Clinical Significance of Extraintestinal *Hafnia alvei* Isolates from 61 Patients and Review of the Literature

Huldrych Günthard and Andreas Pennekamp

From the Department of Internal Medicine, Stadtspital Triemli, and the Department of Medical Microbiology of the University of Zurich, Zurich, Switzerland

Hafnia alvei is a gram-negative bacterium that is rarely isolated from human specimens and is rarely considered to be pathogenic. It has been associated with gastroenteritis, meningitis, bacteremia, pneumonia, nosocomial wound infections, endophthalmitis, and a buttock abscess. We studied 80 *H. alvei* isolates recovered from 61 patients within a period of 30 months. *H. alvei* was cultured from sites that included the respiratory tract (n = 38), the gastrointestinal tract (n = 16), and the urogenital tract (n = 12); the organism was found in blood cultures (n = 8), on central venous catheters (n = 3), and on the skin (n = 3). Only 25% of *H. alvei* isolates were recovered in pure cultures. Fifty-seven (93.4%) of the patients had an underlying illness. *H. alvei* proved to be the etiologic agent in two episodes of septicemia and in one episode of peritonitis and was probably responsible for septicemia in two other patients and pneumonia in one. All six of these patients recovered after receiving antibiotic treatment and/or standard surgical treatment, when needed. Three of these infections were nosocomial, and three were community acquired. Of the strains of *H. alvei* tested in our study, 100% were susceptible to netilmicin, ciprofloxacin, and imipenem; 92% were susceptible to piperacillin; 90% were susceptible to co-trimoxazole; and 88% were susceptible to ceftriaxone and ceftazidime. In this study, we found *H. alvei* to be a rare but significant etiologic agent of nosocomial and community-acquired infections.

Hafnia alvei is a gram-negative facultative rod-shaped anaerobe that belongs to the Enterobacteriaceae; the organism was formerly named *Enterobacter hafniae. H. alvei* is rarely considered to be pathogenic; rather, *H. alvei* has been found to be related to the enteropathogenic *Escherichia coli* on the basis of a single virulence factor. Electron microscopy has demonstrated inflammation and mucosal invasion by *H. alvei* in rabbit bowels, and an attachment-effacement gene like that detected in enteropathogenic *E. coli* was found in *H. alvei* by hybridization [1, 2]. No other distinct virulence factors have been noted in this organism so far [3]. Stool specimens are generally not examined for the presence of *H. alvei.*

Cases of diarrhea due to *H. alvei* have occurred mainly in children. *H. alvei* was reported to have caused acute gastroenteritis in children from Bangladesh and Spain [1–2]. In one study, 16% of Finnish tourists with acute gastroenteritis and diarrhea who were returning from Morocco excreted *H. alvei* in their stools [4]. Seven strains isolated from children with diarrhea expressed the attachment-effacement gene [2]. In two case reports, *H. alvei* was mentioned as a cause of nonbloody diarrhea. One of these cases was presumably associated with reactive arthritis [5, 6]; however, cultures of joint aspirates were negative. A single case of *H. alvei* meningitis in a 1-year-old girl [7] and a case of necrotizing *H. alvei* enterocolitis with septicemia in a 20-day-old boy [8] have also been described. In adults, *H. alvei* has caused bacteremia [9, 10], pneumonia, and nosocomial wound infections [11–13]. *H. alvei* was recovered with *Salmonella arizonae* from a patient with endogenous endophthalmitis who was receiving steroids [14]. Recently, *H. alvei* was isolated from a buttock abscess that resulted from skin puncture with carpet nails in an otherwise healthy middle-aged man [15].

Until now, there have been no data published about the true rate of isolation of *H. alvei* from clinical specimens, and the clinical significance of this bacterium remains to be defined. Therefore, we performed a study on the frequency of isolation of *H. alvei* from clinical specimens (except stools) and correlated the microbiological findings with the clinical data.

Materials and Methods

Patient evaluation. Patients from whom isolates of *H. alvei* were recovered during routine diagnostic testing at the Department of Medical Microbiology, University of Zurich (Zurich) and at the Microbiology Laboratory of the Stadtspital Triemli (Zurich) between January 1992 and May 1995 were identified by reviewing the laboratories' records. The patients' charts were reviewed for data on isolation sites, underlying illnesses, cocultivation of other bacteria, and discrimination between nosocomial infections or community-acquired infections.

Isolation and identification. *H. alvei* was isolated from normally sterile body fluids such as blood, ascitic fluid, and ab-

Received 3 October 1995; revised 16 January 1996.

Reprints or correspondence: Dr. Andreas Pennekamp, Department of Medical Microbiology of the University of Zurich, Gloriastrasse 32, CH-8028 Zürich, Switzerland.

Clinical Infectious Diseases 1996; 22:1040–5

1058–4838/96/2206–0021$02.00

dominal aspirates as well as from postoperative indwelling catheters, central venous lines, and urine collected from catheters. Respiratory tract isolates were cultured from sputum and tracheal and bronchial aspirates. Samples other than blood were plated on selective and differential media, and colonies of Enterobacteriaceae were detected on MacConkey agar (Becton Dickinson, Basel, Switzerland); blood was cultured with use of the BacT/Alert blood culture system (Organon Teknika, Basel).

The identification of Enterobacteriaceae was based on biochemical data obtained by means of commercial identification systems (API20E and RapID 32E; bioMérieux, Geneva, Switzerland) and on lack of lactose fermentation on MacConkey agar. Biochemical reactions for which *H. alvei* was positive included lysine decarboxylase, ornithine decarboxylase, and mannitol fermentation, whereas it was negative for fermentation of sorbitol, inositol, sucrose, and melibiose; these negative reactions differentiated *H. alvei* from *Enterobacter aerogenes.* Strains with T values of <0.50 and probabilities of identification of $<90\%$ in one of the commercial systems were excluded from the study.

Antimicrobial susceptibility testing. Bacteria were tested for susceptibility by the disk diffusion method according to the National Committee for Clinical Laboratory Standards (NCCLS) guidelines. Strains were interpreted as susceptible, intermediately susceptible, or resistant on the basis of the NCCLS criteria. Susceptibilities were compared with use of the χ^2 test. Strains that were susceptible to ampicillin, amoxicillin/clavulanic acid, and cephalothin are most likely not part of the genus *Hafnia* [16] and thus were excluded from the study. We excluded strains of *Salmonella* and *Enterobacter* (one each), which were misidentified as *H. alvei* by the commercial systems, by means of these procedures.

We conducted a MEDLINE search with use of the terms *Hafnia alvei* and *Enterobacter hafnia.* All reports indexed from December 1966 to August 1995 were evaluated if they presented clinically important information.

Results

Within the 30-month study period *H. alvei* was isolated from 80 samples collected from 61 patients. Twenty of these patients were female, and 41 were male. The mean age for all patients was 55.4 years (range, 13–81 years); the mean age for women was 61.8 years, and that for men was 53.5 years. *H. alvei* was cultured from the respiratory tract 38 times for 35 patients (57.4%), from the gastrointestinal tract 16 times for nine patients (14.8%), and from the urogenital tract 12 times for seven patients (11.5%). The organism was isolated from eight blood cultures of seven patients (11.5%), from three central venous catheters of three patients (3.8%), and from the skin of three patients (3.8%). Table 1 shows the sites of isolation of *H. alvei,* which was isolated in pure culture of only 20 samples (25%). Organisms cultured concomitantly with *H. alvei* were Enterobacteriaceae, staphylococci, streptococci, and yeasts. None of these microorganisms showed a predilection for association with *H. alvei* (data not shown).

H. alvei was isolated from 57 patients (93.4%) with underlying illnesses. Twenty (33%) of these patients had malignancies: six had leukemia or lymphoma, seven had carcinomas of the abdomen, five had carcinomas of the throat and bronchi, one had a sarcoma, and one had an endometrial carcinoma. Abdominal surgery was performed on 11 (18%) of the 61 patients; nine (14.8%) were hospitalized because of trauma; nine (14.8%) underwent heart surgery; four (6.6%) had acute or chronic pancreatitis; three (4.9%) had chronic obstructive pulmonary disease; and one (1.6%) underwent lung transplantation. An underlying disease was not detected in four patients (6.6%). Table 2 shows the isolation sites of *H. alvei* among patients with underlying illnesses. Eighteen of 35 respiratory isolates were from intubated patients; almost all respiratory isolates from patients who had undergone cardiac surgery (seven of eight isolates) or who were hospitalized because of trauma (four of five isolates) were recovered from intubated patients. None of the patients who had undergone abdominal surgery had isolates of *H. alvei* recovered from respiratory specimens. Overall, 40 patients (66%) infected with *H. alvei* were intubated, and 19 of them had *H. alvei* isolated from the respiratory tract.

H. alvei was found to be the sole etiologic agent of invasive disease in three (4.9%) of the 61 patients; two had septicemia due to this organism, and one had peritonitis. All three patients recovered after receiving treatment with imipenem/cilastatin. The clinical characteristics of these three cases are displayed in table 3. *H. alvei,* together with other organisms, was possibly responsible for two other cases of septicemia and a case of pneumonia.

Ten additional patients in our review received adequate antibiotic coverage for *H. alvei,* but it was not possible to prove in retrospect that the organism had caused clinically significant infection.

A comparison of the results of antimicrobial susceptibility testing of our strains and those from patients described previously is shown in table 4. The *H. alvei* strains tested in our study were all susceptible to netilmicin and ciprofloxacin; 99% were susceptible to imipenem and tobramycin; 92% to piperacillin; 90% to co-trimoxazole; 89% to piperacillin/tazobactam; and 88% each to ceftriaxone and ceftazidime.

Discussion

H. alvei is rarely considered to be a pathogenic organism. In recent years, case reports of various infections due to *H. alvei* have been published [1–15, 17, 18]. In our retrospective 30-month study, *H. alvei* was recovered in 80 specimens from 61 patients. The majority of these patients (93.4%) had a severe underlying condition; this finding supports other reports that *H. alvei* is primarily isolated from patients with

Table 1. Isolation of *Hafnia alvei* in pure or mixed cultures of specimens from different body sites of 61 patients.

Site involved	No. of isolates recovered in pure cultures	No. of isolates recovered in mixed cultures	Total no. (%) from indicated site (n = 80)
Respiratory tract*	8	30	38 (47.5)
Gastrointestinal tract†	5	11	16 (20)
Blood	3	5	8 (10)
Central venous catheter	1	2	3 (3.75)
Urogenital tract‡	3	9	12 (15)
Skin	0	3	3 (3.75)

NOTE. Twenty (25%) of the isolates were recovered in pure cultures, and 60 (75%) of the isolates were recovered in mixed cultures.

* The following specimens were obtained: tracheal aspirates (16), pharyngeal smears (4), bronchoalveolar lavage fluid (2), nasal smears (1), bronchial aspirates (7), and sputum (8).

† The following specimens were obtained: ascitic fluid aspirates (2), gallbladder (1), abscesses and deep abdominal wounds (10), and pancreatic pseudocysts (3); no stool samples were included.

‡ The following specimens were obtained: urine collected from indwelling catheters (6), clean-catch urine (3), scrotal smears (2), and episiotomy wound (1).

underlying illnesses [11–12], except when it is an enteric pathogen [1, 4–6, 8, 17].

Thirty-eight *H. alvei* isolates were recovered from respiratory specimens, 16 were recovered from the gastrointestinal tract, 12 were recovered from the urogenital tract, eight were recovered from blood, three were recovered from intravenous catheters, and three were recovered from the skin. Only 25% of all *H. alvei* isolates grew in pure culture. *H. alvei* was cultured with a variety of other bacteria and fungi in the respiratory and gastrointestinal specimens.

H. alvei was the only identified pathogen causing two cases of septicemia and one case of acute peritonitis. The peritonitis occurred after a patient with stenosis of the choledochus duct underwent endoscopic retrograde cholangiopancreatography, and *H. alvei* was isolated from his blood and peritoneal fluid. This circumstance indicates that the bacterium's portal of entry

Table 2. Isolation of *Hafnia alvei* from different body sites of 61 patients with and without underlying conditions.

Underlying conditions	Site involved: Respiratory tract*	Gastrointestinal tract	Blood and central venous catheter	Urogenital tract	Skin	Total (%)
Malignancies						
Leukemia or lymphoma	4/1	2	...	...	...	6
Abdominal carcinoma	...	4	1	2	...	7
Throat or bronchial carcinoma	3/1	...	...	1	1	5
Others	1/0	...	...	1	...	2
Total†	...	...	...	...	...	20 (33)
Abdominal surgery‡	...	6	2	2	1	11 (18)
Trauma§	5/4	...	2	1	1	9 (14.8)
Heart surgery‖	8/7	...	...	1	...	9 (14.8)
Pancreatitis	2/2	1	1	...	...	4 (6.6)
Chronic obstructive pulmonary disease	2/0	...	...	1	...	3 (4.9)
Lung transplantation	1/1	...	...	...	...	1 (1.6)
None	4/0	...	...	...	...	4 (6.6)

NOTE. Only one isolate per patient was taken into account. Of the 61 patients, 35 (18 of whom were intubated) had isolates recovered from the respiratory tract; nine, from the gastrointestinal tract; seven, from blood and central venous catheters; seven, from the urogenital tract; and three, from the skin.

* Total no. of isolates/no. of isolates from intubated patients.

† Includes carcinoma (13 patients), acute myelocytic leukemia (3), plasmocytoma (1), non-Hodgkin's lymphoma (1), sarcoma (1), and aplastic anemia of unknown etiology (1).

‡ Includes incarcerated hernia (3 patients), perforation of the sigmoid colon (2), small bowel ileus (2), infrarenal aortic aneurysm (2), intra-abdominal abscess (2), delivery of infant by vacuum extraction (1), and endoscopic retrograde cholangiopancreatography (1).

§ Includes subarachnoidal bleeding (3 patients), polytrauma (2), knife injuries (2), burns (1), femur fracture (1).

‖ Includes aortocoronary bypass surgery (8 patients) and aortic valve replacement (1).

Table 3. Clinical characteristics of patients with *Hafnia alvei* infection.

Age (y)/sex	Type of infection	Site(s) involved	First day organism isolated after admission	Underlying disease	Clinical presentation	Antibiotic treatment, outcome*
37/M	Septicemia	Blood (×2),† pancreatic pseudocyst fluid	38	Acute pancreatitis	Pancreatic pseudocysts, perforation of transverse colon, sepsis syndrome	Imipenem/cilastatin, recovered
49/F	Septicemia	Blood (×2),† central venous catheter	28	Sigmoid diverticulitis	Perforation of the sigmoid colon with sepsis syndrome	Imipenem/cilastatin, recovered
50/M	Peritonitis	Peritoneal fluid	1	Chronic pancreatitis	Stenosis of the choledochus duct, acute abdomen	Imipenem/cilastatin, recovered

* The surgical treatment in these cases is not included because standard procedures were performed; no surgical interventions were primarily done for infection with *H. alvei.*

† Organism isolated in two separate blood cultures.

might have been the gastrointestinal tract, where it is considered to be a commensal [16]. Earlier reports have also mentioned a correlation between abdominal wounds or abdominal surgery and the isolation of *H. alvei* in blood [10]. *H. alvei* was isolated along with other pathogens from three other patients who had septicemia, pneumonia, and cholangitis.

Overall, 11.5% of the patients in our study population had proven (or at least probable) infections caused by *H. alvei,* and 57 of them presented with an underlying illness. Of six patients with *H. alvei* infections, three had nosocomial infections [19], and three had community-acquired infections. The number of infections might even have been higher, but the retrospective nature of our study did not allow correlation of the other *H. alvei* isolates with clinically significant infections. However, 10 additional patients from whom *H. alvei* was isolated were treated with broad-spectrum antibiotics in the absence of a clear diagnosis of infection. This circumstance supports the hypothesis that there was a higher rate of significant infections in our study population. In all six of our patients with proven or probable *H. alvei* infections, the infections were successfully treated with antibiotics chosen according to the results of susceptibility testing.

Table 4. Antimicrobial susceptibility test results for *Hafnia alvei* isolates.

	Present report		Literature review†	
Antibiotic	No. of strains tested	Percent susceptible*	No. of strains tested	Percent susceptible
Amoxicillin/clavulanic acid	77	1	NA	NA
Ampicillin	76	9	23	9
Cephalothin	77	0	23	17
Cefamandole	71	79	NA	NA
Ceftriaxone	73	88	NA	NA
Ceftazidime	73	88	12	42
Cefuroxime	69	77	NA	NA
Gentamicin	NA	NA	23	100
Amikacin	NA	NA	13	100
Netilmicin	75	100	NA	NA
Tobramycin	73	99	NA	NA
Ciprofloxacin	75	100	7	100
Piperacillin	64	92	13	85
Tetracycline	NA	NA	5	84
Piperacillin/tazobactam	19	89	NA	NA
Trimethoprim-sulfamethoxazole	76	90	13	92
Imipenem/cilastatin	73	99	8	100
Colistin	72	75	NA	NA

NOTE. NA = not available.

* Susceptibility testing was performed according to the National Committee for Clinical Laboratory Standards (NCCLS) for the disk diffusion method and interpreted according to NCCLS guidelines.

† Data are from [6, 16–19].

As shown in table 1, 38 (47.5%) of all isolates recovered from 35 patients were of respiratory origin. Eighteen of the patients were intubated at the time that samples were obtained, and 17 were not intubated during their hospital courses. Intubated patients who are immunosuppressed as a result of cardiac surgery or trauma seem to harbor *H. alvei* in their respiratory tracts more often than do patients who have previously undergone abdominal surgery. Whether the oropharyngeal-tracheal regions of these patients had been colonized previously or whether they became colonized as a result of hospital procedures (e.g., intubation) cannot be answered sufficiently. We do not know the prevalence of *H. alvei* colonization of the oropharyngeal-tracheal regions and other bodily sites in healthy persons or patients with underlying diseases. In large studies [20–21], this bacterium was rarely recovered from any site, making nosocomial infection improbable and emphasizing the likelihood of endogenous colonization in most patients before admission to the hospital.

On the other hand, only eight of 30 respiratory tract isolates were recovered from pure cultures, compared with 22 isolates that were recovered from mixed cultures; these mixed cultures mainly consisted of other gram-negative bacteria that are known to colonize the oropharyngeal-tracheal tract in severely ill patients [22]. The presence of *H. alvei* in feces reflects the fact that the organism is part of the normal bowel flora. Case reports of *H. alvei* as the etiologic agent of diarrhea must be evaluated critically because no toxin production or toxic mucosal changes in humans have been detected so far. However, it is worth mentioning that *H. alvei* might cause diarrhea in immunocompromised patients, as case reports of neonates and malnourished children with diarrhea have shown [1, 7, 17].

In comparing the susceptibilities of *H. alvei* isolates, we observed a higher rate of susceptibility to ampicillin/amoxicillin and cephalothin among the strains described in the literature. In conducting this study we used susceptibility to amoxicillin and first-generation cephalosporins as selection criteria; therefore, these data are not comparable to those from previous reports.

In our study the most active antimicrobials were netilmicin (100% of isolates were susceptible), ciprofloxacin (100% susceptible), and imipenem (99% susceptible). These results are similar to the scant results reported in the literature (only a few strains have been tested), where 100% of the *H. alvei* strains were found to be susceptible to amikacin, gentamicin, ciprofloxacin, and imipenem [23–26].

The susceptibility to ceftazidime observed in our study was significantly different from that reported in the literature ($P < .001$). This difference cannot be explained but is probably not caused by the larger number of strains tested in our study because the results were otherwise almost congruent. Another slight difference was observed when susceptibilities to piperacillin were compared: 92% of our strains (64 tested) were susceptible, while 85% of strains in other reports (13 tested) were susceptible. However, the fact that susceptibility results from other reports as well as from our study were comparable for most antimicrobials and that the biochemical features were similar indicates that *H. alvei* was correctly identified as the pathogen.

In summary, this study shows that *H. alvei* is a rare human pathogen; however, the organism may be responsible for serious nosocomial and community-acquired infections. Infections mainly occur in patients with underlying illnesses, and *H. alvei* is often isolated in coculture with different gram-negative rods, which may be due to endogenous colonization of the bowel. Treatment of *H. alvei* infection on the basis of antimicrobial susceptibility testing results is effective. In severe cases, treatment with imipenem or a third-generation cephalosporin in combination with an aminoglycoside is recommended. More data on the role of *H. alvei* and its pathogenicity are needed. In addition, the colonizing rate for this organism in different sites in healthy adults must be determined.

Acknowledgments

The authors are indebted to Professor A. von Graevenitz and Dr. J. Gubler for their helpful comments and careful review of the manuscript.

References

1. Albert MJ, Alam K, Islam M, et al. *Hafnia alvei,* a probable cause of diarrhea in humans. Infect Immun **1991**;59:1507–13.
2. Albert MJ, Faruque SM, Ansaruzzaman M, et al. Sharing of virulence associated properties at the phenotypic and genetic levels between enteropathogenic *Escherichia coli* and *Hafnia alvei.* J Med Microbiol **1992**;37:310–4.
3. Ridell J, Siitonen A, Paulin L, Lindroos O, Korkeala H, Albert J. Characterization of *Hafnia alvei* by biochemical tests, random amplified polymorphic DNA PCR, and partial sequencing of 16S rRNA gene. J Clin Microbiol **1995**;33:2372–6.
4. Ridell J, Siitonen A, Paulin L, Mattila L, Korkeala H, Albert MJ. *Hafnia alvei* in stool specimens from patients with diarrhea and healthy controls. J Clin Microbiol **1994**;32:2335–7.
5. Westblom TU, Milligan TW. Acute bacterial gastroenteritis caused by *Hafnia alvei* [letter]. Clin Infect Dis **1992**;14:1271–2.
6. Newmark JJ, Hobbs WN, Wilson BE. Reactive arthritis associated with *Hafnia alvei* enteritis. Arthritis Rheum **1994**;37:960.
7. Mojtabaee A, Siadati A. *Enterobacter hafnia* meningitis. J Pediatr **1978**; 93:1062–3.
8. Ginsberg HG, Goldsmith JP. *Hafnia alvei* septicemia in an infant with necrotizing enterocolitis. J Perinatol **1988**;8:122–3.
9. Englund GW. Persistent septicemia due to *Hafnia alvei.* Report of a case. Am J Clin Pathol **1969**;51:717–9.
10. Jennis F, Mccarthy SW. Hafnia: an unusual cause of postoperative gram-negative bacteriae. Med J Aust **1967**;1:286–7.
11. Klapholz A, Lessnau KD, Huang B, Talavera W, Boyle JF. *Hafnia alvei.* Respiratory tract isolates in a community hospital over a three-year period and a literature review. Chest **1994**;105:1098–1100.
12. Frick T, Kunz M, Vogt M, Turina M. Typical nosocomial infection with an unusual cause: *Hafnia alvei.* Report of 2 cases and literature review. Schweiz Rundsch Med Prax **1990**;79:1092–4.
13. Berger SA, Edberg SC, Klein RS. *Enterobacter hafnaie* infection: report of two cases and review of the literature. Am J Med Sci **1977**;273: 101–4.

14. Caravalho J Jr, McMillan VM, Ellis RB, Betancourt A. Endogenous endophthalmitis due to *Salmonella arizonae* and *Hafnia alvei*. South Med J **1990**;83:325–7.
15. Agustin ET, Cunha BA. Buttock abscess due to *Hafnia alvei* [letter]. Clin Infect Dis **1995**;20:1426.
16. Sakazaki R. Genus IX. Hafnia. In: Holt JG, ed. Bergey's manual of systematic bacteriology. 7th ed. Baltimore: Williams and Wilkins, **1986**:484–6.
17. Reina J, Hervas J, Borrell N. Acute gastroenteritis caused by *Hafnia alvei* in children [letter]. Clin Infect Dis **1993**;16:443.
18. Eisenstein BI. Enterobacteriaceae. In: Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas and Bennett's principles and practice of infectious diseases. 4th ed. New York: Churchill Livingstone, **1995**:1964–80.
19. Martone WJ, Garner JS, Duma J. Preventing nosocomial infections—progress in the 1980s; plans for the 1990s. In: Martone WJ, Garner JS, eds. Proceedings of the Third Decennial International Conference on Nosocomial Infections. Am J Med **1991**;91:3B–1S.
20. Weber DJ, Rutala WA, Samsa GP, Wilson MB, Hoffmann KK. Relative frequency of nosocomial pathogens at a university hospital during the decade 1980 to 1989. Am J Infect Control **1992**:192–7.
21. Carrel T, Schmid ER, von Segesser L, Vogt M, Turina M. Preoperative assessment of the likelihood of infection of the lower respiratory tract after cardiac surgery. Thorac Cardiovasc Surg **1991**;39:85–8.
22. Palmer LB, Donelan SV, Fox G, Bellemore E, Greene WH. Gastric flora in chronically mechanically ventilated patients. Relationship to upper and lower airway colonization. Am J Respir Crit Care Med **1995**;151:1063–7.
23. Qadri SM, Belobraydic KA. In vitro activity of aztreonam against gram negative bacteria from clinical specimens and its comparison with other commonly used antibiotics. Methods Find Exp Clin Pharmacol **1986**;8:223–6.
24. Thomson KS, Sanders CC, Washington JA II. Ceftazidime resistance in *Hafnia alvei*. Antimicrob Agents Chemother **1993**;37:1375–6.
25. Belobraydic KA, Qadri SM. Antimicrobial activity of imipenem against 1386 clinical isolates. Methods Find Exp Clin Pharmacol **1986**;8:675–8.
26. Washington JA II, Birk RJ, Ritts RE Jr. Bacteriologic and epidemiologic characteristics of *Enterobacter hafniae* and *Enterobacter liquefaciens*. J Infect Dis **1971**;124:379–86.