and

physicians' cognitive bias on the diagnosis of infective endocarditis (IE). As an illustration of these effects, unexpected clustering of IE diagnosis was encountered in a prospectively studied cohort. Transoesophageal echocardiography examinations for suspected IE were performed more frequently following a diagnosis of IE, and were associated with a subsequent cluster of IE cases. The cognitive bias of physicians resulting from a recent case of IE can lead to a transient increase in diagnosing additional cases of IE.

30. Rahimian J, Wilson T, Oram V, Holzman RS. Pyogenic liver abscess: recent trends in etiology and mortality. *Clin Infect Dis* 2004; 39(11):1654-9.
Notes: Gremillion 17 March 06
Abstract: BACKGROUND: Pyogenic liver abscess, a potentially life-threatening disease, has undergone significant changes in epidemiology, management, and mortality over the past several decades. METHODS: We reviewed the data for patients admitted to Bellevue Hospital and New York University Downtown Hospital (New York, New York) over a 10-year period. RESULTS: Of 79 cases reviewed, 43% occurred in patients with underlying biliary disease. The most common symptoms were fever, chills, and right upper quadrant pain or tenderness. The most common laboratory abnormalities were an elevated white blood cell count (in 68% of cases), temperature ≥ 38.1 degrees C (90%), a low albumin level (70.2%), and an elevated alkaline phosphatase level (67%). Seventy percent of the abscesses were in the right lobe, and 77% were solitary. *Klebsiella pneumoniae* was identified in 41% of cases in which a pathogen was recovered. Eighteen (50%) of 36 Asian patients had *K. pneumoniae* isolated, in contrast to 6 (27.3%) of 22 non-Asian patients (not statistically significant). Fifty-six percent of cases involved treatment with percutaneous drainage. Although prior reports noted mortality of 11%-31%, we observed only 2 deaths (mortality, 2.5%). CONCLUSIONS: The data suggest that *K. pneumoniae* has become the predominant etiology of pyogenic liver abscess and that mortality from this disease has decreased substantially.
31. Haber P, DeStefano F, Angulo FJ *et al.* Guillain-Barre syndrome following influenza vaccination. *JAMA* 2004; 292(20):2478-81.
Abstract: CONTEXT: An unexplained increase in the risk of Guillain-Barre syndrome (GBS) occurred among recipients of the swine influenza vaccine in 1976-1977. Guillain-Barre syndrome remains the most frequent neurological condition reported after influenza vaccination to the Vaccine Adverse Events Reporting System (VAERS) since its inception in 1990. OBJECTIVE: To evaluate trends of reports to VAERS of GBS following influenza vaccination in adults. DESIGN, SETTING, AND PARTICIPANTS: VAERS is the US national spontaneous reporting system for adverse events following vaccination. Reports of GBS in persons 18 years or older following influenza vaccination were evaluated for each influenza season from July 1, 1990, through June 30, 2003. The number of people vaccinated was estimated from the National Health Interview Survey and US census data. Beginning in 1994, active follow-up was conducted to verify GBS diagnosis and obtain other clinical details. MAIN OUTCOME MEASURE: Reporting rates of GBS following influenza vaccination over time. RESULTS: From July 1990 through June 2003, VAERS received 501 reports of GBS following influenza vaccination in adults. The median onset interval (13 days) was longer than that of non-GBS reports of adverse events after influenza vaccine (1 day) ($P < .001$). The annual reporting rate decreased 4-fold from a high of 0.17 per 100,000 vaccinees in 1993-1994 to 0.04 in 2002-2003 ($P < .001$). A GBS diagnosis was confirmed in 82% of reports. Preceding illness within 4 weeks of vaccination was identified in 24% of reported cases. CONCLUSIONS: From 1990 to 2003, VAERS reporting rates of GBS after influenza vaccination decreased. The long onset interval and low prevalence of other preexisting illnesses are consistent with a possible causal association between GBS and influenza vaccine. These findings require additional research, which can lead to a fuller understanding of the causes of GBS and its possible relationship with influenza vaccine.
32. van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. *N Engl J Med* 2004; 351(18):1849-59.
Abstract: BACKGROUND: We conducted a nationwide study in the Netherlands to determine clinical features and prognostic factors in adults with community-acquired acute bacterial meningitis. METHODS: From October 1998 to April 2002, all Dutch patients with community-acquired acute bacterial meningitis, confirmed by cerebrospinal fluid cultures, were prospectively

evaluated. All patients underwent a neurologic examination on admission and at discharge, and outcomes were classified as unfavorable (defined by a Glasgow Outcome Scale score of 1 to 4 points at discharge) or favorable (a score of 5). Predictors of an unfavorable outcome were identified through logistic-regression analysis. RESULTS: We evaluated 696 episodes of community-acquired acute bacterial meningitis. The most common pathogens were *Streptococcus pneumoniae* (51 percent of episodes) and *Neisseria meningitidis* (37 percent). The classic triad of fever, neck stiffness, and a change in mental status was present in only 44 percent of episodes; however, 95 percent had at least two of the four symptoms of headache, fever, neck stiffness, and altered mental status. On admission, 14 percent of patients were comatose and 33 percent had focal neurologic abnormalities. The overall mortality rate was 21 percent. The mortality rate was higher among patients with pneumococcal meningitis than among those with meningococcal meningitis (30 percent vs. 7 percent, $P < 0.001$). The outcome was unfavorable in 34 percent of episodes. Risk factors for an unfavorable outcome were advanced age, presence of otitis or sinusitis, absence of rash, a low score on the Glasgow Coma Scale on admission, tachycardia, a positive blood culture, an elevated erythrocyte sedimentation rate, thrombocytopenia, and a low cerebrospinal fluid white-cell count. CONCLUSIONS: In adults presenting with community-acquired acute bacterial meningitis, the sensitivity of the classic triad of fever, neck stiffness, and altered mental status is low, but almost all present with at least two of the four symptoms of headache, fever, neck stiffness, and altered mental status. The mortality associated with bacterial meningitis remains high, and the strongest risk factors for an unfavorable outcome are those that are indicative of systemic compromise, a low level of consciousness, and infection with *S. pneumoniae*.

33. Minneci PC, Deans KJ, Banks SM, Eichacker PQ, Natanson C. Meta-analysis: the effect of steroids on survival and shock during sepsis depends on the dose. *Ann Intern Med* 2004; 141(1):47-56.
Abstract: BACKGROUND: Previous meta-analyses demonstrated that high-dose glucocorticoids were not beneficial in sepsis. Recently, lower-dose glucocorticoids have been studied. PURPOSE: To compare recent trials of glucocorticoids for sepsis with previous glucocorticoid trials. DATA SOURCES: Systematic MEDLINE search for studies published between 1988 and 2003. STUDY SELECTION: Randomized, controlled trials of sepsis that examined the effects of glucocorticoids on survival or vasopressor requirements. DATA EXTRACTION: Two investigators independently collected data on patient and study characteristics, treatment interventions, and outcomes. DATA SYNTHESIS: The 5 included trials revealed a consistent and beneficial effect of glucocorticoids on survival ($I^2 = 0\%$; relative benefit, 1.23, [95% CI, 1.01 to 1.50]; $P = 0.036$) and shock reversal ($I^2 = 0\%$; relative benefit, 1.71 [CI, 1.29 to 2.26]; $P < 0.001$). These effects were the same regardless of adrenal function. In contrast, 8 trials published before 1989 demonstrated a survival disadvantage with steroid treatment ($I^2 = 14\%$; relative benefit, 0.89 [CI, 0.82 to 0.97]; $P = 0.008$). In comparison with the earlier trials, the more recent trials administered steroids later after patients met enrollment criteria (median, 23 hours vs. < 2 hours; $P = 0.02$), for longer courses (6 days vs. 1 day; $P = 0.01$), and in lower total dosages (hydrocortisone equivalents, 1209 mg vs. 23 975 mg; $P = 0.01$) to patients with higher control group mortality rates (mean, 57% vs. 34%; $P = 0.06$) who were more likely to be vasopressor-dependent (100% vs. 65%; $P = 0.03$). The relationship between steroid dose and survival was linear, characterized by benefit at low doses and increasing harm at higher doses ($P = 0.02$). LIMITATIONS: We could not analyze time-related improvements in medical care and potential bias secondary to nonreporting of negative study results. CONCLUSIONS: Although short courses of high-dose glucocorticoids decreased survival during sepsis, a 5- to 7-day course of physiologic hydrocortisone doses with subsequent tapering increases survival rate and shock reversal in patients with vasopressor-dependent septic shock.
34. Dial S, Alrasadi K, Manoukian C, Huang A, Menzies D. Risk of *Clostridium difficile* diarrhea among hospital inpatients prescribed proton pump inhibitors: cohort and case-control studies. *CMAJ* 2004; 171(1):33-8.
Notes: Reviewed March 30 by Riysuke Miyamoto
Abstract: BACKGROUND: Antibiotic disruption of the normal intestinal flora is a well-known risk factor for *Clostridium difficile*-associated diarrhea. Reduced gastric acidity has been suggested as a risk factor, and we hypothesized that proton pump inhibitors, because of their potency, may be an independent risk factor for this problem. METHODS: For the cohort study we identified from a

pharmacy database 1187 inpatients at a Montreal teaching hospital who received antibiotics over a 9-month period beginning in August 2002. We compared patients in this group who had also received a proton pump inhibitor or an H₂ blocker with patients who had not received acid suppressive therapy. Hospital laboratory reports of positive assay results for *C. difficile* toxin were used to ascertain cases in the cohort. To assess the possibility that proton pump inhibitors were prescribed to patients who were sicker and had other risk factors for *C. difficile* infection, we did a case-control study at a second Montreal teaching hospital. Cases were defined as patients who were positive for *C. difficile* toxin and who had a history of diarrhea (n = 94). Control subjects were selected from among patients who had received an antibiotic and were matched to cases by ward, age within 5 years and class of antibiotics (n = 94). RESULTS: In the cohort study, *C. difficile* diarrhea developed in 81 (6.8%) of the 1187 patients who received antibiotics while in hospital. In a multivariate analysis, *C. difficile* diarrhea was significantly associated with use of proton pump inhibitors (adjusted odds ratio [OR] 2.1, 95% confidence interval [CI] 1.2- 3.5), receipt of 3 or more antibiotics (OR 2.1, 95% CI 1.3- 3.4) and admission to a medical ward (OR 4.1, 95% CI 2.3- 7.3). In the case-control study *C. difficile* diarrhea was associated with female sex (adjusted OR 2.1, 95% CI 1.1-4.0), prior renal failure (adjusted OR 4.3, 95% CI 1.5-11.9), hospital admission in the 3 months before the index admission (adjusted OR 2.6, 95% CI 1.4-5.2) and use of proton pump inhibitors (adjusted OR 2.7, 95% CI 1.4-5.2). INTERPRETATION: Patients in hospital who received proton pump inhibitors were at increased risk of *C. difficile* diarrhea.

35. Ibanez-Nolla J, Nolla-Salas M, Leon MA *et al.* Early diagnosis of candidiasis in non-neutropenic critically ill patients. *J Infect* 2004; 48(2):181-92.
 Abstract: OBJECTIVE: To determine a method for the early diagnosis of candidiasis in non-neutropenic critically ill patients in order to reduce mortality. METHODS: A prospective study in non-neutropenic critically patients in whom *Candida* spp. were detected, was made in an intensive care unit (ICU) during an 8-year period from 3389 patients admitted. A diagnostic and therapeutic protocol was designed. Invasive candidiasis was defined according to dissemination and multifocality. RESULTS: *Candida* spp. were found in 145 cases (4.3%): 120 (83%) were considered as invasive candidiasis and 25 as colonisation (17%). The hospital mortality was 46% (67/145). A post-mortem study was carried out in 54% (36/67) of hospital deaths. *Candida albicans* was the most frequently isolated species (87%), followed by *Candida glabrata* (18%). There were 24 candidemias and three cases of endophthalmitis. Digestive and respiratory samples and non-*C. albicans* yeasts were risk factors for invasive candidiasis. The mortality rate was related statistically to invasive candidiasis and inversely to the appropriate antifungal treatment. CONCLUSIONS: Invasive candidiasis is related to digestive and respiratory samples and to the presence of non-*C. albicans* species. A simpler definition of invasive candidiasis in non-neutropenic critically ill patients will permit more rapid and accurate specific antifungal therapy.

36. Kawada J, Kimura H, Ito Y *et al.* Systemic cytokine responses in patients with influenza-associated encephalopathy. *J Infect Dis* 2003; 188(5):690-8.
 Abstract: Influenza-associated encephalopathy, a severe neurologic complication of influenza, is being reported more frequently in Japan. We investigated the transcription of cytokine genes in peripheral blood leukocytes and compared patients with influenza and with encephalopathy or febrile convulsions and patients with influenza but without neurologic complications. A quantitative polymerase chain reaction (PCR) revealed that transcription of the interleukin (IL)-6, IL-10, and tumor necrosis factor-alpha genes was up-regulated to a greater extent in patients with encephalopathy than in those without neurologic complications. Plasma IL-6 levels also were higher in patients with encephalopathy, although the difference was marginal. Viral RNA in throat swabs was quantified using a real-time quantitative PCR. The virus load was similar among patients with encephalopathy or febrile convulsions or without neurologic complications. Furthermore, virus load was not correlated with either the transcription of cytokine genes or plasma cytokine concentrations. These results suggest that influenza-associated encephalopathy might be a consequence of systemic immune responses.

37. Yu KH, Luo SF, Liou LB *et al.* Concomitant septic and gouty arthritis--an analysis of 30 cases. *Rheumatology (Oxford)* 2003; 42(9):1062-6.

Abstract: OBJECTIVES: To analyse the clinical features and outcomes of gouty patients with concomitant septic arthritis in a medical centre. METHODS: From the hospital database, we collected 30 hospitalized cases with concomitant septic arthritis and gouty arthritis from 1987 to 2001. All patients had positive bacterial culture and monosodium urate crystals in the affected joints. Medical records of the patients were analysed in detail. RESULTS: The mean age of patients was 52.8+/-12.5 yr. One-third of patients were afebrile at presentation, 30% had a normal blood leucocyte count and 10% had a synovial fluid leucocyte count less than 6000/mm³. The knee joint was the most common site of involvement, followed by the ankle, shoulder and wrist joints. Most patients had long-standing disease and subcutaneous tophi. Subcutaneous tophi rupture with secondary wound infection is the most common route of infection. Causative micro-organisms were *Staphylococcus aureus* (16 cases, 7 of whom were oxacillin-resistant), *Streptococcus* sp. (5 cases), *Pedococcus* sp. (1 case), and Gram-negative bacilli (9 cases). Fourteen patients received surgical debridement, among them two patients had an arthrodesis owing to severe joint destruction and one received above-knee amputation. Two patients died. One died of septic complications and the other died of acute myocardial infarction. CONCLUSIONS: Septic arthritis coexistent with gout presented a diagnostic difficulty. An early diagnosis requires a high level of suspicion. Prompt aspiration and analysis of the synovial fluid is imperative, regardless of the absence of fever or leucocytosis. Culture of the aspirated synovial fluid is warranted in gouty attack, even when it has a low white cell count or the Gram stain reveals no organisms.

38. Hasbun R, Abrahams J, Jekel J, Quagliarello VJ. Computed tomography of the head before lumbar puncture in adults with suspected meningitis. *N Engl J Med* 2001; 345(24):1727-33.
Abstract: BACKGROUND: In adults with suspected meningitis clinicians routinely order computed tomography (CT) of the head before performing a lumbar puncture. METHODS: We prospectively studied 301 adults with suspected meningitis to determine whether clinical characteristics that were present before CT of the head was performed could be used to identify patients who were unlikely to have abnormalities on CT. The Modified National Institutes of Health Stroke Scale was used to identify neurologic abnormalities. RESULTS: Of the 301 patients with suspected meningitis, 235 (78 percent) underwent CT of the head before undergoing lumbar puncture. In 56 of the 235 patients (24 percent), the results of CT were abnormal; 11 patients (5 percent) had evidence of a mass effect. The clinical features at base line that were associated with an abnormal finding on CT of the head were an age of at least 60 years, immunocompromise, a history of central nervous system disease, and a history of seizure within one week before presentation, as well as the following neurologic abnormalities: an abnormal level of consciousness, an inability to answer two consecutive questions correctly or to follow two consecutive commands, gaze palsy, abnormal visual fields, facial palsy, arm drift, leg drift, and abnormal language (e.g., aphasia). None of these features were present at base line in 96 of the 235 patients who underwent CT scanning of the head (41 percent). The CT scan was normal in 93 of these 96 patients, yielding a negative predictive value of 97 percent. Of the three misclassified patients, only one had a mild mass effect on CT, and all three subsequently underwent lumbar puncture, with no evidence of brain herniation one week later. CONCLUSIONS: In adults with suspected meningitis, clinical features can be used to identify those who are unlikely to have abnormal findings on CT of the head.
39. Ramirez JA, Bordon J. Early switch from intravenous to oral antibiotics in hospitalized patients with bacteremic community-acquired *Streptococcus pneumoniae* pneumonia. *Arch Intern Med* 2001; 161(6):848-50.
Notes: Kazuki Yoshida
Abstract: BACKGROUND: The identification of *Streptococcus pneumoniae* bacteremia in hospitalized patients with community-acquired pneumonia is considered by some investigators to be an exclusion criterion for early switch from intravenous to oral therapy. OBJECTIVE: To determine whether the switch from intravenous to oral therapy in such patients, once the patient reaches clinical stability, is associated with poor clinical outcome. METHODS: The medical records of 400 patients with community-acquired pneumonia hospitalized at the Veterans Affairs Medical Center of Louisville (Louisville, Ky) were reviewed to identify patients with bacteremic *S pneumoniae*. Four criteria were used to define when a patient reached clinical stability and should be considered a candidate for switch therapy: (1) cough and shortness of breath are improving, (2) patient is afebrile

for at least 8 hours, (3) white blood cell count is normalizing, and (4) oral intake and gastrointestinal tract absorption are adequate. RESULTS: A total of 36 bacteremic patients were identified. No clinical failures occurred in 18 patients who reached clinical stability and were switched to oral therapy or in 7 patients who reached clinical stability and continued intravenous therapy. Clinical failures (5 deaths) occurred in the group of 11 patients who did not reach clinical stability. CONCLUSION: Once a hospitalized patient with community-acquired pneumonia reaches clinical stability, it is safe to switch from intravenous to oral antibiotics even if bacteremia caused by *S pneumoniae* was initially documented.

40. Martin C, Viviani X, Leone M, Thirion X. Effect of norepinephrine on the outcome of septic shock. *Crit Care Med* 2000; 28(8):2758-65.
Abstract: OBJECTIVE: Despite increasingly sophisticated critical care, the mortality of septic shock remains elevated. Accordingly, care remains supportive. Volume resuscitation combined with vasopressor support remains the standard of care as adjuvant therapy, and many consider dopamine to be the pressor of choice. Because of fear of excessive vasoconstriction, norepinephrine is considered to be deleterious. The present study was designed to identify factors associated with outcome in a cohort of septic shock patients. Special attention was paid to hemodynamic management and to the choice of vasopressor used, to determine whether the use of norepinephrine was associated with increased mortality. DESIGN: Prospective, observational, cohort study. SETTING: Intensive care unit of a university hospital. PATIENTS: Ninety-seven adult patients with septic shock. MEASUREMENTS AND MAIN RESULTS: Data from these patients were examined to select variables independently and significantly associated with outcome during the hospital stay. Nineteen clinical, biological, and hemodynamic variables were collected at study entry or during the first 48-72 hrs and analyzed for each patient. A stepwise logistic regression analysis and a model building strategy were used to identify variables independently and significantly associated with outcome. The overall hospital mortality was 73% (71 patients). Five variables were significantly associated with outcome. One factor was strongly associated with a favorable outcome: the use of norepinephrine as part of the hemodynamic support of the patients. The 57 patients who were treated with norepinephrine had significantly lower hospital mortality (62% vs. 82%, $p < .001$; relative risk = 0.68; 95% confidence interval = 0.54-0.87) than the 40 patients treated with vasopressors other than norepinephrine (high-dose dopamine and/or epinephrine). Four variables were associated with a poor outcome and significantly higher hospital mortality: pneumonia as a cause of septic shock (82% vs. 61%, $p < .03$; relative risk = 1.47; 95% confidence interval = 1.07-1.77), organ system failure index ≤ 3 (92% vs. 60%, $p < .001$; relative risk = 1.47; 95% confidence interval = 1.17-1.82), low urine output at entry to the study (88% vs. 60%, $p < .01$; relative risk = 1.44; 95% confidence interval = 1.06-1.87), and admission blood lactate concentration > 4 mmol/L (91% vs. 63%, $p < .01$; relative risk = 1.60; 95% confidence interval = 1.27-1.84). CONCLUSIONS: Our results indicate that the use of norepinephrine as part of hemodynamic management may influence outcome favorably in septic shock patients. The data contradict the notion that norepinephrine potentiates end-organ hypoperfusion, thereby contributing to increased mortality. However, the present study suffers from some limitation because of its nonrandomized, open-label, observational design. Hence, a randomized clinical trial is needed to clearly establish that norepinephrine improves mortality of patients with septic shock, as compared with high-dose dopamine or epinephrine. Pneumonia as the cause of septic shock, high blood lactate concentration, and low urine output on admission are strong indicators of a poor prognosis. Multiple organ failure is confirmed as a reliable predictor of mortality in septic patients.
41. Colditz GA, Brewer TF, Berkey CS *et al.* Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature. *JAMA* 1994; 271(9):698-702.
Abstract: OBJECTIVE--To quantify the efficacy of BCG vaccine against tuberculosis (TB). DATA SOURCES--MEDLINE with index terms BCG vaccine, tuberculosis, and human. Experts from the Centers for Disease Control and Prevention and the World Health Organization, among others, provided lists of all known studies. STUDY SELECTION--A total of 1264 articles or abstracts were reviewed for details on BCG vaccination, concurrent vaccinated and unvaccinated groups, and TB outcome; 70 articles were reviewed in depth for method of vaccine allocation used to create comparable groups, equal surveillance and follow-up for recipient and concurrent control groups,

and outcome measures of TB cases and/or deaths. Fourteen prospective trials and 12 case-control studies were included in the analysis. DATA EXTRACTION--We recorded study design, age range of study population, number of patients enrolled, efficacy of vaccine, and items to assess the potential for bias in study design and diagnosis. At least two readers independently extracted data and evaluated validity. DATA SYNTHESIS--The relative risk (RR) or odds ratio (OR) of TB provided the measure of vaccine efficacy that we analyzed. The protective effect was then computed by $1-RR$ or $1-OR$. A random-effects model estimated a weighted average RR or OR from those provided by the trials or case-control studies. In the trials, the RR of TB was 0.49 (95% confidence interval [CI], 0.34 to 0.70) for vaccine recipients compared with nonrecipients (protective effect of 51%). In the case-control studies, the OR for TB was 0.50 (95% CI, 0.39 to 0.64), or a 50% protective effect. Seven trials reporting tuberculous deaths showed a protective effect from BCG vaccine of 71% (RR, 0.29; 95% CI, 0.16 to 0.53), and five studies reporting on meningitis showed a protective effect from BCG vaccine of 64% (OR, 0.36; 95% CI, 0.18 to 0.70). Geographic latitude of the study site and study validity score explained 66% of the heterogeneity among trials in a random-effects regression model. CONCLUSION--On average, BCG vaccine significantly reduces the risk of TB by 50%. Protection is observed across many populations, study designs, and forms of TB. Age at vaccination did not enhance predictiveness of BCG efficacy. Protection against tuberculous death, meningitis, and disseminated disease is higher than for total TB cases, although this result may reflect reduced error in disease classification rather than greater BCG efficacy.

42. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. *Am J Med* 1994; 96(3):200-9.
- Abstract: PURPOSE: This study was designed to develop improved criteria for the diagnosis of infective endocarditis and to compare these criteria with currently accepted criteria in a large series of cases. PATIENTS AND METHODS: A total of 405 consecutive cases of suspected infective endocarditis in 353 patients evaluated in a tertiary care hospital from 1985 to 1992 were analyzed using new diagnostic criteria for endocarditis. We defined two "major criteria" (typical blood culture and positive echocardiogram) and six "minor criteria" (predisposition, fever, vascular phenomena, immunologic phenomena, suggestive echocardiogram, and suggestive microbiologic findings). We also defined three diagnostic categories: (1) "definite" by pathologic or clinical criteria, (2) "possible," and (3) "rejected." Each suspected case of endocarditis was classified using both old and new criteria. Sixty-nine pathologically proven cases were reclassified after exclusion of the surgical or autopsy findings, enabling comparison of clinical diagnostic criteria in proven cases. RESULTS: Fifty-five (80%) of the 69 pathologically confirmed cases were classified as clinically definite endocarditis. The older criteria classified only 35 (51%) of the 69 pathologically confirmed cases into the analogous probable category ($p < 0.0001$). Twelve (17%) pathologically confirmed cases were rejected by older clinical criteria, but none were rejected by the new criteria. Seventy-one (21%) of the remaining 336 cases that were not proven pathologically were probable by older criteria, whereas the new criteria almost doubled the number of definite cases, to 135 (40%, $p < 0.01$). Of the 150 cases rejected by older criteria, 11 were definite, 87 were possible, and 52 were rejected by the new criteria. CONCLUSION: Application of the proposed new criteria increases the number of definite diagnoses. This should be useful for more accurate diagnosis and classification of patients with suspected endocarditis and provide better entry criteria for epidemiologic studies and clinical trials.