

An examination of healthcare-associated infections in elderly patients

Serap İSKENDER¹, Gürdal YILMAZ^{2*}, İftihar KÖKSAL²

¹Department of Infectious Diseases and Clinical Microbiology, Kanuni Training and Research Hospital, Trabzon, Turkey

²Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey

Received: 14.06.2017 • Accepted/Published Online: 09.10.2017 • Final Version: 19.12.2017

Background/aim: Healthcare-associated infections (HCAIs) are increasing due to the growing numbers of elderly people requiring long-term care and immunosuppressive therapies. The purpose of this study was to examine HCAIs occurring in elderly inpatients in our hospital.

Materials and methods: This study prospectively investigated HCAIs developing in all patients hospitalized over a 1-year period. Diagnosis was based on Centers for Disease Control criteria. The results were subjected to statistical analysis between patients aged over and under 65.

Results: A total of 24,692 patients were evaluated and 894 HCAIs were identified. Of these infections, 214 were seen in patients aged 65 or over. The rate of HCAIs in elderly patients was 15.1, compared to 2.9 in the under-65 patient group ($P < 0.001$). Seventy-nine (36.9%) infections in elderly patients were urinary system infections, 60 (28.0%) were bacteremia, 43 (20.1%) were pneumonia, 29 (13.6%) were surgical site infections, and 3 (1.4%) were other infections. Forty-three of the 187 elderly patients followed with a diagnosis of HCAI died. Seventeen patients had mortality attributable to HCAI.

Conclusion: Awareness that HCAIs seen in the elderly have different clinical and microbiological characteristics than those of other patients, and the appropriate precautions being taken, will reduce the problems that may result from these diseases with high mortality and morbidity.

Key words: Elderly patients, healthcare-associated infections, infection control

1. Introduction

Aging is a continuous and universal process seen in all organisms. It causes a decrease in all functions and describes the entirety of gradual irreversible structural and functional changes at all levels. Age 65 years or over is regarded as old age, and the number and proportion of elderly people is continually rising in Turkey and worldwide as death and birth rates decrease (1). The prevalence of healthcare-associated infections (HCAIs) in the elderly is growing due to increases in the number of elderly people requiring long-term care and immunosuppressive therapies (2,3). Infections, and particularly HCAIs, are the most important cause of morbidity and mortality in the elderly population. The majority of studies of HCAIs in the elderly have involved patients living in long-term care homes, but the amount of information concerning these infection types, risk factors, and incidences in elderly people in hospitals is negligible (2,3). This study was planned in order to rectify this deficiency and examine the HCAIs seen in elderly patients.

2. Materials and methods

HCAIs developing in all patients hospitalized at the Karadeniz Technical University Medical Faculty Farabi Hospital over a 1-year period were investigated prospectively. The study was approved by the Medical Ethics Board of the Medical Faculty (ethical approval no. 30032006-06-02). Infections acquired in the hospital, which were not in the incubation stage and with no signs or symptoms of infection at the time of admission to the hospital, were regarded as HCAIs. Infection as a complication or extension of an existing infectious event during hospitalization was not regarded as HCAI. Diagnosis of HCAIs was based on Centers for Disease Control criteria (4). HCAIs were investigated by physicians from the Infectious Diseases Department and Infection Control Committee nurses using active surveillance in the entire hospital and were recorded onto prepared monitoring forms. Patients were divided into two groups, above and below 65 years of age.

* Correspondence: gurdalyilmaz53@hotmail.com

Rates of HCAI were calculated using the following formula: Rate of HCAs = (number of HCAs / number of patient days × 1000).

2.1. Statistical analysis

Statistical analysis was performed using the chi-square test. Statistical significance was set at P < 0.05. In the comparison of HCAI rates, the chi-square (χ^2) value was calculated using the formula $\chi^2 = (O - E)^2 / V$, and the P-value was determined from the chi-square table (5).

3. Results

During the study period, 24,692 patients were admitted and monitored for 252,327 days; 1430 (5.8%) of these patients were aged 65 or over. These patients were admitted and monitored for 14,214 days. The mean age of the patients aged 65 or over was 72.8, ranging between 65 and 95. The mean age of the patients aged under 65 was 45.3 years, ranging between 18 and 64. The demographic characteristics of the patients aged over 65 are shown in Table 1.

Eight hundred ninety-four HCAs were observed in our study, and the HCAI rate was calculated at 3.5. Of these infections, 214 were observed in patients aged over 65 and 680 in patients under 65. One attack was observed in 167 patients, two attacks in 14, three attacks in five, and four attacks in one. The rate of HCAs among elderly patients was 15.1, compared to a rate of 2.9 in the patients aged under 65. The difference in HCAI rates between the two groups was statistically significant (P < 0.001). Of the HCAs in the elderly patients, 36.9% were urinary system infections (USIs), 28.0% were bloodstream infections

(BSIs), 20.1% were pneumonia, 13.6% were surgical site infection (SSIs), and 1.4% were other infections. Rates were 5.6 for USIs, 4.2 for BSIs, 3.0 for pneumonia, and 2.0 for SSIs. Comparisons of patients aged over and under 65 in terms of types of HCAI are shown in Table 2.

Gram negative microorganisms were frequently the agents involved in HCAs, the most common agent being *Escherichia coli*, followed by *Enterococcus* spp., *Staphylococcus aureus*, and *Acinetobacter baumannii* (Table 3). Presence of extended spectrum beta-lactamases (ESBLs) was determined in 36.1% of *E. coli* strains and 21.4% of *Klebsiella* strains. Methicillin resistance was present in 50% of *S. aureus* strains. Vancomycin resistance was determined in two *Enterococcus* strains. Carbapenem resistance was present in 55.6% of *A. baumannii* strains, and all strains were susceptible to colistin. All *Pseudomonas aeruginosa* strains were susceptible to carbapenem.

Gram positive microorganisms were isolated in 32 BSIs and gram-negative microorganisms in 27, while *Candida* growth was determined in four. Only 18 BSIs were catheter-associated. The most common agent in USIs was *E. coli* (59.5%). Secondary bacteremia was observed in 13.9% of the 79 attacks monitored with a diagnosis of USI. Urinary catheter use was present in 96.2% of these infections. Nephrostomy catheter was also present in six patients. No microorganism agent could be determined in 72% of cases of pneumonia. The most common agent determined in 12 attacks was *A. baumannii*. Secondary bacteremia was observed in 16.6% of these infections. Mechanical ventilation was present in 25.6% of the patients diagnosed with pneumonia, and these patients

Table 1. The demographic characteristics of the patients aged over 65.

| Characteristics | Mean ± SD / no. (%) |
|----------------------------------|---------------------|
| Age | 72.8 (65–95) |
| Sex | |
| Male | 97 (51.9) |
| Female | 90 (48.1) |
| Mean days to development of HCAI | 15.3 ± 15.8 |
| Clinic | |
| Internal diseases clinics | 129 (60.3) |
| Surgical clinics | 66 (30.8) |
| Intensive care unit | 19 (8.9) |
| Comorbid disease | |
| Malignancy | 52 (27.8) |
| Hypertension | 48 (25.7) |
| Renal failure | 44 (23.5) |
| Diabetes mellitus | 33 (17.6) |
| Mortality | 43 (22.9) |

Table 2. A comparison of HCAI rates in patients aged over and under 65.

| HCAI type | Aged under 65 | | Aged over 65 | | P |
|--------------------------|---------------|-----------|--------------|-----------|--------|
| | HCAI (no.) | HCAI rate | HCAI (no.) | HCAI rate | |
| Bacteremia | 354 | 1.5 | 60 | 5.6 | <0.001 |
| Urinary system infection | 120 | 0.5 | 79 | 4.2 | <0.001 |
| Pneumonia | 77 | 0.3 | 43 | 3.0 | <0.001 |
| Surgical site infection | 79 | 0.3 | 29 | 2.0 | <0.001 |
| Other | 50 | 0.2 | 3 | 0.2 | 0.763 |
| Total HCAs | 680 | 2.9 | 214 | 15.1 | <0.001 |

Table 3. Distribution of HCAI agent microorganisms.

| Microorganism | Bacteremia | USI | Pneumonia | SSI | Other | Total |
|------------------------------------------|------------|-----|-----------|-----|-------|-------|
| Gram-positive | 32 | 11 | 3 | 7 | 2 | 65 |
| CNS | 8 | 0 | 1 | 0 | 2 | 11 |
| <i>S. aureus</i> | 13 | 0 | 2 | 3 | 0 | 18 |
| <i>Enterococcus</i> spp. | 9 | 11 | 0 | 4 | 0 | 24 |
| <i>S. pneumoniae</i> | 0 | 0 | 1 | 0 | 0 | 1 |
| Gram-negative | 27 | 66 | 11 | 27 | 1 | 132 |
| <i>E. coli</i> | 6 | 47 | 1 | 7 | 0 | 61 |
| <i>Acinetobacter baumannii</i> | 8 | 1 | 5 | 4 | 0 | 18 |
| <i>Klebsiella</i> spp. | 3 | 8 | 0 | 3 | 0 | 14 |
| <i>P. aeruginosa</i> | 3 | 3 | 3 | 6 | 1 | 16 |
| <i>Serratia marcescens</i> | 2 | 1 | 1 | 2 | 0 | 6 |
| <i>Enterobacter</i> spp. | 2 | 2 | 0 | 4 | 0 | 8 |
| Other | 3 | 4 | 1 | 1 | 0 | 9 |
| Candida | 4 | 4 | 0 | 0 | 0 | 8 |
| <i>C. albicans</i> | 1 | 4 | 0 | 0 | 0 | 5 |
| <i>Candida</i> spp. non- <i>albicans</i> | 3 | 0 | 0 | 0 | 0 | 3 |

were monitored with a diagnosis of ventilator-associated pneumonia. The most commonly identified agent in SSIs was *P. aeruginosa*. Secondary bacteremia was present in four of these infections.

Forty-three (22.9%) of the patients treated with a diagnosis of HCAI died. Mortality was attributed to HCAI in 17 (39.5%) cases.

4. Discussion

Recent advances in technology mean that it is now possible to survive for extended periods with diseases that were once fatal. HCAs affect patients' quality of life and perhaps even their survival. These infections are diseases that can be prevented and reduced (6). The first step in the prevention and control of HCAs is the acquisition of sufficient and reliable data. Appropriate strategies can

be developed if all centers are aware of their own patient profile and the distribution and prevalence of HCAs and if they receive feedback concerning these (7,8). Surveillance programs for HCAs, a dynamic process that changes over time, must be brought up to date in light of new infection risks (6,8). All potential causes are being investigated in detail in order to prevent and eliminate HCAs. HCAs developing in a number of special patient groups, such as newborns, intensive care patients, hematology patients, and the geriatric age group, are being examined in particular detail. Although many studies have considered HCAs developing in groups such as neonatal and intensive care patients, there are insufficient studies in the literature involving elderly patients.

The rate of HCAs determined in the elderly patients in our study, 15.1, is similar to the figure of 16.1 reported

by Beaujean et al. (2). Engelhart et al. determined a rate of HCAs of 6 in patients in care homes (9). Strausbaugh reported that this rate varied between 1.8 and 13.5 (10). We attribute the high HCAI rate in our study to various factors, such as primary disease in our patients being more severe than in other studies, prolonged hospitalization, and inadequate socioeconomic conditions.

HCAI rates in the elderly patient group in our study were significantly higher than among subjects aged under 65. The elderly may be highly susceptible to HCAs and community-acquired infections. Advanced age is a recognized risk factor for HCAI (2,3).

USIs represented 36.9% of all HCAs in elderly patients. The rate of USIs was 5.6. USI has been reported to be the most common HCAI, with the HCAI-USI rate ranging between 1.86 and 14.7 (11,12). The prevalence of USIs in our study may be due to the presence of urinary catheter in 96.2% of our patients. In addition to a high level of new bacteremia episodes being seen in long-term urinary catheterization, some microorganisms are able to colonize the urinary system, after which clinically significant USIs may develop (11,12). The level of urinary catheter use in our study was high, for reasons such as our patients being elderly and the presence of impaired consciousness and urological problems such as urinary incontinence and prostatism, together with comorbid diseases such as acute kidney failure. In agreement with previous studies, *E. coli* was the most common microorganism in HCAI-USIs in our study (11,12). The microorganisms causing HCAI-USIs derive either from the patient's fecal flora or from the hospital flora. Together with catheter use in elderly patients, the presence of fecal incontinence, constipation, and dementia also causes microorganism transmission. The markedly low levels of Tamm-Horsfall protein, which plays a protective role against *E. coli*-associated USI, in the elderly may also explain the incidence of USIs developing through this agent (13).

The rate of HCAI bacteremia in elderly patients was 4.22, with bacteremia constituting 28% of all HCAs. Advanced age is the most important host-related factor for HCAI bacteremia. Other risk factors include previously existing diseases, severity of underlying disease, and nutritional deficiency. Since the majority of these risk factors apply to the elderly, they are particularly disposed to the development of HCAI. An increase in invasive procedures and extended length of hospitalization also contribute to this (14).

Thirty-nine percent of gram-negative HCAI agents were microorganisms producing ESBL. ESBL production was present in 47.8% of *E. coli* strains and 42.8% of *K. pneumoniae* strains. ESBL levels vary significantly between different countries and regions, and even between hospitals. Studies have reported high levels of ESBL, such

as 67% in *E. coli* and 73.3% in *K. pneumoniae* (15). The level of ESBL in the *K. pneumoniae* strains in our study was compatible with that in the previous literature, while the level of ESBL in *E. coli* strains was higher than in the literature. The high ESBL levels may be attributed to all age groups being included in other studies, while only elderly patients were included in our study. The patients in our study therefore had greater risk factors for ESBL, such as frequent use of antibiotics such as cephalosporins and quinolones, frequent use of invasive equipment, and more comorbid diseases.

Gram positive microorganisms were the agent in 50% of bacteremia cases, gram-negative microorganisms in 40%, and *Candida* in 5%, while polymicrobial growth was determined in 5%. The most commonly isolated gram-positive microorganism was methicillin-resistant coagulase-negative staphylococci (13.3%), followed by methicillin-susceptible *S. aureus* (11.6%) and *E. faecalis* (11.6%). Methicillin-resistant *S. aureus* (MRSA) was determined as the agent in 8.3% of bacteremia cases. The most common agent among gram-negative microorganisms was *A. baumannii* (13.4%), followed by *E. coli* (10%). The most commonly observed microorganism in our study was also *S. aureus*, at 21.6%. Sucu et al. also identified *S. aureus* as the most common agent in a study evaluating bacteremia in our hospital (16). Crane et al. also identified *S. aureus* as the most common agent in their study of elderly patients (17). MRSA colonization is a significant problem in elderly patients. Simor et al. reported MRSA colonization together with an increased risk of staphylococcal infections in elderly hospitalized patients (18). Awareness of microorganism colonization in the body before the onset of infection will therefore be a useful guide in beginning empirical treatment. When the 18 catheter-associated bacteremia attacks were analyzed, the most common agent was identified as MRSA (27.8%), followed by *E. faecalis* (22.2%). In a previous study performed in our hospital evaluating total parenteral nutrition catheters, Yilmaz et al. identified coagulase-negative staphylococci as the most common agent, followed by *S. aureus*, *P. aeruginosa*, and *Acinetobacter* spp., with a level of 3.2% for *Enterococcus* spp. (19). The high MRSA and *E. faecalis* levels in our study may be explained by greater staphylococcal and enterococcal colonization due to the advanced age of our patients.

The third most prevalent HCAI in elderly patients was pneumonia, at a rate of 3.2. Pneumonia, the third most common HCAI in elderly patients after USI and bacteremia, was also the third most common HCAI in the hospital generally. Strausbaugh reported a HCAI respiratory tract infection rate of 0.3–4.7 in elderly patients (10). The incidence of HCAI pneumonia, which we calculated at 0.48 in the hospital in general, was

reported at 0.88 in the hospital in general by Abdel-Fattah (20). Engelhart et al. identified respiratory tract infections as the most common infection in care homes (9). HCAI pneumonia, which constituted 20.1% of all HCAIs in the elderly in our study, represented 10.3% of all infections in a study by Beaujean et al. and 20% in a study by Trivalle et al. (2,21). Numerous factors contribute to the development of HCAI pneumonia, including previously impaired respiratory defense mechanisms (chronic obstructive pulmonary disease), advanced age, presence of underlying disease and complications (such as renal failure, diabetes mellitus, and immune system suppression), invasive procedures, and corticosteroid use (2,20,21). The presence of these factors in the majority of the elderly patient group in our study may have contributed to the development of HCAI pneumonia. Gram-negative microorganisms were determined as the agent in 50% of patients, while gram-positive growth was determined in 25% and polymicrobial growth in 25%. *A. baumannii* was the most commonly observed microorganism at 41.6%, followed by *P. aeruginosa* (25%) and MRSA (16.6%). Blood culture positivity was determined in 4.65% of our patients, while Meehan et al. reported positivity in blood culture at a level of 7.1% in their study of pneumonia in elderly patients (22).

The fourth most common HCAI in our elderly patients was SSI, at a rate of 2.04. SSIs constitute 13.6% of all HCAIs in the elderly. SSIs were the fourth most common HCAI in elderly patients, after USI, bacteremia, and pneumonia, and also the fourth most common in the hospital in general. Kaye et al. reported that SSIs constituted 11% of all HCAIs (23). Gram-negative microorganisms were the agents in 72.4% of SSIs, gram-positive microorganisms in 10.3%, and polymicrobial agents in 17.2%. The most frequent agents were *E. coli*, *P. aeruginosa*, and *A. baumannii*. The most common agents among the gram-positive microorganisms were *E. faecalis* and MRSA. SSI agents vary considerably, depending on the type of operation, and transmission occurs from exogenous and/

or endogenous sources. As in other HCAIs, gram-negative microorganisms represent a problem in terms of SSIs in our hospital. This may be due to cross-contamination with inadequate personnel numbers and training, increased colonization with gram-negative microorganisms resulting from prolonged hospitalization, and poor hand hygiene. As the studies from various findings show, SSIs constitute an important group among HCAIs, and advanced age is a risk factor for such infection.

Health care-associated central nervous system infections are relatively rare in the HCAI category. However, since they are important causes of morbidity and mortality, they are some of the most severe HCAIs. The fifth most common HCAI that we observed in our elderly patients was central nervous system infection, at a rate of 0.21. Health care-associated central nervous system infections represented 1.4% of all HCAIs. Previous studies have reported that they constitute 0.4% of all HCAIs (24). These were the fifth most frequent infection in elderly patients after USI, bacteremia, pneumonia, and SSI. Similarly to our own findings, the most important risk for health care-associated central nervous system infections in previous studies was the presence of venous drainage.

The duration of healthcare-related infections in the study and the nutritional status of the patients were not assessed. It is important to know the nutritional status and hospitalization time of patients when evaluating infections in elderly patients. These shortcomings are a limiting aspect of the study.

In conclusion, HCAIs, and particularly those in the elderly, are an important problem. Awareness that HCAIs seen in the elderly may have different clinical and microbiological characteristics than those in other patients, and the taking of appropriate precautionary measures, will reduce problems that may be caused by these diseases, with their high mortality and morbidity. Every center should identify its own principal problems, identify its microorganism profile, and take appropriate precautions.

References

1. Giray H, Meseri R, Saatlı G, Yüceci N, Aydın P, Uçku R. Proposal for elderly health care system in Turkey. TAF Prev Med Bull 2008; 7: 81-86 (in Turkish with abstract in English).
2. Beaujean DJ, Blok HE, Vandenbroucke-Grauls CM, Weersink AJ, Raymakers JA, Verhoef J. Surveillance of nosocomial infections in geriatric patients. J Hosp Infect 1997; 36: 275-284.
3. Laurent M, Bastuji-Garin S, Plonquet A, Bories PN, Le Thuaut A, Audureau E, Lang PO, Nakib S, Liuu E, Canoui-Poitrine F et al. Interrelations of immunological parameters, nutrition, and healthcare-associated infections: prospective study in elderly in-patients. Clin Nutr 2015; 34: 79-85.
4. CDC/NHSN. Surveillance definition of healthcare-associated infection and criteria for specific types of infections in the acute care setting Am J Infect Control 2008; 36: 309-332.
5. dos Santos Silva I. World Health Organization International Agency for Research on Cancer, Cancer Epidemiology: Principles and Methods. Lyon, France: International Agency for Research on Cancer; 1999.
6. Arefian H, Vogel M, Kwetkat A, Hartmann M. Economic evaluation of interventions for prevention of hospital acquired infections: a systematic review. PLoS One 2016; 11 : e0146381.

7. Yilmaz G, Caylan R, Aydın K, Topbas M, Koksal I. Effect of education on the rate of and the understanding of risk factors for intravascular catheter-related infections. *Infect Control Hosp Epidemiol* 2007; 28: 689-694.
8. Ritchie L, McIntyre J. Standardising infection control precautions. *Nurs Times* 2015; 111: 17-20.
9. Engelhart ST, Hanes-Derendorf L, Exner M, Kramer MH. Prospective surveillance for healthcare-associated infections in German nursing home residents. *J Hosp Infect* 2005; 60: 46-50.
10. Strausbaugh LJ. Emerging health care-associated infections in the geriatric population. *Emerg Infect Dis* 2001; 7: 268-271.
11. Haber N, Paute J, Gouot A, Sevali Garcia J, Rouquet ML, Sahraoui L, Gamard MN, Jarlier V, Chaibi P, Cambau E. Incidence and clinical characteristics of symptomatic urinary infections in a geriatric hospital. *Med Mal Infect* 2007; 37: 664-672.
12. Vincitorio D, Barbadoro P, Pennacchietti L, Pellegrini I, David S, Ponzio E, Prospero E. Risk factors for catheter-associated urinary tract infection in Italian elderly. *Am J Infect Control* 2014; 42: 898-901.
13. Reinhart HH, Obedeau N, Robinson R, Korzeniowski O, Kaye D, Sobel JD. Urinary excretion of Tamm-Horsfall protein in elderly women. *J Urol* 1991; 146: 806-808.
14. Kaye KS, Marchaim D, Chen TY, Baures T, Anderson DJ, Choi Y, Sloane R, Schmader KE. Effect of nosocomial bloodstream infections on mortality, length of stay, and hospital costs in older adults. *J Am Geriatr Soc* 2014; 62: 306-311.
15. Chen YH, Hsueh PR, Badal RE, Hawser SP, Hoban DJ, Bouchillon SK, Ni Y, Paterson DL. Antimicrobial susceptibility profiles of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections in the Asia-Pacific region according to currently established susceptibility interpretive criteria. *J Infect* 2011; 62: 280-291.
16. Sucu N, Çaylan R, Aydın K, Yılmaz G, Aktoz Boz G, Köksal İ. Prospective Evaluation of Blood Cultures in Medical Faculty Hospital of Blacksea Technical University. *Mikrobiyol Bul* 2005; 39: 455-464 (in Turkish with abstract in English).
17. Crane SJ, Uslan DZ, Baddour LM. Bloodstream infections in a geriatric cohort: a population-based study. *Am J Med* 2007; 120: 1078-1083.
18. Simor AE, Ofner-Agostini M, Paton S, McGeer A, Loeb M, Bryce E, Mulvey M; Canadian Nosocomial Infection Surveillance Program. Clinical and epidemiologic features of methicillin-resistant *Staphylococcus aureus* in elderly hospitalized patients. *Infect Control Hosp Epidemiol* 2005; 26: 838-841.
19. Yilmaz G, Koksal I, Aydın K, Caylan R, Sucu N, Aksoy F. Risk factors of catheter-related bloodstream infections in parenteral nutrition catheterization. *JPEN-Parenter Enter* 2007; 31: 284-287.
20. Abdel-Fattah MM. Nosocomial pneumonia: risk factors, rates and trends. *East Mediterr Health J* 2008; 14: 546-555.
21. Trivalle C, Chassagne P, Bouaniche M, Landrin I, Marie I, Kadri N, Menard JF, Lemeland JF, Doucet J, Bercoff E. Nosocomial febrile illness in the elderly frequency, causes and risk factors. *Arch Intern Med* 1998; 158: 1560-1565.
22. Meehan TP, Chua-Reyes JM, Tate J, Prestwood KM, Scinto DJ, Petrillo MK, Metersky ML. Process of care performance, patient characteristics, and outcomes in elderly patients hospitalized with community-acquired or nursing home-acquired pneumonia. *Chest* 2000; 117: 1378-1385.
23. Kaye KS, Schmader KE, Sawyer R. Surgical site infection in the elderly population. *Clin Infect Dis* 2004; 39: 1835-1841.
24. Morris A, Low DE. Nosocomial bacterial meningitis, including central nervous system shunt infections. *Infect Dis Clin North Am* 1999; 13: 735-750.