Risks for Infection With Carbapenem-Resistant *Klebsiella pneumoniae* Strains

*Carbapenem Resistance Among Klebsiella pneumoniae Isolates: Risk Factors, Molecular Characteristics, and Susceptibility Patterns.*


Treatment of ESBL-producing *K. pneumoniae* with carbapenems is a significant risk factor for development of CRKP infection.

**Background:** Extended spectrum b-lactamase (ESBL)-producing *Klebsiella pneumoniae* have emerged as important nosocomial pathogens. Carbapenems are recommended for treatment of infections caused by these organisms. Resistance to carbapenems among *K. pneumoniae* strains has been reported, and the spread of these strains is occurring in a number of settings.

**Objective:** To identify risk factors for infection with carbapenem-resistant *K. pneumoniae* (CRKP).

**Design:** Retrospective cohort study.

**Methods:** All patients with inpatient cultures positive for *K. pneumoniae* from January 1, 2006, through April 30, 2007, were identified. Case patients were defined as having a first isolate resistant to imipenem (minimum inhibitory concentration [MIC] ≥8 μg/mL), while control patients had isolates susceptible to imipenem (MIC <8 μg/mL). Emergence of resistance was defined as isolation of a resistant strain after isolation of a susceptible one. Standard methods were used to determine susceptibility to other antibiotics, and pulsed-field gel electrophoresis (PFGE) was used for strain characterization. Potential risk factors were assessed through chart review of an electronic health record. Univariate and multivariate analyses were performed to identify significant risk factors.

**Results:** 1055 inpatients had at least 1 *K. pneumoniae* isolate, 583 (55%) of whom had the initial isolate >48 hours after admission. Full data were available for 498 patients (85%). There were 88 case patients (18%), 373 control patients (75%), and 37 patients (7%) with emergence of CRKP resistance. More than one-half (51%) of the latter 37 patients initially had an ESBL-producing isolate. Carbapenems were used significantly more frequently in patients with CRKP-emergent strains compared to patients with only susceptible isolates (OR, 10). For all CRKP strains, the lowest frequencies of resistance were to colistin (4.5%), gentamicin (7%), and tigecycline (15%); ≥95% were resistant to fluoroquinolones, cephalosporins, and amikacin. After multivariate analysis, independent risk factors included prior fluoroquinolone use (OR, 1.87), previous receipt of a carbapenem (OR, 1.83), admission to the ICU (OR, 4.27), and exposure to at least 1 antibiotic prior to *K. pneumoniae* isolation (OR, 3.93). All CRKP isolates had either a *KPC-2* or *KPC-3* b-lactamase gene, and the 90% of those analyzed had a single PFGE profile.

**Conclusions:** CRKP isolates are multidrug resistant and most isolates appear related, suggesting nosocomial transmission.

**Reviewer's Comments:** Carbapenems are recommended for treatment of ESBL-producing strains of the *Enterobacteriaceae*. An increasing prevalence of CRKP strains is being recognized in many areas around the world, and not surprisingly, many patients who develop infection with these strains have been treated previously with carbapenems. Recognition of infection or colonization with CRKP strains is important so that appropriate infection control precautions can be used to limit further transmission to other at-risk patients.

Additional Keywords: None

Print Tag: Refer to original journal article
**Background:** *Streptococcus pyogenes*, or group A streptococcus (GAS), is a common, community-acquired pathogen that can also be transmitted nosocomially. Infection control precautions for a case patient include contact and droplet precautions before and for the first 24 hours after effective antimicrobial therapy is started. A severe case of invasive GAS disease occurred in a health-care worker (HCW) after exposure to a patient with GAS toxic shock syndrome.

**Design:** Case report and contact investigation. **Case Reports:** Pharyngeal swabs and questionnaires were administered to contacts of the index case and the HCW to screen for GAS colonization or disease. GAS isolates were compared using pulsed-field gel electrophoresis (PFGE) and sequencing of the M protein gene (*emm*) typing. The index patient was a 34-year-old homeless alcoholic woman who presented with weakness, vomiting, arthralgias, and severe leg, hip, and back pain 1 week after a fall. She was febrile and hypotensive and had an ecchymotic, tender left thigh without crepitus or bullae. She received ceftriaxone and clindamycin as empiric therapy while awaiting surgical evaluation. She subsequently underwent hip disarticulation for massive thigh myonecrosis. GAS was grown from blood and surgical cultures. Contact precautions were instituted within the first 24 hours of admission. Additional debridements, followed later by grafting and flap procedures, were needed. A HCW presented to the emergency center 6 days later and was found to have GAS pneumonia with respiratory failure and required prolonged ventilatory support. An outbreak investigation was initiated. The HCW, who worked as a respiratory therapist, first had contact with the index patient approximately 51 hours after admission of the index patient and also on the following day. A total of 705 HCWs with direct contact with either the index patient or the affected HCW were screened for GAS by pharyngeal culture. Fourteen were positive, 4 of who were symptomatic. Seven family members of the 14 HCWs were also GAS culture-positive. All persons were treated with penicillin or azithromycin. The index patient and affected HCW had identical GAS isolates by PFGE and M protein gene typing; none of the other GAS isolates were identical to the initial 2 isolates.

**Conclusions:** There appeared to be GAS transmission between the index patient and the affected HCW, and this may have occurred after >48 hours of antibiotic therapy. The appropriate duration of contact and droplet precautions for invasive GAS infection may need re-evaluation.

**Reviewer’s Comments:** Current Centers for Disease Control and Prevention/Healthcare Infection Control Practices Advisory Committee guidelines call for contact and droplet precautions for severe disease until 24 hours after appropriate antibiotic therapy is initiated. This case report suggests that transmission may still occur >48 hours after initiation of ceftriaxone. Other reports have shown the potential for droplet transmission of GAS. Appropriate isolation precautions for serious GAS disease should include droplet precautions, as recommended by current guidelines.
For patients with bacteremic CAP who were producing sputum, sputum Gram stain had high sensitivity, specificity, positive predictive value, and negative predictive value for identification of the etiologic agent.

**Background:** The utility of sputum Gram stain in determining the etiology of bacterial pneumonia is controversial.

**Objective:** To determine the accuracy and utility of sputum Gram stain in diagnosing the etiology of bacteremic community-acquired pneumonia (CAP).

**Participants/Methods:** A prospective study of all patients with a diagnosis of CAP at 2 hospitals in Greece was undertaken between January 2002 and June 2008. To be included in the study, patients had to meet the CAP clinical criteria, have had no antimicrobial therapy in the past 2 weeks, lack evidence for infection outside of the pulmonary system, and have the same organism isolated from blood and sputum cultures. Sputum was collected upon admission, and Gram stain was performed and read by 2 experts who were blinded to the blood and sputum culture results. Gram stain was interpreted as follows: Gram-positive diplococci indicated Pneumococcal pneumonia, Gram-positive cocci in clusters indicated staphylococcal pneumonia, and Gram-negative coccobacilli suggested *Haemophilus influenzae* pneumonia.

**Results:** Of the 1390 patients with CAP, 178 were producing quality sputum and had the same microorganism isolated from sputum and blood culture. Of these selected patients, 52% had pneumococcal pneumonia, 14% had staphylococcal pneumonia, 16% had *H. influenzae* pneumonia, and 18% had Gram-negative bacilli pneumonia. The Gram stain sensitivity was 0.82 for pneumococcal pneumonia, 0.76 for staphylococcal pneumonia, 0.79 for *H. influenzae* pneumonia, and 0.78 for Gram-negative bacilli pneumonia. The Gram stain specificity was 0.93 for pneumococcal pneumonia, 0.96 for staphylococcal pneumonia, 0.96 for *H. influenzae* pneumonia, and 0.95 for Gram-negative bacilli pneumonia. The positive predictive value was highest for pneumococcal pneumonia, whereas the negative predictive value was highest for nonpneumococcal pneumonia etiologies.

**Conclusions:** For patients with bacteremic CAP who were producing sputum, sputum Gram stain had high sensitivity, specificity, positive predictive value, and negative predictive value for identification of the etiologic agent.

**Reviewer’s Comments:** The use of Gram stain to assist with the diagnosis and management of CAP has its adherents and detractors. This study, which provides data in support of using sputum Gram stains in patients with CAP, has several strengths. It was done in a prospective fashion with active efforts to obtain high-quality sputum; the Gram stain was done by 2 persons blinded to additional results, and it included data from 4 major distinct causes of pneumonia rather than focusing of pneumococcal disease alone. Its major disadvantage is that it studied a highly selected portion (approximately 15%) of patients with CAP meaning that these data cannot be generalized to all CAP patients. Nevertheless, these data demonstrate that, when bacteremic patients with CAP are producing good quality sputum, Gram stain of the sputum could assist with the early identification of the etiologic agent.

**Additional Keywords:** None

**Print Tag:** Refer to original journal article
A monoclonal antibody against anthrax protective antigen ameliorates experimental inhalational anthrax in rabbits and monkeys.

**Background:** Inhalation anthrax causes high mortality primarily as a result of injury due to toxins produced by *Bacillus anthracis*. Antitoxin-specific pharmaceuticals may improve the outcome of disease due to *B. anthracis*.

**Objective:** To determine the effectiveness of raxibacumab, a human IgG1 lambda monoclonal antibody directed against *B. anthracis* protective antigen, in animal models of *B. anthracis* disease as well as the safety of raxibacumab in healthy humans.

**Methods:** The efficacy of raxibacumab as a prophylactic and therapeutic agent was determined in rabbits and monkeys challenged with 100 times (prophylactic evaluation) and 200 times (therapeutic evaluation) the lethal dose of aerosolized *B. anthracis*. In the therapeutic intervention, animals were monitored for a significant increase in temperature or the presence of protective antigen in their serum; if detected, the animals then received either placebo or raxibacumab at 20 mg/kg or 40 mg/kg. The primary end point was survival at day 14 (rabbits) or day 28 (monkeys). Safety studies were done by infusing 40 mg/kg of raxibacumab in healthy humans.

**Results:** The administration of raxibacumab as prophylaxis increased survival in both rabbits and monkeys, from 70% to 90% among treated animals depending on dose versus 0% in animals that received placebo. The administration of raxibacumab therapeutically increased rabbit survival from 0% in the placebo group to 28% in the 20-mg/kg group and 44% in the 40-mg/kg group. A similar increase in survival was observed in monkeys treated in a therapeutic fashion with survival rates of 50% in the 20-mg/kg group and 64% in the 40-mg/kg group compared to 0% in the placebo group. The administration of raxibacumab at 40 mg/kg to healthy humans did not result in a significant difference in adverse events compared to persons who received a placebo infusion.

**Conclusions:** The administration of a monoclonal antibody directed at *B. anthracis* protective antigen significantly increased survival in rabbits and monkeys challenged with *B. anthracis* in a preventive and therapeutic fashion.

**Reviewer's Comments:** The events of 2001 clearly demonstrate that new treatments for inhalation anthrax are needed as mortality remains high even after treatment with antimicrobials. Given that most, if not all, of the clinical manifestations of anthrax are the result of toxin-mediated disease, anthrax may be particularly amenable to a targeted antibody strategy as outlined in this manuscript. I was particularly impressed by the ability of raxibacumab to cure established anthrax disease, as we often see data regarding the efficacy of preventive measures, which have little clinical applicability. The fact that human challenge with anthrax is unethical means these data may result in the use of raxibacumab along with antibiotics in future cases of inhalation anthrax.

Additional Keywords: None

Print Tag: Refer to original journal article
Periurethral colonization of *E. coli* peaks 2 to 3 days before rUTI.

**Background:** Recurrent urinary tract infections (rUTI) due to *Escherichia coli* cause significant morbidity and health-care resource utilization. The pathophysiology of *E. coli* rUTI remains poorly understood.

**Objective:** To characterize the temporal sequence of bacterial presence and host inflammatory events immediately preceding *E. coli* rUTI.

**Participants/Methods:** Women (age range, 18 to 49 years) diagnosed with acute cystitis and who had a history of UTI within the past year, self-collected daily periurethral and urine samples. Patients were taught to perform daily leukocyte esterase testing of the urine and to record urinary symptoms and episodes of sexual intercourse. Cytokines were measured on urine specimens. *E. coli* rUTI was defined as the presentation of the subject to the clinic for symptoms of acute cystitis along with an *E. coli* concentration in the urine of ≥1 x 10^2 CFU/mL.

**Results:** 104 women were enrolled in the cohort, with 85% of the enrollment UTIs being caused by *E. coli*. Among the 104 women, 36 subjects had a total of 49 rUTIs with 38 episodes being due to *E. coli*; 67% of the *E. coli* rUTIs were caused by the same *E. coli* strain as the initial infection as determined by pulsed-field gel electrophoresis (PFGE). The periurethral prevalence of the rUTI *E. coli* strain increased from 46% 14 days before the rUTI to 90% 1 day before the rUTI. The presence of bacteruria was 7% 14 days before the rUTI and increased to 70% 1 day before rUTI. The presence of detectable urine leukocyte esterase was 31% 14 days before rUTI and increased significantly to 64% the day before the rUTI. Eleven women had the combination of *E. coli* bacteruria along with urinary symptoms in the 2 to 3 days prior to presenting to the clinic (so-called preclinical UTI). Strains of *E. coli* from patients with preclinical UTI were less likely to have known *E. coli* virulence determinants such as P fimbriae. The peak prevalence of periurethral carriage of *E. coli* and sexual intercourse occurred 3 days before rUTI. Urinary cytokines (IL-6 and IL-8) rose significantly on the day of rUTI.

**Conclusions:** The prevalence of periurethral *E. coli*, bacteruria, pyuria, and sexual intercourse increased dramatically in the days immediately preceding an *E. coli* rUTI.

**Reviewer’s Comments:** Understanding the clinical and microbiological events leading to recurrent infections, such as rUTI, is critically important to designing rational prevention strategies. This well-done, prospective, cohort study clearly shows that the prevalence of *E. coli* and host inflammation are dramatically increased in the days immediately preceding a recurrent *E. coli* UTI. Sexual intercourse in the setting of periurethral *E. coli* colonization appears to be the most important trigger for rUTI among young women. This constellation of findings suggests that a pre-emptive antimicrobial strategy could be designed in patients at high risk of rUTI.

Additional Keywords: None

Print Tag: Refer to original journal article
Asymptomatic Bacteriuria Occurs Frequently in Diabetic Women

Long-Term Escherichia coli Asymptomatic Bacteriuria Among Women With Diabetes Mellitus.


Treatment of asymptomatic bacteriuria in diabetic women does not reduce long-term infections with these nondisease causing strains.

**Background:** Urinary tract infections are seen frequently in women with diabetes. In addition, asymptomatic bacteriuria (ASB) also occurs more frequently in diabetic women. *Escherichia coli* is the most common infecting organism. It is unclear if the persistent *E. coli* in diabetic women with ASB is from the same strain and whether therapy eradicates the organism.

**Objective:** To determine whether the persistent *E. coli* ASB in diabetic patients is caused by the same *E. coli* strain and what the effect of treatment is in patients who genetically carry similar versus different *E. coli* strains.

**Participants/Methods:** 70 women who had at least 2 consecutive urine samples over a 2-week period were randomized to receive a trial of antimicrobial agents or no antimicrobial treatment unless they developed a symptomatic infection. Women were followed for 36 months. *E. coli* isolates were typed as well as analyzed for particular virulence factors.

**Results:** There were 517 total *E. coli* isolates. Seventeen percent of the women had bladder neuropathy and 16% had undergone previous genitourinary surgery. The women had ASB during 36% of the follow-up time, with a mean duration of 2.6 months. They carried a single unique strain for an average of 2.8 months. Approximately 25% of women who had follow-up for >6 months remained continuously colonized with a single strain for at least 6 months. Of the 34 women, 22 in the no-treatment group had a symptomatic UTI at least once during the follow-up. Sixty-four percent of the women who received treatment for ASB had recurrent *E. coli* bacteriuria with a new strain.

**Reviewer's Comments:** This study illustrates a few interesting points about diabetic women with ASB. First, untreated diabetic women can carry the same strain of *E. coli* for a long period of time. These strains do not possess many of the virulence factors that disease-causing strains have. Second, if you treat these women with antibiotics, a new strain will eventually take the old one's place. Therefore, the repeated use of antibiotics does not reduce the amount of ASB over the long term in diabetic women, and treatment should be focused on those who present with symptomatic disease.

Additional Keywords: None

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The onset of symptoms occurs more quickly when Gram-negative pathogens cause PJIs compared to Gram-positive pathogens.

Background: Prosthetic joint infections (PJIs) occur in approximately 1% to 2% of all patients at most medical centers. Most PJIs are caused by Gram-positive pathogens, but Gram-negative pathogens are also found in a significant number of cases, and they can be difficult to treat. Risk factors and outcomes in patients with PJIs caused by Gram-negative pathogens are not as well studied.

Objective: According to the authors, their objective was, "...to evaluate the demographic characteristics and outcomes of patients treated for Gram-negative (GN) PJI and to identify prognostic factors that would lead to treatment failure."

Design: Retrospective case cohort study.

Participants/Methods: Patients diagnosed with PJI in the hip or knee from January 2000 through December 2006 were included in the study. A GN PJI was defined as the presence of at least 1 GN pathogen at the infected site regardless of the total number of different strains present.

Results: There were 53 first-time episodes of GN PJI in 50 patients, which accounted for 15% of all the first-time episodes of culture-positive PJI. The most commonly isolated organism was Pseudomonas aeruginosa, with 21 episodes, followed by Escherichia coli with 10 episodes. Only 27% of patients with debridement had a 2-year survival free of treatment failure. This compared to 87% who had a 2-stage exchange arthroplasty and 69% in those who had resection arthroplasty. Out of 27 patients treated with debridement and retention, treatment failure was seen in 74%. The only risk factor that was found for those who failed treatment was a longer duration of symptoms before the treatment (11 days vs 5 days).

Conclusions: Gram-negative pathogens cause a significant number of PJIs. Debridement and retention of the prosthesis is successful only in a small percentage of patients and should be used only in those who have had symptoms of short duration.

Reviewer's Comments: This study was a nice reminder that Gram-negative pathogens are not an infrequent cause of PJIs. The major points that the clinician should be aware of are the fact that debridement with retention of the prosthesis (even with prolonged antibiotics) did not lead to treatment success in the majority of patients. For the approximately 25% of patients who did respond to this approach, they had surgery within days of the patient's onset of symptoms. The authors propose using this treatment approach only in these patients. The increased virulence and antibiotic resistance seen in Gram-negative pathogens makes treating these patients challenging.
For patients with latent tuberculosis infection, a 4-month course of rifampin is associated with a better completion rate than a 9-month course of isoniazid.

**Background:** The number of annual active tuberculosis (TB) cases in the United States continues to decline. Lately, an increased emphasis has been placed on treating cases of latent TB infection (LTBI), because many cases of TB represent reactivation disease. Currently, the most widely used and preferred regimen to treat LTBI is a 9-month course of isoniazid. While this regimen is effective in preventing active TB, there is a relatively high treatment default rate; nonadherence is reported in 24% to 47% of patients. One alternative treatment regimen is a 4-month course of rifampin. Few previous studies have compared the completion rates of the 2 regimens. In a large recently conducted, randomized trial, the completion rates of the rifampin regimen were significantly higher, and the rate of severe adverse events was lower.

**Objective:** To evaluate the completion rates, adverse events, and clinical charges for patients receiving rifampin or isoniazid for the treatment of LTBI.

**Design:** This was a retrospective chart review of clinical data of adult patients who were started on LTBI treatment at a public health clinic in Worcester, Massachusetts, between 2003 and 2007. The calculated cost of therapy included laboratory assays for liver enzyme monitoring, doctor visits, radiographs, and medications.

**Methods:** The investigators reviewed the medical records of 639 patients who were prescribed isoniazid and 138 patients who were prescribed rifampin. The choice of regimen was at the discretion of the provider.

**Results:** Patients who were prescribed rifampin had a significantly better completion rate than those receiving isoniazid (90% vs 65%). Also, the patients who were prescribed rifampin had a better completion rate than those who completed at least 4 months or 6 months of isoniazid. Patients prescribed isoniazid were more likely to develop neuropathy and have symptomatic elevations of ALT than patients receiving rifampin. The hepatotoxicity was reversible in all 15 patients who experienced it (14 patients in the isoniazid group and 1 patient in the rifampin group). The calculated cost of a full course of rifampin was higher than that of isoniazid.

**Conclusions:** A 4-month course of rifampin for the treatment of LTBI is associated with a higher completion rate and less hepatotoxicity than a 9-month course of isoniazid, albeit at a higher cost.

**Reviewer's Comments:** This U.S.-based, retrospective study confirms the findings from a multinational, prospective, randomized study. A 4-month regimen of rifampin is less hepatotoxic and is more likely to be associated with treatment completion than isoniazid. The cost projections in this study do not include the cost of treatment-active TB cases that would be prevented by completion of the rifampin regimen. However, such a cost projection would require knowing the efficacy and effectiveness of these 2 regimens, which is not known at this point.

Additional Keywords: None

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Disseminated Coccidioidomycosis Presents in Many Ways

The Spectrum and Presentation of Disseminated Coccidioidomycosis.
Adam RD, Elliott SP, Taljanovic MS; Am J Med 2009; 122 (August): 770-777

Appropriate specimens for culture and histology have better sensitivity than serological studies for diagnosing disseminated coccidioidomycosis in both immunocompetent and immunocompromised patients.

**Objective:** To review the clinical experience at one institution with patients who have disseminated coccidioidomycosis.

**Participants:** 150 patients with extrapulmonary nonmeningeal disseminated coccidioidomycosis seen at the University Medical Center (UMC) at the University of Arizona College of Medicine from 1996 to 2007.

**Methods:** All cases of disseminated coccidioidomycosis seen at the UMC or one of its affiliate clinics from 1996 to 2007 were retrospectively reviewed. Patients were included if they had evidence of extrathoracic infection or if there was diffuse nodular pulmonary disease because this was thought to represent hematogenous dissemination. Patients who had central nervous system (CNS) infection were included only if other sites were involved.

**Results:** 207 patients with disseminated coccidioidomycosis were identified, but 57 were excluded because their only manifestation of disseminated disease was CNS infection. There were 136 patients with extrathoracic infection and 14 patients who had both CNS infection and extrathoracic infection. The most frequent manifestation of disseminated coccidioidomycosis was hematogenous disease, in 41 patients. This type of presentation was frequently quite fulminate, associated with rapid death. Twenty-eight patients had axial skeletal involvement, frequently associated with substantial morbidity requiring multiple surgical debridements. African-American males were especially prone to this manifestation. Twenty-six patients had peripheral skeletal disease; more than one-half of these had joint involvement, usually with adjacent osteomyelitis. Fourteen patients had soft-tissue infection usually involving muscle or lymph nodes in the upper part of the body. Thirteen patients had skin involvement, and 7 had various visceral organs affected. Corticosteroid therapy was a risk factor for disseminated disease in 45% of patients. Males accounted for two-thirds of cases. As was true in previous reports, African-American males were 11 times more likely to have disseminated disease. When appropriate specimens were obtained, the diagnostic yields of histology and culture were high (88% and 93%, respectively). Serological studies were less sensitive in immunocompromised patients (61%) but had good sensitivity in immunocompetent patients (88%). Sixteen percent of patients died, most commonly those with hematogenous dissemination.

**Conclusions:** Disseminated coccidioidomycosis can present with a myriad of manifestations, involving multiple organs. A high index of suspicion must be maintained in patients from endemic regions. Appropriate serology, histology, and cultures are usually adequate for diagnosis.

**Reviewer's Comments:** This is a nice review of the clinical manifestations of disseminated coccidioidomycosis from a center in one of the major endemic regions. As the authors emphasize, given the substantial morbidity and mortality of this infection, a high index of suspicion must be maintained in immunocompromised individuals who have traveled to or lived in endemic regions. Appropriate laboratory studies (including culture, histology, and serology) need to be obtained.

Additional Keywords: None

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Corticosteroids may be beneficial in patients with *Cryptococcus gattii* CNS infection who have persistent mental status abnormalities along with focal lesions on brain scans in spite of having received adequate antifungal therapy.

**Objective:** To describe the results of dexamethasone treatment of 4 patients with *Cryptococcus gattii* central nervous system (CNS) infection who had persistent mental status changes in spite of adequate antifungal therapy and control of intracranial pressure.

**Participants:** 4 patients with complicated CNS disease from a group of 17 patients with *C. gattii* infection.

**Methods:** The charts of all patients with *C. gattii* infection who were treated with systemic corticosteroids at 3 hospitals in the greater Vancouver area were retrospectively reviewed. Four patients were identified who had CNS involvement, but these patients also had persistent or worsening mental status abnormalities after receiving adequate antifungal therapy and mechanical control of increased intracranial pressure.

**Results:** Between January 1, 2004, and December 31, 2007, 17 patients were identified with culture-proven *C. gattii* infection. Eleven of these patients had CNS infection, and 6 were administered corticosteroids; 2 received these steroids before a definitive diagnosis of *C. gattii* infection was made. Four patients were identified who had been treated with amphotericin B for periods of time (range, 26 to 56 days), and had been documented to have achieved negative cerebrospinal fluid cultures. Despite adequate antifungal therapy and control of increased intracranial pressure by lumbar drains or ventriculoperitoneal shunting in 2 patients, these 4 patients had persistent mental status changes. Furthermore, 3 of the 4 patients demonstrated new or worsening CNS lesions on brain imaging. Therapy with dexamethasone resulted in improvement of mental status changes, in most cases within just 1 to 2 days. These clinical changes were accompanied by radiographic improvement as well. No significant adverse events were noted.

**Conclusions:** In patients treated for *C. gattii* CNS infection who have persistent mental status changes accompanied by radiographic abnormalities, dexamethasone may provide effective adjunctive therapy.

**Reviewer's Comments:** *C. gattii* has a greater propensity to affect immunocompetent patients than does *C. neoformans*. Because most affected individuals have normal immunological function, antifungal therapy may result in a paradoxical clinical exacerbation akin to the immune reconstitution inflammatory syndrome seen in AIDS patients with opportunistic infections who are started on HAART. This paper provides anecdotal evidence that corticosteroid therapy may be beneficial in the subgroup of patients who appear to have that paradoxical exacerbation. The authors suggest that further studies should be performed to test this particular therapeutic strategy.

Additional Keywords: None

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Successful management of *Candida* endocarditis requires a combined approach using cidal antifungal agents (preferably echinocandins) and aggressive surgery.

**Objective:** To review information on the treatment and outcomes of *Candida* endocarditis.

**Participants:** 13 patients from the Italian Study on Endocarditis (SEI) national cohort who fulfilled the Duke criteria for possible or definite infective endocarditis due to a *Candida* species.

**Methods:** 18 centers in Italy actively participated in the SEI. Patients were prospectively enrolled in the study between January 2004 and December 2007 if they met the Duke criteria for possible or definite endocarditis and the responsible organism was a *Candida* species. Patient data were recorded onto a standardized case report form that included >200 pieces of data.

**Results:** Of a registry of 903 cases of infective endocarditis, 15 patients with *Candida* were identified. Intravascular devices were present in 86.6% of patients at the time of diagnosis. Of these 15 patients, 8 had prosthetic valve endocarditis, 5 had native valve endocarditis, 1 had a pacemaker wire infection, and 1 had infection of a ventricular patch. A history of admission to the ICU (73.3%) or open heart surgery within the last 12 months (60%) was common. *Candida albicans* and *C. parapsilosis* were the most frequent isolates, causing 5 cases each; *C. kruzei*, *C. tropicalis*, *C. glabrata*, and *C. famata* each caused 1 case. Eleven of the 15 patients had positive blood cultures; in the other 4 patients, the diagnoses were made by histological examination of tissues. Clinical features associated with *Candida* infective endocarditis that were significantly different than other conventional causative agents included the presence of larger vegetations (19.4 vs 14 mm), the presence of central lines (46.6% vs 9.8 %), and higher in-hospital mortality (46.6% vs 16.1%). Therapeutic modalities were quite variable; however, 10 patients were initially treated with caspofungin alone (7) or in combination with other drugs (3). Five patients had valve replacement, all of whom were discharged without signs of infective endocarditis. The 6 patients who did not have surgery all died. Three of 4 patients treated with medical therapy alone were cured, but these patients all had catheter- or pacemaker-related infections and received prolonged therapy.

**Conclusions:** *Candida* endocarditis usually affects individuals who have intravascular prosthetic devices. The diagnosis is frequently delayed, resulting in substantial morbidity and mortality. Successful therapy usually requires the use of cidal antifungal agents, most commonly caspofungin, along with surgery.

**Reviewer’s Comments:** The in-hospital mortality for *Candida* endocarditis approaches 50%; consequently, newer approaches to therapy need to be sought. In this study, most patients received caspofungin, a much safer and easier drug to administer than amphotericin B. In vitro studies support the use of echinocandins instead of amphotericin B.

Additional Keywords: None

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Infrequent HIV-1 RNA monitoring results in increased resistance in patients on NNRTI-based regimens.

**Background:** In resource-poor countries, there is often limited HIV-1 RNA monitoring. Since most regimens are nonnucleoside reverse transcriptase (NNRTI)-based regimens, there is great concern with accruing cross-class NNRTI mutations and multiple nucleoside reverse transcriptase inhibitor (NRTI) mutations if failure is gauged primarily by CD4 or clinical assessment rather than HIV-1 RNA testing. High-level resistance compromises second-line therapy (especially in resource-poor countries where options of antiretrovirals are limited) and increases the risk of transmitted resistance.

**Objective:** To assess resistance outcomes by differing viral monitoring frequencies.

**Methods:** The authors present a systematic review of studies reporting genotypic resistance in patients infected with HIV with a CD4 <200 treated with a World Health Organization recommended regimen of 2 NRTIs. NNRTI was performed to assess the effect of variable monitoring on the emergence of resistance after therapy.

**Results:** 8376 patients from 8 cohorts and 2 prospective trials were included and stratified into studies with frequent monitoring (more frequently than every 12 weeks), infrequent (less frequent than every 12 weeks), and no monitoring. The majority of cohorts used generic fixed-dose combinations of stavudine, lamivudine and nevirapine, or zidovudine, lamivudine, and efavirenz. At 48 weeks, evidence of NNRTI resistance was greater in the infrequently monitored and no monitoring groups than in the frequently monitored group (88% vs 61%; \(P < 0.001\)). Lamivudine resistance was similarly greater in infrequently monitored patients (81% vs 40%, \(P < 0.001\)). The prevalence of at least one thymidine analog mutation was also higher in infrequently monitored patients (28% vs 12%; \(P < 0.01\)).

**Conclusions:** Genotypic resistance at 48 weeks to NRTIs and NNRTIs is substantially higher in patients with less-frequent monitoring.

**Reviewer's Comments:** This is the largest analysis of resistance patterns after the rollout of NNRTI-based regimens in resource-poor settings. It provides evidence that resistance can be decreased with frequent monitoring. It also highlights the tremendous need for cheap point-of-care viral load tests that can be utilized in resource-poor countries to identify early failures.

Additional Keywords: None

Print Tag: Refer to original journal article
Herpes simplex virus is activated in the lower respiratory tract of critically ill patients.

**Background:** Published reports have demonstrated the presence of herpes simplex virus (HSV) in the upper airways of ICU patients. Lower respiratory tract HSV infections are thought to occur by either aspiration of virus from the upper airways or by reactivation of the virus in the trachea or lungs. Recently, longer ICU stays and increased mortality have been reported in patients with HSV detected in the upper airways compared with HSV DNA-negative patients. The role of HSV in the lower airways is unclear in its association with increased morbidity or mortality. In order to define the role of HSV in the lower respiratory tract, a better quantitative diagnostic test would be helpful.

**Objective:** To prospectively evaluate a quantitative real-time PCR assay in lower respiratory tract specimens obtained from ICU patients.

**Methods:** Adults admitted to the ICU of a Belgian hospital from August 2006 to June 2007 were prospectively evaluated for HSV infection. All patients were mechanically ventilated and were not immunosuppressed. Ventilator-associated pneumonia was diagnosed using published American Thoracic Society criteria. Tracheal aspirates or undiluted bronchial aspirates were obtained on day 3 of intubation and then twice a week until extubation. A quantitative PCR assay detected HSV DNA from samples processed daily. The lower limit of detection was 100 copies/mL.

**Results:** 105 nonimmunosuppressed mechanically ventilated, ICU patients were included in the study. HSV DNA was detected in 62% of patients; 74% of these HSV-positive patients were intubated for >10 days. Nineteen of 40 HSV DNA-negative patients died during HSV monitoring. Factors associated with HSV DNA detection in the lower respiratory tract were steroid use and HSV IgG antibody detected at the start of the monitoring. HSV DNA-positive patients had significantly longer lengths of hospitalization than did HSV DNA negative patients. Hospital-associated deaths were not significantly different between the HSV DNA-positive patients and HSV DNA-negative patients. HSV DNA was usually detectable by day 7 after intubation. An increase in HSV viral load of >1 log copies/mL occurred approximately 12 days after intubation.

**Conclusions:** Quantitative PCR was found to be reliable and rapid in detecting HSV in the lower respiratory tract samples. HSV DNA was detected in the lower respiratory tract in 62% of mechanically ventilated patients. Finding HSV DNA in the lower respiratory tract was associated with longer ventilation needs and longer ICU stays.

**Reviewer's Comments:** The authors conclude that reactivation of HSV is probably responsible for their findings. However, the size of the control group and the loss of 40 patients who never completed the study point out the weakness in extending these preliminary observations. Nevertheless, if larger prospective studies confirm these results, a trial of antivirals versus placebo would definitely be warranted.

Additional Keywords: None

Print Tag: Refer to original journal article
New species of *Nocardia* have been identified, and the most common underlying condition for nocardiosis is now HIV infection.

**Background:** *Nocardia* infections occur in both immunosuppressed and immunocompetent patients. The spectrum of infections has undergone changes because of the increased employment of trimethoprim-sulfamethoxazole (TMP/SMX) prophylaxis, the defining of new categories of immunosuppressed patients, and the use of molecular techniques to identify isolates. *Nocardia asteroides* was considered to be the predominant organism, and TMP/SMX prophylaxis was thought to be consistently protective against this organism.

**Objective:** To describe the incidence of nocardiosis in a general hospital.

**Methods:** The records of patients with *Nocardia* isolates in a general, tertiary, referral hospital were reviewed from 1995 to 2006. Forty-three adult patients had one or more positive clinical specimens. All isolates were identified by both phenotyping and genotyping. Susceptibility testing used a broth microdilution method. Clinical data were reviewed after discharge or death. A MEDLINE search of the literature from 1966 to 2008 used the key words "*Nocardia*" and "nocardiosis" in both English and Spanish to retrieve published series.

**Results:** No increase was found in the incidence of *Nocardia* infections during the study periods 1995-1998 and 2003-2006. Of the 43 patients with *Nocardia*-positive cultures, 6 were considered to be colonized. Invasive nocardiosis was identified in 37 patients with a mean age of approximately 56 years. HIV infection was the most common underlying condition. The other major underlying conditions included chronic obstructive pulmonary disease, autoimmune disease, solid organ transplantation, and cancer. More than 60% of infected patients were on corticosteroids. The most common site of involvement was the lung (70%). Only 2 cases involved the central nervous system. Using molecular techniques, new species were identified. Species identified were *N. cyriacigeorgica*, *N. farcinica*, and *N. otitidiscaviarum*. All isolates were sensitive to linezolid and amikacin, but 30% were intermediately susceptible to minocycline; 10% were resistant to TMP/SMX. Attributable mortality to *Nocardia* infection was 21.6%.

**Conclusions:** The most common underlying condition for nocardiosis is now HIV infection. The main risk factor appears to be previous steroid use. Administration of TMP/SMX prophylaxis appears to be less reliable than previously reported.

**Reviewer’s Comments:** This is a good update on an uncommon but serious infection. Although HIV-infected patients are now the number 1 target, the overall incidence of nocardiosis did not appear to change at the beginning of the 21st century. Most importantly, TMP/SMX did not guarantee absolute protection against *Nocardia* infection. The authors have a clear discussion of the new species classification such that *Nocardia* asteroides complex is now considered to be composed of several different species. There is a brief discussion of treatment options, which do not differ significantly from current recommendations. Finally, there is a review of previously published series summarized in one complete table. For these reasons, this series is worth reviewing in more detail in order to be up on this serious but uncommon infection.