FEBRILE URINARY TRACT INFECTION IN RESIDENTS OF TWO MANITOBA LONG TERM CARE FACILITIES

BY

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ABSTRACT

Bacteriuria is common in the institutionalized elderly. However, determination of the contribution of urinary infection to febrile morbidity in this population is problematic due to difficulties in clinical ascertainment. In this non-interventional study, episodes of fever were identified prospectively over a two year period in residents of two long term care (LTC) facilities in Manitoba. The incidence of febrile episodes was determined, as well as the proportion and incidence of episodes attributable to invasive urinary infection using clinical and serologic criteria.

The incidence of febrile episodes was 1.34/1,000 patient days. Of the 372 febrile episodes enrolled, 147 (40%) met clinical criteria for respiratory infection 26(7%) for genitourinary infection, 25 (6%) gastrointestinal infection, 13 (35) skin and soft tissue infection, 2 (1%) were non-infectious and 159 (43%) were of unknown etiology. C-reactive protein was significantly and independently associated with patient age and outcome, but not with fever source. Bacteriuria was present in approximately 50% of initial urine cultures, and was not predictive of clinical genitourinary infection. The incidence of invasive urinary infection in this population was 0.93 and 1.09/10,000 patient days by clinical and serologic criteria respectively, and less than 10% (6.9% and 8.2% by clinical and serologic criteria) of febrile episodes in this study were attributable to this source. Serologic results suggest that the sensitivity of the clinical definition used in this study is poor for the identification of invasive urinary infection.

In bacteriuric subjects, identifying a urinary source of fever remains problematic. Prospective studies to evaluate the empiric management of selected clinical presentations in the LTC facilities are needed.

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

CRP - C-reactive protein

ELISA - Enzyme linked immunosorbent assay

GFR - Glomerular filtration rate

IL - Interleukin

LTC - Long Term Care

MHSC - Manitoba Health Services Commission

MOMP - Major outer membrane protein

PCH - Personal Care Home

RPF - Renal plasma flow

UTI - Urinary tract infection

1. INTRODUCTION

Long term care (LTC) facilities may be defined as institutions such as nursing homes and custodial care hospitals which serve a chronically ill, predominantly elderly, population. Many elderly persons in industrialized countries will be resident for extended periods in long term care (LTC) facilities (1), and these individuals are at increased risk for developing infections (2). While elderly populations have an impaired febrile response relative to younger populations (3), significant infections are usually accompanied by fever (4,5). Limited information, however, is available to describe the occurrence, causes and management of fever in the institutionalized elderly.

The distinction between infectious and non-infectious processes, as well as the localization of fever source, is problematic in this population. Localizing symptoms and clinical signs maybe absent in the elderly, and laboratory investigations including white blood cell count and erythrocyte sedimentation rate are neither sensitive nor specific diagnostic markers. C-reactive protein (CRP), an acute phase protein that reacts with the somatic C polysaccharide of Streptococcus pneumoniae, has been shown in some studies of the elderly to correlate with the presence and severity of infection, as well as the response to antimicrobial therapy (7-9). However, it has not been useful in the localization of infection in this population. Other laboratory investigations including microbiologic cultures of sputum, blood, urine and other fluids or tissues may be difficult to obtain and interpret in the elderly.

Older LTC residents are characterized by a high prevalence of bacteriuria, which is generally asymptomatic (6). The incidence and prevalence of febrile morbidity attributable to urinary infection in the institutionalized elderly has not been clearly established, reflecting diagnostic uncertainty due to factors such as a high prevalence of chronic genitourinary

symptoms in this population (10), difficulties in the communication of symptoms, and the low specificity of a positive urine culture for identification of symptomatic urinary infection in a population with a prevalence of bacteriuria of 30-50% (6). Attributing fever in a bacteriuric subject to invasive urinary infection in the absence of reliable clinical or diagnostic indicators is problematic. An estimate of the contribution of urinary infection to febrile morbidity is important, however, in order to understand the clinical impact of the substantial prevalence and incidence of bacteriuria in this highly impaired population, and to assist in developing optimal approaches to management, including appropriate use of antimicrobials for episodes of fever.

This prospective study was undertaken in order to:

a) Determine the incidence of febrile episodes in residents of two Winnipeg LTC facilities.

b) Determine the proportion and incidence of febrile episodes attributable to invasive urinary infection, using clinical criteria as well as serologic test for antibody rise as an objective measure of invasive infection.

Episodes of fever were identified in two LTC facilities during a 24 month period, and standard definitions using clinical and laboratory criteria were used to identify the presumed source of fever. The contribution of invasive urinary infection to febrile morbidity was measured using both clinical and serologic critiera. During the study, a third objective was added to the two identified above: to assess the diagnostic and prognostic significance of C-reactive protein levels taken acutely during febrile episodes in this population. Acute serum samples were measured for CRP and analyzed according to patient characteristics, clinical diagnosis and outcome. The study explores the implications of the results for our

understanding of the epidemiology of fever in the elderly, and for the clinical care of residents of LTC facilities.

2. REVIEW OF THE LITERATURE

2.0 The Aging Population

2.0.0 Canada

Over the last three decades the elderly population has increased in Canada, both in absolute numbers and as a proportion of the total population (11). In 1986 approximately 11% of the Canadian population was 65 years of age or older (12). Projections based on standard assumptions of a stable fertility rate , slowly declining mortality rate and unaltered immigration/emigration patterns, have predicted a 96% increase in the proportion of the population $\geq$ 65 years, from 11% in 1985 to 21% in 2030 (11). Within the elderly population, the number of those over 75 years (the "oldest - old") will increase particularly rapidly (11).

At present over 5% of the Canadian population over age 65 are permanent residents of institutions (13). It has been noted that the utilization of long term care facilities (LTC), such as nursing homes and chronic hospitals, increases uniformly with age in Canada (14), and correlates more closely with aging than with the presence of serious illness (15). Over the past decade, utilization of LTC facilities per 1000 total population has steadily increased in Canada, but the rate per 1000 population over 65 has remained stable (16). The prevalence of institutionalization of the elderly is lower in European countries such as Denmark and Britain, which have 50-70% as many LTC beds per 1000 population over 65 years of age as in Canada (17).

2.0.1 Manitoba

In Manitoba 12.7% of the population were $\geq$ 65 years old in the fiscal year 1989-1990 (18). During this period, when our study was conducted, the number of Personal Care Home (equivalent to nursing home) beds in the province was 7.4 per 1,000 population (18). Approximately 8,136 persons (0.7% of the provincial population) occupied 8,351 Personal Care Home (PCH) beds; 70.6% were female and 29.4% were male. Individuals less than 65 years of age comprised only 4.8% of the PCH population, with a PCH bed utilization rate of 0.4 per 1,000 population. The remaining PCH population was $\geq$ 65 years of age; 50.8% of residents were $\geq$ 85 years old. The PCH bed utilization rate rose from 7.3 per 1,000 persons 65-69 years of age, to 293.7 per 1,000 persons $\geq$ 85 years.

The level of care required by residents in Manitoba facilities is defined by the amount of nursing care required, with level 1 representing the lightest care requirements and level 4 the heaviest. During this period 4.7% of PCH residents were at level 1 care, 32.3% at level 2, 33.5% at level 3 and 29.5% at level 4 (18). While 22.9% of PCH residents age 65-69 years were at level 4, 30.2% of those $\geq$ 85 years required level 4 care.

During the 1989-1990 fiscal year the province spent almost $198 million on PCH services, or approximately $23,678 per bed (18). Resident services comprise 95.6% of these expenditures, with remaining costs attributable to the provision of drugs (2.8%), adult day care (0.7%) and therapy services (0.8%) (18). The budget for PCH services in Manitoba represents 14.4% of total Manitoba Health Services Commission (MHSC) expenditures; in comparison 3.2% of expenditures are on the Pharmacare Program, 18.0% on Medical Services, 60.8% on Hospital Services, and 3.6% on administration and other health services (ambulance etc.). In addition to the provincial PCH service budget, the cost of insured medical and dental services to PCH residents was $175 per capita in 1989-1990.

Although it can be seen that the costs of services to PCH residents in Manitoba represent a relatively small proportion of total MHSC expenditures, the economics of health care to this population are of concern for the following reasons:

1) There has been a 30.1% increase in PCH service costs, and 27.7% increase in per capita insured medical costs for PCH residents, between 1986/87 and 1989/90 (18). This compares to a 34.5% rise in costs of hospital services over the same period, and is larger than the gains seen (22.7%) in the costs of insured medical services. However, during this period the population $\geq$ 65 years grew by only 7.8%.

2) Data are absent regarding whether the increased expenditures noted above have resulted in improved health of PCH residents, as measured by morbidity, mortality, or more subtle indicators of well-being. In a study of Manitoba residents of PCHs, Shapiro and Tate (19) noted that 45.4% of this population died over a four year period (1987-1991). Attempts to measure outcomes such as urinary tract infection, decubitus ulcers, and gangrene were hampered by failure to computerize ICD9 diagnostic codes which are longer than three digits.

3) Data are absent regarding whether the increased institutionalization rate of the elderly in Manitoba and other Canadian provinces, compared to European countries, has resulted in improved health of the elderly.

Observations that many disabled elderly individuals in the community are as impaired as those in PCHs, and that lack of community support is an important risk factor for institutionalization, have led to calls for an increase in home care services in order to enable the elderly to remain longer in their communities (20). Quality of care for the institutionalized elderly, as measured by specific disease morbidity and mortality, as well as cost-benefit analyses of diagnostic and therapeutic interventions, will be important areas of future research for clinicians and health care economists.

2.1 Infections in the Institutionalized Elderly

2.1.0 Incidence and Prevalence

Infections are an important cause of morbidity and mortality in the institutionalized elderly. Although cardiovascular and cerebrovascular disease as well as arthritis are the three most common diagnoses in patients who enter LTC facilities, infectious diseases including urinary tract infection, pneumonia and decubitus ulcers are the most common new diagnoses made after admission (21). American surveys of the elderly in extended care LTC facilities reveal a prevalence of infection of 10-20% (Table 1) (22-26). One fifth of infections in the elderly in LTC Facilities occur during the first year of institutionalization, and the risk of developing infection decreases during subsequent years in the facility (25, 26). Several of the studies listed in Table 1 originate from Veterans Administration facilities, which include a largely male population of wide age range, in contrast to the female preponderance of most community nursing homes (27). The studies also differ in their design and duration of surveillance.

2.1.1 The Elderly as Compromised Hosts

The institutionalized elderly may be considered "compromised hosts" with regard to infection, primarily due to the effects of age on the immune system, the frequent presence of underlying diseases and risk factors for nosocomial acquisition of pathogens.

a) The Effects of Ageing on the Immune System

Immune defects associated with aging include decreased macrophage clearance, involution of the thymus, reduced response of helper and suppressor T cells to mitogens and reduced B cell antibody response to extrinsic antigens (28-32). Altered regulation of cytokine production has been noted in the elderly, characterized by reduced synthesis of interleukin-2 (IL-2) and increased synthesis of interleukin-6 (IL-6) (33,34). Waning cell mediated immunity has also been noted in the elderly (28,35,36). Impairment of the skin structure and function with age, including atrophy as well as impaired vascularity and inflammatory responses, may constitute risk factors for skin and wound infections in the elderly (37). Mucosal changes in the oropharynx, gastrointestinal and genitourinary tract, associated with reduced fibronectin, gastric acid and estrogen levels respectively, may contribute to infection in these systems (38-41).

b) Underlying Disease

Frequently the underlying diseases and associated investigations and treatments in the elderly result in impairment of the immune system and increased susceptibility to infection. The frequency and severity of infection in diabetics are associated with impaired leukocyte function due to hyperglycemia, as well as the consequences of vascular and neuropathic complications (eg. infection of foot ulcers).

Table 1. PREVALENCE AND INCIDENCE STUDIES OF NOSOCOMIAL INFECTION IN THE INSTITUTIONALIZED ELDERLY

Reference	Population	Study Duration	Design	Number	Prevalence	Incidence	Urinary Tract	Skin	Comment
Setta et al 1985	Long term care division of County Hospital Mean age=77 years	6 mos.	prospective	460	12%		16% (In uncatheterized)	43%	symptomatic bacteriuria =UTI definition
Magnusson et al 1980	Long term care division of Veterans Hospital Mean age=71	2 mos.	prospective	398	18%		72% (In catheterized/ uncatheterized)	11%	CDC definition of UTI Frequent (50%) use of catheters in population studied
Franson et al 1986	Nursing Home facility within a Veterans Hospital Mean age=78	1 mos.	retro-spective	176	13%		18% (In uncatheterized)	23%	CDC definition of UTI
Nicolle et al 1984	Elderly male residents of a Veterans Hospital Mean age=79	12 mos.	prospective	68		193 per 100 patient years	3% (In pts. without Indwelling catheters) (not fever)	19%	UTI=Positive urine culture plus symptoms or signs supportive of urinary tract source
Garibaldi et al 1981	Seven skilled care nursing Mean age=81	1 day	prevalence	532	16%		14% of all pts. (catheterized/ uncatheterized)	33%	CDC definition of UTI 13% of population used catheters

Compromised respiratory defenses are seen in patients with neurologic disease who are unable to cough, leading to pneumonia. Prostatic hypertrophy or functional bladder abnormalities lead to incomplete bladder emptying with accompanying symptomatic or asymptomatic infection.

c) Nosocomial Acquisition of Infection

Institutionalization in itself constitutes a risk factor for infection, through impairment of the immune response and exposure to nosocomial pathogens. Sedatives are frequently prescribed to elderly individuals, and may alter cough and gag reflexes. Intravenous catheters, feeding tubes and urinary catheters provide portals of entry for infection. Restraints and improper positioning of patients may impair skin integrity leading to soft tissue infections. The proximity of groups of individuals, who are at increased risk for infection, promotes nosocomial transmission of infection via shared airspace, caregivers and equipment.

2.1.2 Diagnostic Difficulties in Assessing Infection

Diagnosis of infection may be difficult in the elderly due to the absence of "classic" symptoms and signs. Neurologic disease, including dementia and dysphasia, may impair the patient's ability to recognize and report his or her symptoms to health care workers. Co-exisiting disease may obscure the diagnosis. For example, joint infections may be difficult to diagnose in the presence of existing rheumatoid arthritis or osteoarthritis. The symptoms and signs of pulmonary infection may be difficult to elicit in patients with fibrotic or obstructive lung disease. Altered physiologic responses to infection in the elderly frequently result in the absence of symptoms and signs seen in younger patients, or variations in the classic manifestations of illness. For example, both acute cholecystitis and appendicitis may progress to gangrene and perforation in the elderly without evidence of significant peritoneal

irritation (42,43). Fever may be absent in the elderly despite the presence of serious infection, possibly due to defects in interleukin-1 (IL-1) production by macrophages, or diminished response to interleukin at the hypothalamic level (44,45). Diagnostic difficulties may also result from social, cultural and economic factors which may delay access to appropriate health care. Depression, denial, poor mobility, poverty, communication difficulties and issues of access to appropriate technology may result in failure to obtain initial and ongoing medical attention (3).

2.2 Urinary Tract Infection in the Elderly

2.2.0 Methodologic Issues: Definitions and Populations

It will be noted that although the prevalence data for nosocomial infection in the elderly are remarkedly similar in different institutions (Table 1), the relative proportions attributed to urinary tract infection, as defined by the presence of symptoms and/or signs of inflammatory disease, vary widely (22-26). Differences in the diagnostic criteria used for the definition of urinary tract infection, and differences in study populations, may account for some of the observed variation.

The distinction between asymptomatic bacteriuria, defined by the presence of bacteria in the urine in the absence of signs or symptoms of local or systemic inflammation, and symptomatic urinary tract infection characterized by microbial invasion of tissue, has not always been evident in the published studies. Although attempts to differentiate the two conditions may be problematic, evidence suggests that their associated morbidity and mortality are different (23,46-53).

Bacteriuria has most commonly been defined by bacterial counts of $\geq 10^8$ colony forming units (cfu) per litre of voided urine ($\geq 10^5$ cfu/ml) (54). Amongst the most highly functionally disabled institutionalized elderly the prevalence of bacteriuria is over 50% for

both males and females (46,47,55). In less functionally impaired institutionalized groups the prevalence of bacteriuria ranges from 10-30%, with a higher prevalence in women (55-57). This prevalence of bacteriuria is substantially higher in the institutionalized compared to the non-institutionalized elderly (58).

Clinical criteria for symptomatic urinary tract infection which have been developed for younger non-institutionalized populations, including the presence of dysuria, frequency, incontinence, flank pain and fever, are not sensitive or specific indicators in the elderly. While some episodes of symptomatic infection in the elderly may present acutely with these "classical" symptoms, chronic genitourinary symptoms, including dysuria and incontinence, occur with equal frequency in the bacteriuric and non-bacteriuric institutionalized population (10,59,60).

The interpretation of cause of fever in the bacteriuric institutionalized elderly, when a site of infection is not apparent, is also problematic. Fever with a positive urine culture in the absence of other localizing findings is generally considered sufficient for a diagnosis of invasive urinary infection in an otherwise well individual. However, with a prevalence of bacteriuria of 50%, fever developing in bacteriuric individuals will frequently not be of urinary origin. Most episodes of fever without localizing findings occurring in the bacteriuric institutionalized elderly are more likely to be due to viral infections, such as influenza, than to urinary infection (23). However, because of the difficulty of unequivocably excluding invasive urinary infection in a non-communicative elderly individual with bacteriuria, antimicrobials are frequently given for therapy.

Differences noted in the prevalence of urinary tract infection may also be attributable to variations in the populations studied with respect to the presence of risk factors for infection, including underlying disease, institutionalization and catheterization

(53,618). The prevalence of asymptomatic bacteriuria has been shown to increase proportionately with age, and in the elderly the prevalence correlates with increased level of disability (39.55). Elderly noncatheterized males in the community have a bacteriuria rate of 5-10% (62). The prevalence increases to 20-50% in elderly male and female residents of nursing homes or acute care hospitals (55). Incontinence per se does not appear to be an independent risk factor for either bacteriuria or symptomatic urinary tract infection (22,61,63). Although bacteriuria is more common in females in all age groups, the relative proportion in females versus males decreases with age, possibly due to the role of prostatic obstruction and microcalculi in the elderly male (64). Other etiologic factors cited in the literature with respect to bacteriuria in both sexes include increased instrumentation and catheter use in the elderly, increased residual volume secondary to prolonged bed rest or bladder prolapse in the female, concurrent neuromuscular disease, and loss of bactericidal activity of prostatic secretions in the elderly male (55,39,64). Sobel and Kaye (64) found that waning estrogen levels in the postmenopausal women are not associated with increased uroepithelial cell adherence of uropathogens such as Escherichia coli.

2.2.1 The Natural History of Asymptomatic Bacteriuria and Symptomatic Urinary Tract Infection

In an eighteen month prospective study of 523 elderly mobile residents of self-care apartments and a nursing home, Boscia et al (10) distinguished between two groups of asymptomatic bacteriuric subjects: a small cohort with persistent bacteriuria (6% of women, 1% of men) and a larger group with intermittent or transient bacteriuria (30% of women, 11% of men). Similarly, in a study of relatively healthy mobile residents of a nursing home Kasviki-Charvati et al (57) noted "positive" conversion rates from non- bacteriuria upon entry to the home, to bacteriuria at one year post entry, of 11% in men and 23% in women.

"Negative" conversion rates, from bacteriuria to nonbacteriuria, of 22% and 27% were found for men and women respectively. Nicolle et al (46) showed similar results in their prospective study of elderly highly functionally disabled institutionalized males, in which 10% of the initial nonbacteriuric population became bacteriuric in every 3 month period.

Although E. coli remains the most common urinary pathogen in elderly women, proportionately more infections are due to Klebsiella species (spp), Proteus spp, and Pseudomonas spp, compared to younger populations (65,66). Recent microbiologic studies in the elderly female have demonstrated that the normal flora of the introitus, periurethral skin and distal urethra is replaced by gram negative organisms that can produce urinary tract invasion (67). Proteus mirabilis is the most common urinary tract pathogen isolated in the elderly male (68). For both males and females, up to 30% of all infections may be due to multiple organisms (46). Spontaneous changes in the urinary bacterial flora of the elderly have been demonstrated, rendering surveillance culture and sensitivity testing unreliable as the basis for empiric therapy of presumed urinary tract infection (66).

The true morbidity associated with asymptomatic bacteriuria is unknown. Tables 2 and 3 outline the few studies which have attempted to look at this question, using markers for renal function (glomerular filtration rate [GFR], renal plasma flow [RPF], serum creatinine) febrile episodes and symptoms such as hematuria, incontinence, dysuria, skin infection and bacteremia as measures of morbidity. Marketos et al (69) showed a significantly greater fall in GFR and RPF over time in bacteriuric compared to nonbacteriuric elderly patients, but a cause and effect relationship was not established. More recent studies by Carty et al (70), Klarskov et al (71), Akhtar et al (60) and Nicolle et al (47) have failed to show any significant difference in serum creatinine between bacteriurics and nonbacteriurics.

The problem of attributing febrile episodes to a urinary tract source is apparent in studies by Warren et al (48) and Nicolle et al (23). In the former study, febrile episodes were defined as being "of possible urinary origin" if the source could not be identified by using a set of 44 criteria for fever of various causes. Using this definition, an incidence of 0.4 febrile episodes of possible urinary origin per 100 patient days was found in noncatheterized elderly institutionalized women. In a prospective study of elderly institutionalized noncatheterized males, Nicolle et al (23) used a stricter definition in which fever with bacteriuria was said to be secondary to urinary tract infection only if accompanying signs and symptoms supported a urinary tract source. The study found an incidence of febrile episodes of 43/100 patient years, and the urinary tract was felt to be the possible source in only 2.7% of cases. In a separate study looking at other possible indicators of morbidity such as hematuria, incontinence, dysuria and skin infection, Nicolle et al (47) found no difference in the incidence of these parameters in treated versus untreated elderly bacteriuric institutionalized females. The incidence of morbidity that could definitely be ascribed to bacteriuria was only 0.9 episodes/patient year.

Table 3 outlines several studies of bacteremia in the elderly and other hospitalized groups (23,72-75). The urinary tract has been identified as a major source of infection in elderly patients with bacteremia; the majority of these patients are catheterized. Furthermore, pyelonephritis in females is more likely to lead to bacteremia in the elderly than in the young. Reports of associated mortality have ranged from 26% of all community acquired bacteremias in those over 65 years of age, to 70% in gram-negative rod bacteremias in hospitalized patients over 55 years old (72,73). Mortality is significantly higher in those over 55 years compared to those age 16-55 years (72). The identification of the urinary tract as the source of bacteremia is fraught with difficulty. Patients may be

afebrile, and symptoms such as back pain, dysuria, urgency or frequency are often absent (73,76). The diagnosis rests on the isolation of the same pathogen in blood and urine in the absence of other sources of infection.

Estimates of morbidity associated with bacteriuria and urinary tract infection must also take into account the effects of antimicrobial therapy. Inappropriate antibiotic therapy of asymptomatic bacteriuria exposes patients to drug toxicity, which occurs more frequently in the elderly than in younger patients (77,78). The addition of antibiotics to the multiple drugs which the institutionalized elderly frequently receive increases the potential for adverse drug interactions. In addition, the urine of the bacteriuric elderly with asymptomatic infection is a reservoir of potentially pathogenic organisms. Recurrent antimicrobial courses to "cure" asymptomatic bacteriuria, or inappropriate treatment of perceived "symptomatic" episodes, contributes to the emergence of resistant organisms (47,79,80). These resistant organisms may subsequently cause infections which are more difficult to manage not only in the bacteriuric individual but also in other residents of the institution if the organism is transmitted (81-83). Several outbreaks of infection with resistant bacteria in acute care institutions have been reported where the source of the organism was a patient admitted from a LTC (84,85).

Conflicting data have been published regarding the possible association of increased mortality with bacteriuria in the elderly institutionalized noncatheterized population (Table 4). A prospective study by Dontas et al (50) showed excess mortality in elderly bacteriuric males and females from a nursing home. However, concurrent conditions which are associated with both mortality and bacteriuria, such as cardiovascular and cerebrovascular disease, were not controlled for. Therefore a "cause and effect" relationship was not demonstrated. More recent studies by Heinemaki et al (52) and Nicolle et al (53), although

Table 2: MORBIDITY OF BACTERIURIA IN THE ELDERLY

Reference	Population	Study Duration	Design	Number	Renal Function GFR/RPF	Serum Creatinine	Febrile Episodes "Of Possible Urinary Tract Origin"	Other Parameters of Morbidity (Hematuria, Incontinence, Dysuria, skin infections)
Marketos et al 1969	Ambulant elderly residents of Nursing Home	7-46 mos.	Prospective	27	Greater fall over time in bacteriurics			
Carty et al 1981	Consecutive autopsies on geriatric pts. from a general hospital		Retrospective	100		Urinary infection did not correlate with serum creatinine or B.P.		
Klarskov et al 1972	Noncatheterized females over 60 years admitted to Orthopedic Ward of a General Hospital	9 mos.	Prospective	65		No correlation of serum creatinine and bacteriuria		
Akhtar et al 1972	Elderly from the community		Prevalence study	466		No correlation of creatinine, urea or B.P. with bacteriuria		
Warren et al 1987	Noncatheterized elderly females from chronic care hospitals	11,200 patient days	Prospective	49			0.4/100 patient days	
Nicolle et al 1984	Elderly institutionalized males	12 mos.	Prospective	68			Comprise 16% of total febrile episodes	
Nicolle et al 1987	Elderly institutionalized females	1 yr.	Prospective	50		No change in serum creatinine in bacteriuric group		Incidence of definite morbidity in bacteriurics = 0.9 /patient year

Table 3. BACTEREMIA IN THE ELDERLY

Reference	Population	Study Design	Number	Comments
Hodgin 1965	Hospitalized patients with blood cultures positive for non-salmonella gram negative bacilli	Retrospective	100	Most common source was the urinary tract (39% of cases). Most cases associated with indwelling urinary catheters. Mortality in gram negative bacteremia higher in those over 55 yrs. old
Esposito et al 1980	Geriatric patients with Community acquired bacteremia	Retrospective	100	Most common source was the urinary tract (34%), and 24% of those with urosepsis had indwelling urinary catheters
Gleckman et al 1982	Elderly patients requiring hospitalization	Prospective	34	Most common source of gram negative rod bacteremia was the urinary tract
Nicolle et al 1984	Elderly institutionalized males	Prospective	68	Nosocomial incidence of bacteremia = 5.2/100 patient years. All cases with a urinary tract source had underlying GU abnormalities
Gleckman et al 1985	Females admitted to hospital with acute pyelonephritis	Prospective	68	Bacteremia occurs more frequently in elderly than in young females with nonobstructive pyelonephritis

Table 4. BACTERIURIA AND MORTALITY IN THE ELDERLY

Reference	Population	Study Duration	Design	Number	Comments
Dontas et al 1981	Ambulatory elderly residents of nursing homes	10 years	prospective	342	Excess mortality in bacteriuric subjects
Nordenstam et al 1986	Ambulatory and institutionalized elderly subjects	5-9 years	prospective	2010	Increased mortality in male bacteriuric subjects attributable to increase occurrence of cancer in this group.
Heinamaki et al 1986	Elderly from the community, nursing homes and hospitals	5 years	prospective	674	No relation between mortality rates and bacteriuria
Nicolle et al 1987 (Am. J. Med.)	Elderly institutionalized females	1 year	prospective	50	No difference in mortality between bacteriuric patients who did or did not receive antimicrobial therapy
Nicolle et al 1987 (Ann. Int. Med.)	Elderly male residents of a Veterans Hospital	5 years	prospective	91	No relation between mortality rate and bacteriuria

also not controlling for associated chronic disease, have failed to show any excess mortality in the elderly bacteriuric population. Nordenstam et al (51) found an increased incidence of cancer and increased mortality in a bacteriuric male subgroup. However, among men with bacteriuria but without cancer, mortality was not increased.

2.2.2 Laboratory Tools in the Diagnostic and Prognostic Assessment of Urinary Tract Infection

The difficulties in determining the source of fever in the elderly, and in the diagnosis of invasive urinary tract infection, have been described. Recent attention has focused on the use of two laboratory parameters in the diagnosis and prognostic assessment of urinary tract infection.

a) MOMP Serology

An antibody rise to the major outer membrane protein complex of Escherichia coli occurs with invasive infection in the elderly, and may be measured by an enzyme linked immunosorbent assay developed by Nicolle et al (86). The antibody is widely cross-reactive with other Enterobacteriaceae, because major outer membrane proteins are antigenically similar among Enterobacteriaceae (86-88). IgG antibody to non-Enterbacteriaceae can be measured by a formalin inactivated whole cell enzyme-linked immunoassay (89). The assay was studied in 14 young woman and 152 elderly ambulatory and institutionalized men and women grouped as controls, those with asymptomatic bacteriuria, and those with clinically invasive urinary tract infection. An antibody rise, defined by a convalescent titre $\geq$ 3 standard deviations above the acute titre, or an initial ELISA optical density ratio to pooled controls of $\geq$ 15, gave a sensitivity of 95%, specificity of 82%, positive predictive value of 82%, and negative predictive value of 95% for identification of invasive infection in the bacteriuric elderly.

Limitations to the test as a clinical tool include the following:

1) Some elderly individuals may fail to produce antibody due to age-associated impairment of B cell response.

2) Antibody rises may occur due to infection with Enterobacteriaceae at other sites (eg. invasive gastrointestinal infection).

3) Antibody rises would not occur with invasive urinary tract infection due to gram positive organisms (eg. Enterococcus fecalis).

4) The test does not provide immediate clinically useful information at the time the patient presents with symptoms, as acute and convalescent sera must be collected over a 3-4 week period.

b) CRP

First described in 1930, C-reactive protein (CRP) is an acute phase protein that reacts with the somatic C polysaccharide of Streptococcus pneumoniae. The development of nephelometry as a sensitive and reproducible method of measuring CRP has led to a renewed interest in the role of this acute phase reactant as a diagnostic marker for infection and inflammation. Synthesized by hepatocytes in response to interleukin-6 (IL-6) stimulation, CRP is known to bind to bacterial cell walls and neutrophils, and to activate the classical complement pathway (90,91). However, the role of CRP in host defense and repair remains unknown.

In a prospective study of elderly patients admitted to hospital, Kenny et al found CRP to be a sensitive marker for presence and severity of infection, as well as response to antimicrobial therapy (7). In a similar study of patients admitted to a geriatric hospital unit, Cox et al. noted elevated CRP levels in those with infection, and a significantly higher CRP on admission in those who died compared to those who survived (9). However neither of

these studies reported positive and negative predictive values, and examples of false positive as well as false negative CRP determinations were noted. In a study of institutionalized and non-institutionalized elderly individuals, Katz et al found that although CRP levels were significantly elevated in those with infection and/or inflammation, the low positive and negative predictive values of measurements in individual patients (62% and 69% respectively for CRP $\geq$ 40 mg/L) limits their usefulness in an unselected geriatric population (92). In this heterogeneous group of patients, CRP was not found to be a significant predictor of mortality at 6 months.

The use of CRP in localizing the source of infection in general, and in distinguishing upper from lower urinary tract infection in particular, has not been studied in the elderly. In a cohort of middle-aged women with urinary tract infection, Sanderberg et al found that 94% of those with pyelonephritis had serum CRP Levels $\geq$ 30 mg/L compared to 5% of those with cystitis (93). The role of CRP in the diagnosis and localization of UTI has been more extensively studied in the pediatric literature. In a study of children aged 3 months to 16 years with urinary tract infection, those who had a CRP $\geq$ 30 µg/ml were more likely than those with CRP < 30 µg/ml to manifest signs of upper tract infection including greater temperature elevation, greater frequency of urologic abnormalities and presence of antibody coated bacteria in the urinary sediment (94). Marild et al compared children aged 2 weeks to 1.2 years with asymptomatic bacteriuria versus febrile UTI; median CRP was 0 and 85 mg/L ($P < 0.01$) respectively (95). The same authors in a subsequent study of children age 0.2 to 6 years with bacteriuria, found significantly higher CRP levels in those with fever compared to those without (96). In a study of 692 children with first-time UTI, de Man et al demonstrated that fever, CRP and ESR are significantly correlated, representing different measures of the systemic host-response triggered by cytokine release (97).

3. METHODS

3.0 Objectives

The study objectives outlined in the Introduction were designed to answer the following questions:

1. What is the incidence of febrile episodes in residents of LTC facilities in Winnipeg?
2. Using clinical and serologic criteria, what proportion of those febrile episodes are attributable to invasive urinary infection?
3. Is CRP useful as a laboratory tool in the diagnosis and prognostic assessment of febrile residents of LTC facilities?

The decision to add the third question to the study objectives, while the study was underway, arose from a review of the published medical literature on CRP. It was apparent that in Britain and Scandinavia CRP is used clinically as a marker for infection or inflammation, similar to the use of the erythrocyte sedimentation rate (ESR) in North America. As noted in the previous chapter, CRP has been thought to be of help in distinguishing upper from lower tract urinary tract infection in children; however, it's use in the elderly with urinary tract infection has not been studied. In order to answer this question the stored frozen samples of acute serum from enrolled patients were analyzed for CRP in the laboratory of Dr. F. Paraskevas (Health Sciences Centre, Winnipeg).

3.1 Patient Population and Institutional Characteristics

The study population consisted of residents of two LTC facilities in Winnipeg, Canada who developed fever and were enrolled between January 1, 1989 and December 31, 1990 inclusive. The Deer Lodge Centre (facility one) is a former veterans hospital. The number of long term care beds at this facility increased from 198 to 258 beds in April, 1989.

During the study period the male to female ratio was 3:1. This facility had on site radiologic and diagnostic laboratory facilities and 24 hour house medical officer coverage. Residents requiring increased clinical monitoring or intravenous therapy may be transferred temporarily within the facility to four beds on one ward dedicated to this purpose. The Tache Nursing Centre (facility two) is a personal care home with 316 long term care beds and a male to female ratio of 0.5:1 during the study. Medical care is provided by private practitioners who visit once weekly, or as necessary. Twenty-four hour on site physician coverage is not available, and clinical specimens are sent to an outside laboratory facility. Residents requiring intravenous therapy are transferred to an acute care hospital. The majority of residents at both facilities are over 65 years of age. A small number of young individuals with chronic neurologic disabilities who require permanent institutional care are also resident.

Funding of long term care facilities in the province of Manitoba is determined by the level of care of the resident population. Residents in personal care are classified on the basis of functional levels from level 1 (least dependent), to level 4 (most dependent). For facility one, funding for the 198 personal care beds is on the basis of 1/3 level 2 and 2/3 level 3 and 4. The average census during this study was 78 beds (39%) level 2 and 120 beds (61%) level 3 and 4. The additional beds opened in April 1989 were all chronic care beds, a functional level more impaired than personal care. For facility two the level of care was 77 beds (25%) level 2 and 239 beds (75%) level 3 and 4. The number of residents with indwelling catheters was 24(9.3%) for facility one and 18(5.7%) for facility two.

3.2 Study Design and Surveillance Methods

The study design was prospective and descriptive, involving identification of LTC facility residents who developed febrile episodes over the 24 month study period. Residents

with fever were identified through active surveillance conducted by a study nurse who visited each facility at least twice weekly. Temperatures of residents in both facilities are not monitored routinely. They are obtained by physician order, or by nursing staff when an alteration in the resident's clinical status is noted. Residents with fever were identified through consultation with the ward staff and chart review. Informed consent from the patient or guardian was obtained for all study subjects. Lack of informed consent was the only exclusion criterion. A record was kept of patients with febrile episodes not enrolled for data collection.

Residents with more than one episode of fever during the study period were re-entered as a distinct episode if they had been afebrile for at least 14 days prior to the repeat episode. If fever recrudesced within 14 days, it was considered one episode. Information was collected, using a standard data form, on clinical symptoms and signs, laboratory and radiologic investigations, therapy, and outcome. The study was non-interventional, and investigators were not involved in the examination, investigation or management of fever.

3.3 Laboratory methods

Urine specimens for urinalysis and urine culture, and serum specimens were obtained at enrollment from all consenting residents and repeated at four weeks following enrollment. All other investigations including hematology, biochemistry, microbiologic and radiologic studies were ordered at the discretion of the attending physician and performed using standard procedures at the facility. Urine specimens were collected by a clean catch technique, the use of an external drainage device for men (98), or in and out catheterization. Patients with long term indwelling catheters had specimens collected by aspiration through the catheter port.

Acute CRP levels were analyzed by rate nephelometry. Serum antibody to the major outer membrane protein (MOMP) of E. coli was measured by a previously described enzyme linked immunosorbent assay (86). Subjects with bacteriuria with organisms other than Enterobacteriaceae, which would not cross-react with the MOMP antigen, had IgG antibody to the infecting organism measured by a formalin inactivated whole cell enzyme-linked immunoassay (89).

3.4 Study Definitions

Fever was defined as one or more temperatures >38°C obtained at any site (oral, rectal, axilla or tympanic membrane) (99). Residents could also be enrolled if the temperature was 1°C above baseline temperature for that resident. Individual baseline temperatures were not, however, determined in a standardized fashion and were based on admission temperature or temperatures measured with previous clinical alterations for that subject.

Determination of source of fever used definitions proposed by McGeer et al for use in long term care facilities (99). These definitions are primarily based on clinical presentation, reflecting the limited access to laboratory or radiologic investigations for many long-term care facilities. Diagnosis of symptomatic urinary infection in residents without indwelling catheters required at least three of the following: fever or chills, new or increased lower tract irritative symptoms, new flank or suprapubic pain or tenderness, change in character of urine, or worsening mental or functional status. Residents with an indwelling catheter required only two of the following criteria: fever or chills, new flank or suprapubic pain or tenderness, change in character of urine, or worsening of mental or functional status. In addition, for the purposes of this study, the presence of bacteriuria, if the initial culture was obtained prior to antimicrobial therapy, was required for the diagnosis

of symptomatic urinary infection. The fever source was considered unknown if the episode failed to meet the criteria for infection at a specific site using information available from history, physical examination and laboratory investigation, or if the information was consistent with more than one potential site of infection.

Bacteriuria was defined as one or two organisms in quantitative counts $\geq 10^8$ colony forming units (cfu)/L ($\geq 10^5$ cfu/ml) for voided specimens from men or women (47). Voided specimens with three or more organisms present at quantitative counts $\geq 10^8$ cfu/L were considered unevaluable. A positive condom catheter specimen was defined as $\geq 10^8$ cfu/L of one to three organisms; over three organisms $\geq 10^8$ cfu/L was considered non-evaluable (98). Urine specimens obtained by straight catheterization or by aspiration from a catheter port were considered positive with any quantitative bacterial count.

3.5 Statistical Analysis

3.5.1 Expected Occurrence of Febrile Episodes

Two previous studies (23,48) identified 60 episodes of febrile illness in 60 elderly men during a one year period, and 0.4 episodes of fever per 100 patient days in a female population. Thus, for a highly functionally disabled institutionalized population one would anticipate one febrile episode per resident per year, or for the proposed study population, approximately 640 episodes in one year. However, the present study population was not as functionally disabled as the populations described above and the number of episodes was conservatively estimated at approximately 50% of this or 300-320 episodes per year. If a maximum of 5% of these episodes were due to urinary tract infection, then 15-20 episodes per year or 30-40 episodes in a 2 year period would be attributable to invasive urinary tract infection.

3.5.2 Statistical Power

For the consideration of differences between residents with fever due to urinary infection compared with other causes it was anticipated that there would be approximately 40 cases in the former and 600 cases in the latter. These estimates would allow the identification of differences of 0.20 or greater between groups with $\alpha = 0.05$ and $\beta = 0.75$.

3.5.3 Data Analysis

The incidence of febrile episodes was determined for 1,000 resident days of observation, and invasive genitourinary infection for 10,000 resident days. The unpaired T-test and analysis of variance were used to compare means for continuous data. Comparison of proportions was by Chi square statistic, or Fisher exact test for small expected values. Correlation co-efficients were used to compare quantitative variables, with logarithmic transformation of CRP to satisfy the assumption of homogeneity of variance. Multiple linear regression was performed to adjust for the effects of age, fever duration and outcome on CRP.

"Normal" values for changes in antibody levels between acute and convalescent specimens were determined for three "control" groups in whom Enterobactereaceae infection from a urinary or other source was excluded or unlikely. The first group were 36 residents with negative initial urine cultures obtained prior to antimicrobials, no antibiotics in the past week, no past history of urinary infection, and no clinical diagnoses which might be associated with Enterobactereaceae infection at other sites. The second group were 28 subjects with a clinical illness consistent with influenza during the four week influenza outbreak in study year one. The third group included 31 subjects with clinical symptoms and signs of respiratory infection and chest x-ray documentation of a new infiltrate consistent with pneumonia. The mean ratios ($\pm$SD) of ELISA optical density for convalescent to

acute episodes were 1.12 $\pm$ 0.37, 1.02 $\pm$ 0.22, and 1.10 $\pm$ 0.28 for the three groups respectively. The lowest value for mean ratio of optical density plus two standard deviations (1.46 in the second "control" group of subjects with an influenza-like illness) was used as an upper limit of normal to identify episodes of invasive urinary infection. A significant decrease, defined as a decline in convalescent antibody to less than the mean control ratio minus two standard deviations (0.58), when the initial antibody level was elevated, was also considered potentially consistent with invasive urinary infection (86).

3.6 Ethical Considerations

Informed consent was obtained from resident or legal guardian prior to study enrollment. The study was approved by the medical directors of the two LTC facilities and by the Faculty Committee on the Use of Humans in Research, University of Manitoba. No interventions or change in the usual management occurred as a result of the study. The collection of acute urine and blood samples would be considered appropriate to the usual management of fever. The collection of convalescent blood would in most cases not be required for the usual care of patients recovering from a febrile episode. Venipunctures were timed to coincide with the drawing of other blood specimens whenever possible, in order to minimize any associated patient discomfort.

3.7 Methodologic Issues

Potential problems which were anticipated in the study design pertained to the internal and external validity of the project.

3.7.1 Internal Validity

The use of standard published definitions and criteria for patient evaluation in this study is important to the internal validity and reproducibility of our results.

However, the following issues remain:

1. Although the clinical criteria used here for patient evaluation were accepted in consensus conference (99) by experts in the field of nosocomial infection, their validity cannot be assessed in the absence of a "gold standard". They are, in essence, the best available published guidelines.

2. The descriptive nature of our study entails the recording of observations, investigations and treatments as determined by the attending health care workers. Thus the accuracy of data to which we apply our study criteria depends on the skills, protocols and resources of the institutions and their staff. For instance, routine daily temperatures are not obtained at either facility, but are taken when a variation in resident status is observed. The lack of routine monitoring implies that some febrile episodes in residents may not be identified. Similarly, if other clinical symptoms or signs are not observed, or if procedures (eg. blood cultures, radiographs, autopsies in the case of death etc) are not performed, the study results may be inaccurate.

Recognizing these concerns, it is felt that the non-interventional descriptive study design best reflects the "real-life" situation of patient care in LTC facilities, thus maximizing the external validity of the results. During previous studies (23,47,53) it was felt that the level of care provided at the two LTC facilities met accepted institutional and professional standards. In reality it is possible that staff awareness of the study, despite it's non-interventional nature, may have indirectly improved standards of care or use of investigations ("Hawthorne effect").

Limitations in the use of an outer membrane protein serologic test to identify invasive UTI have already been described in the literature review (86). A serologic response may fail to occur in individuals with an impaired humoral response or in the less

common case of exclusive gram positive infection. Alternatively, an antibody rise may be falsely attributed to a UTI if gram negative infection at another location is not appreciated. However, acknowledging these constraints, and in the absence of a "gold standard" for the diagnosis of invasive UTI, it is reasonable to expect that a positive MOMP antibody response will help identify episodes of invasive UTI in bacteriuric patients who may lack the classic signs and symptoms of systemic infection (86).

The addition of the third objective to study CRP during the study introduced the possibility of a selection bias in this analysis. Of the 187 enrolled residents experiencing 372 episodes of fever, acute serum was unavailable in 25 episodes occurring in 10 individuals. In one episode the study nurse was unable to draw blood; in the remaining 24 episodes there was insufficient quantity of serum remaining for CRP analysis after hematologic and serologic testing was performed. Comparison of episodes and individuals for whom serum for CRP analysis was and was not available showed no significant difference between the two populations in age, sex, number of chronic diseases, history of urinary infection or genitourinary surgery, functional level, urine culture, fever source, fever duration or outcome. Therefore it is likely that the population in whom CRP was studied reflects and is representative of the total enrolled study population, and that the results of the CRP analysis can be applied to the study group as a whole.

3.7.2 External Validity

The Deer Lodge and Tache Nursing Centre were chosen as study sites for the following reasons:

1) They represent two types of LTC facilities. Tache Nursing Centre is a community nursing home for patients with a broad range of disabilities. Like most community nursing homes, it does not have a laboratory, x-ray

unit, or "in-house" physician coverage. Deer Lodge Centre is a former veterans hospital converted to a chronic care facility for women as well as men, although the majority of patients continue to be men. It has "in-house" laboratory, x-ray unit, and physician coverage.

2) Previous research studies on infections in the elderly had been performed at these centres. In both locations the administration, staff, patients and their relatives had demonstrated an interest in actively participating in this research, which was viewed as of potential benefit rather than harm to the patients. At the same time, staff were comfortable with the non-interventional nature of the study methodology.

The validity of applying the study results to the general population of LTC facilities in Manitoba must take into account these characteristics of the chosen study population. As noted in the previous chapter, 37% of all LTC facility residents in Manitoba in 1989-90 were at level 1 and 2 care, and 63% were at level 3 and 4 care. In our combined study population, 27% of residents were at level 1 and 2 care, and 73% were at level 3 and 4 care. Our study population at the two LTC facilities was comprised of 52% men and 48% women, whereas 29% of the population of all Manitoba LTC facilities were male and 71% were female during this period. For these reasons, analysis of our results included comparisons of the two study facilities.

Selection bias is possible due to the requirement for informed consent from patient or legal guardian. It is possible that patients, or the guardians of these patients, who were less acutely ill with fever were likely to agree to participate in the study. The converse is also possible, if there were a perception that participating in a study might improve care and/or outcome. Attempts to minimize selection bias were made through patient, family

and staff education regarding the study aims and procedures during a 3 month start-up period prior to commencement of enrollment and data collection.

The high level of interest among staff and patients at the study centres may have created a "Hawthorne effect", as mentioned previously. Staff may have recognized, investigated or treated more diligently, or patients who enrolled may have been less sick than those who did not. Thus it is possible that our study site and population may not be entirely representative of Manitoba LTC facilities as a whole. Application of the results to other centres must ensure that similar populations and institutions are being compared.

4. RESULTS

4.0 Incidence of fever

During the 24 study months 491 episodes of fever were identified in 257 residents at the two institutions. The cumulative follow-up was 367,024 resident days, an incidence of 1.34 febrile episodes/1,000 patient days. The incidence was 1.58/1,000 patient days for facility one and 1.14/1,000 patient days for facility two. For 25 (6.7%) of these episodes, the maximal temperature measured was less than 38°C, with 22 between 37.5°C and 38°C. For facility one, 123 (30%) of 404 residents present for any time in the facility during the study period had at least one episode of fever identified, and for facility two, 133 (32%) of 412 residents. One hundred eighty-seven (73%) residents experiencing 372(76%) of the 491 episodes of fever were enrolled for specimen and data collection, 224(60%) at facility one and 148(40%) at facility two. The remaining 33(13%) episodes at facility one and 86(37%) at facility two were excluded from data and specimen collection due to lack of consent.

Table 5. Demographic Characteristics of Residents with Fever at Two Long Term Care Facilities

	Facility One	Facility Two
Number residents/episodes	105/224	82/148
Mean age (mean ±SD)	75.8±9.5	74.4±16
(median, range)	(79, 38-98)	(75,24-97)
Months residence (mean±SD)	27.1±30.3	53.0±63.4
(median, range)	(18, 0-211)	32, 1-312)
Sex (F/M)	32/73	47/35
Mean chronic diseases±SD	3.8±1.5	3.5±1.4
(median, range)	(4;1-8)	(3;1-8)
Underlying illnesses (number, %):		
diabetes	14(13)	13(16)
neurologic	88(84)	71(87)
cardiovascular disease	62(59)	28(34)
respiratory disease	34(32)	15(18)
Functional status (number, %):		
incontinent urine	62(59)	45(55)
indwelling catheter	13(12)	6(7)
incontinent bowel	37(35)	31(38)
impaired mobility*	90(86)	74(90)
impaired mental status**	62(59)	39(48)
tube feeding	16(15)	1(1)
gastrostomy/jejunostomy	10(10	1(1)
Medication (number, %):		
all medications (mean ±SD)	9.8±4.3	10.0±4.3
(median, range)	(10,1-22)	(9-4-25)
long term corticosteroids	5 (5)	1 (1)
non-steroidal anti-inflammatory drugs	12 (11)	8 (9.7)
enteric acetylsalyclic acid	12 (11)	12 (15)

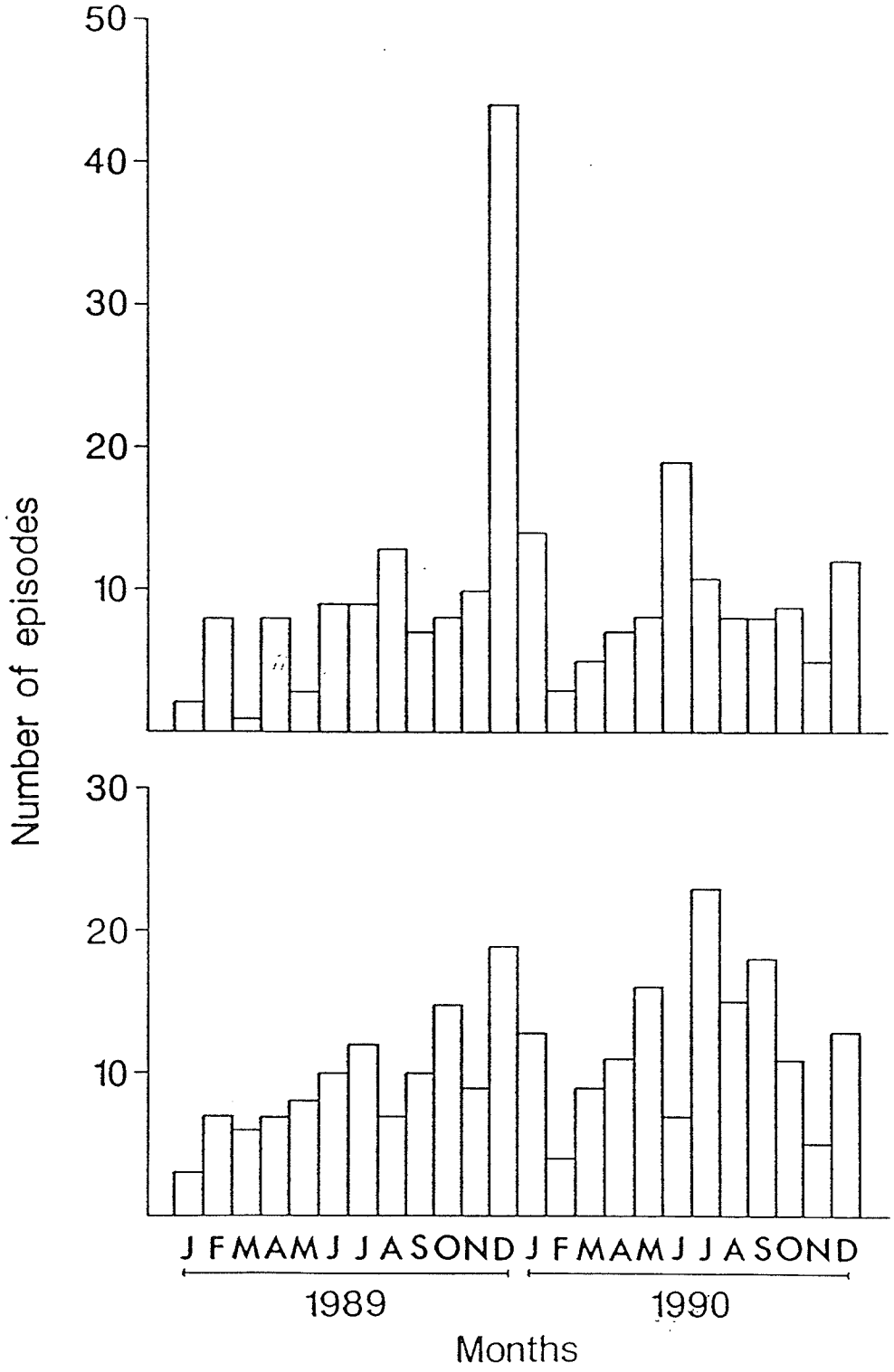
* chair or bed-bound, or requiring assistance
** demented, confused, or obtunded

The monthly occurrence of episodes of fever at the two centres is shown in Figure 1. Forty-four (36%) febrile episodes identified at facility two occurred in December 1989, coincident with a community outbreak of influenza A. Twenty-four of 28 febrile episodes occurring in 27 residents enrolled in that month were clinically compatible with influenza; all three patients with viral serology obtained had serologic evidence of influenza A infection. Twenty-one of 24 residents with clinical illness compatible with influenza had received influenza vaccination; one died. Nine subjects at facility one were enrolled with influenza-compatible illness in December 1989; influenza A was isolated in viral culture from throat swabs in two of these individuals. Only 3 of the 9 subjects had been vaccinated. Two residents died; one had been vaccinated and one had not. The influenza strain circulating in the community was A Shanghai 11/87 H_3N_2 and the vaccine strain contained A Taiwan 1/86 H_1N_1, A Shanghai 16/89 H_3N_2, and B Amagata 16/88.

4.1 Resident characteristics and management of fever

Characteristics of the 187 subjects enrolled with fever at the two facilities are shown in Table 5. For facility one, 51 (49%) residents enrolled had only one episode identified, 24 (23%) had two, 12 (11%) had three, and 18 (17%) had over three episodes. For facility two, 48 (59%) residents had one episode, 18 (22%) had two episodes, 5 (6%) had three episodes and 11 (13%) had more than three episodes, including one resident with 19 episodes. Residents with repeated episodes of fever did not differ in age, sex, number of underlying diseases, or medication use. However, individuals with multiple episodes were characterized by a shorter duration of institutional residence [44.9 months (±52.3 SD, range 0-304) vs 31.2 months (±44.8 SD, range 0-312), p=0.055], increased frequency of feeding tubes [(12 (14%) of 88 vs 5 (5%) of 99; p=0.04], incontinence of urine [(67 (76% of 88 vs

Figure 1. Episodes of Fever Identified monthly from January 1989 to December 1990 at Facility 1 (lower) and Facility 2 (upper).



59 (60%) of 99; p =0.02)], indwelling catheters [(14 (16%) of 88 vs 5 (5%) of 99; p = 0.02)] and, for residents without indwelling catheters, a positive urine culture for the initial febrile episode [34 (47%) of 73 vs 26 (30%) of 88; p = 0.03]. Five (5.1%) of 99 residents with one episode of fever had indwelling catheters, 5 (12%) of 42 with two episodes and 9 (20%) of 46 with more than two episodes (p=0.02). When residents who died after their first episode of fever, potentially a more impaired population, were excluded from this analysis, the observations remained statistically significant. Laboratory and radiologic studies were obtained more frequently in facility one, due to the presence of on site diagnostic capabilities (Table 6). Antimicrobials were prescribed for 295 (79%) of the 372 febrile episodes. They were more frequently prescribed and for a longer duration for episodes in facility one. In 72 (19%) episodes residents had received an antimicrobial medication within one week prior to onset of this episode. Antipyretics were almost universally prescribed, being given for 362 (97%) episodes. At facility one, residents were transferred to the facility's acute care beds in 27 (12%) episodes, and one resident (.4%) was transferred to an acute care hospital. For facility two, 9 episodes (6.1%) required transfer of the resident to an acute care institution.

4.2 Source of fever and outcome

The sources of fever identified using standard clinical and laboratory criteria are listed in Table 7. Forty-three percent of episodes had no apparent source or criteria consistent with more than one source of fever. The distribution of fever source was similar for the two institutions with 92 (41%) episodes of unknown source at facility one and 67 (45%) at facility two. The increased access to and use of diagnostic facilities at facility one may have increased the likelihood of identification of a clinical source.

Table 6. Management of Episodes of Fever in Two Long Term Care Facilities

	Facility One	Facility Two
Episodes/Subjects	224/105	148/82
Laboratory/Radiologic Investigations:		
Chest roentgenogram (% of episodes)	111(50%)	10(7%) *
New infiltrate (% of tests)	39(35)	4(40)
Complete blood count	176(79)	20(14) *
Leukocytes >15,000	43(24)	0
Microbiology studies:		
sputum culture	33	4*
stool culture	5	0
blood culture*	36	9***
positive	5(14%)	0
skin culture	16	2***
throat swab	9	3
Antimicrobials prescribed	192 (86%)	103 (70%)+
Mean days antimicrobials (median)	15.2±12.2 (10)	10.9±7.4 (7)**
Antipyretics for this episode	214 (96%)	148(100%)***
More than one temperature elevation:	189 (84%)	115 (78%)

* $p \leq 0.001$

** $p \leq 0.01$

*** $p < 0.05$

Table 7: **Clinical Source of Fever and Prevalence of Bacteriuria for Episodes of Fever.***

Clinical source	Number(%)	Number with bacteriuria/evaluable specimens (%)					
		All episodes			Episodes without indwelling catheter		
		all	no prior antibiotics**	4 weeks follow-up	all	no prior antibiotics**	4 weeks follow-up
Unknown	159 (43)	88/151/(58%)	66/111(59%)	89/140 (64%)	57/118(8%)	46/91(51%)	60/108(56%)
Respiratory tract	147 (40)	45/140(32%)	25/68(37%)	29/124(23%)	29/124(23%)	17/60(28%)	33/109(30%)
Genitourinary tract	26 (7)	23/26(88%)	15/15(100%)	16/25(64%)	12/13(92%)	9/9(100%)	6/12(50%)
Gastro-intestinal tract	25 (6)	18/24(75%)	14/18(78%)	16/23(70%)	13/19(68%)	11/15(73%)	12/19(63%)
Skin/soft tissue	13 (3)	5/13(38%)	1/6(17%)	5/11(45%)	4/11(36%)	1/5(20%)	4/9(44%)
Non-infectious	2 (1)	0/2	0/0	1/1	0/2	0/0	1/1
All episodes	372	179/356(50%)	121/218(56%)	174/323(54%)	115/287(40%)	84/180(47%)	116/258(45%)

* excludes subjects with no urine culture or with non-evaluable urine culture results

** urine specimens obtained prior to initiation of antimicrobial therapy

Thirty-two residents died within four weeks of fever onset, including 25 individuals at facility one, (24% of subjects and 11% of episodes) and 7 individuals at facility two (9% of subjects and 5% of episodes). Eight residents died of causes unrelated to the fever, including five with a cerebrovascular accident, one of heart disease and two of noninfectious respiratory failure. Five residents with fever of unknown source died of unknown causes but without clinical evidence for ongoing infection. Sixteen residents with a respiratory source of fever died of respiratory failure associated with infection, one resident with noninfectious fever attributed to tumour died of his underlying cancer, and two residents, one with a respiratory source and one an unknown source, died with a clinical presentation consistent with sepsis. Thus, 9% of febrile episodes were associated with mortality within 4 weeks. Death was felt to be directly attributable to infection for 4.8% of episodes, including 17(12%) of 147 episodes with a respiratory fever source and one (0.6%) of 159 episodes of an unknown source.

4.3 C-Reactive Protein

Acute CRP levels were analyzed in 347 febrile episodes occurring in 177 residents. There was no signficant association between acute CRP levels and gender, number or type of underlying chronic disease, number of medications or functional status in terms bladder, bowel, mentation and mobility (Table 8). CRP increased linearly with age in those $\leq$ 80 years ($r = +0.25$, $p < 0.0001$); for those > 80 years old there was a significant negative linear correlation between acute CRP levels and age ($r = -0.20$, $p < 0.05$) (Table 8, Figure 2). CRP did not vary significantly with fever source. However, controlling for age, CRP correlated positively with fever duration ($r = .13$, 95%, CI 0.02, 0.23, $p < 0.05$).

Table 8. Acute C-Reactive Protein (CRP) Levels in Febrile Episodes Occurring in Institutionalized Long Term Care Patients

Patient/Episode Characteristic	Mean CRP (S.D.)	Correlation Coefficient (r)	Significance (P)
Sex			
Male	88.7 (87.3)		0.5
Female	82.1 (82.6)		
Age (yrs):			
$\leq$ 80		+0.26	< 0.0001
$\geq$ 80		-0.20	< 0.05
No. Medications		0.09	> 0.05
No. Chronic Diseases		0.02	> 0.05
History of Chronic Disease			
Diabetes			
present	89.8 (80.2)		0.8
absent	86.0 (86.3)		
Cardiovascular D.			
present	86.4 (82.3)		0.9
absent	86.4 (88.7)		
Respiratory D			
present	94.7 (91.0)		0.6
absent	84.2 (84.2)		
Neurologic D			
present	85.1 (85.2)		0.5
absent	97.8 (90.3)		
Malignancy			
present	79.6 (68.2)		0.7
absent	86.7 (86.5)		
Bladder Status:			
Normal	93.4 (85.0)		
Incontinent	85.9 (86.3)		0.6
Indwelling Catheter	79.0 (85.0)		
Bowel Status:			
Continent	83.0 (87.3)		0.6
Incontinent	91.7 (83.1)		
Mental Status:			
Impairment	83.6 (79.4)		0.5
No Impairment	89.5 (92.3)		

Table 8. (continued ....)

Patient/Episode) Characteristic	Mean CRP (S.D.)	Correlation Coefficient (r)	Significance (P)
Mobility:			
Impairment	94.6 (81.0)		0.5
No Impairment	85.6 (86.2)		
Fever Source:			
Genitourinary	74.3 (71.4)		
Respiratory	98.3 (91.1)		
Skin/Soft Tissue	114.5 (96.6)		0.1
Gastrointestional	90.4 (66.0)		
Noninfectious	134.4 (130.8)		
Unknown	73.3 (82.6)		
Fever Duration		0.13	< 0.05

Figure 2. Acute CRP [mean (± SD)] by Age Group in Febrile Institutionalized Long Term Care Residents.

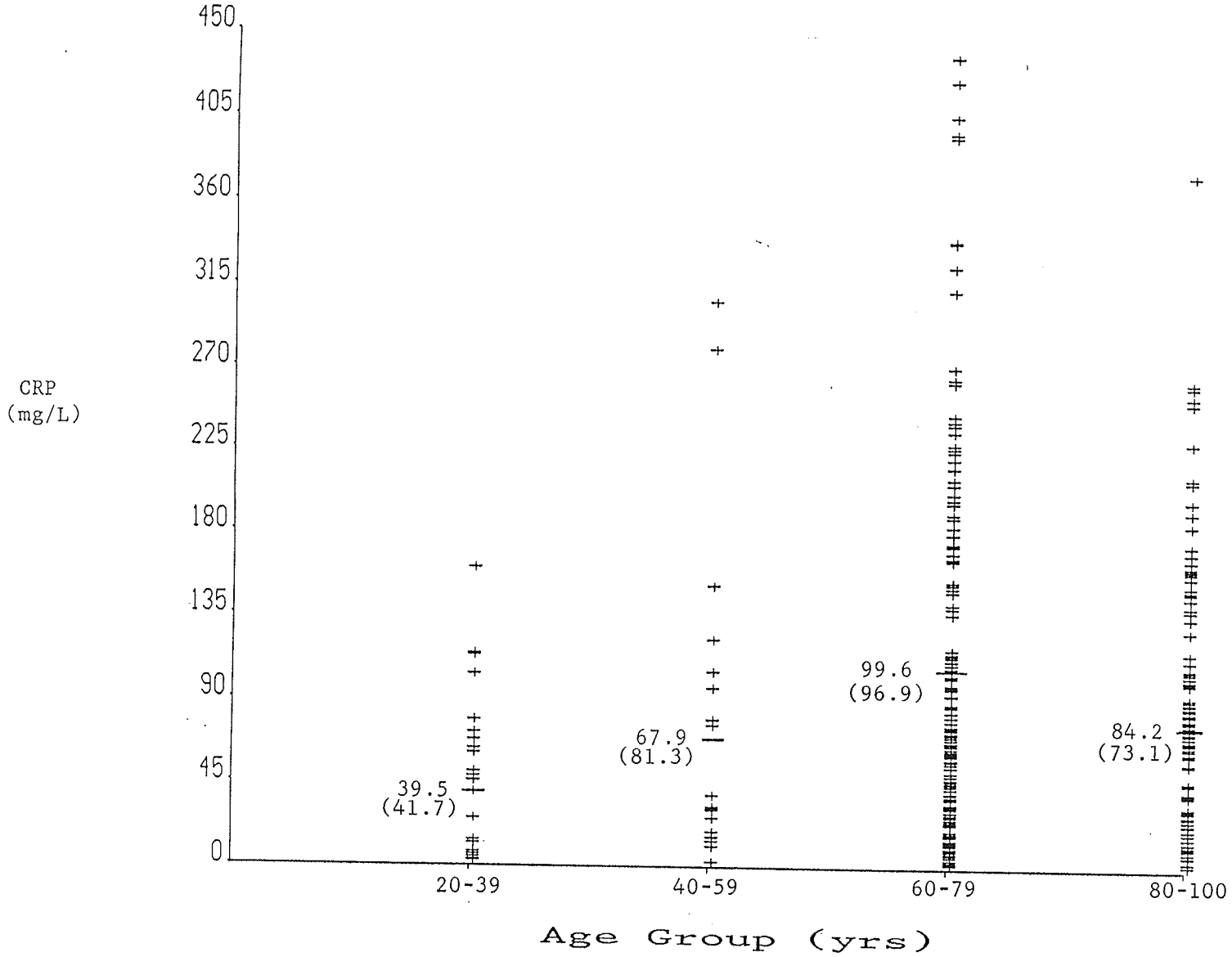
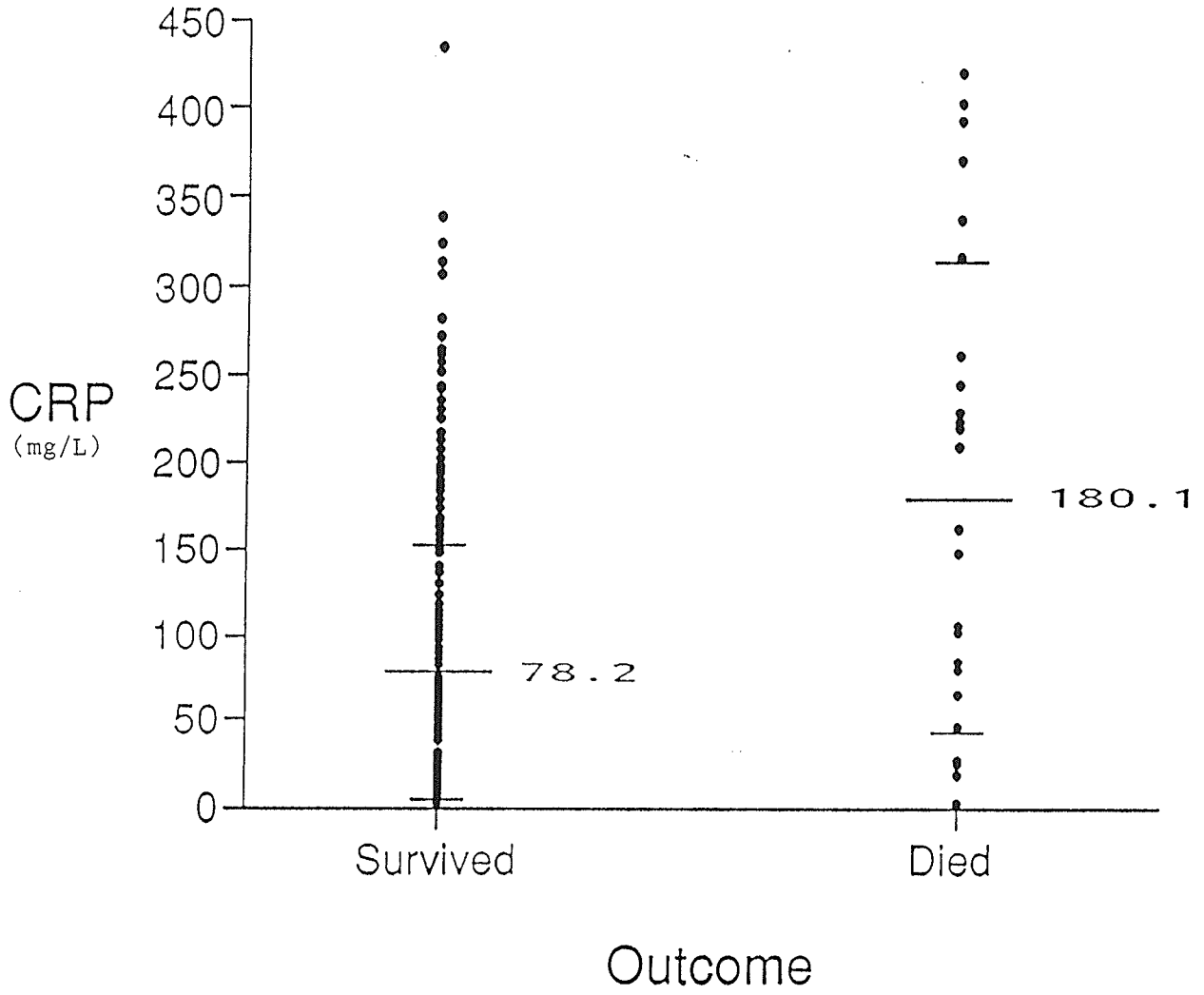


Figure 3. Acute CRP Levels in those who survived or died within four weeks of fever onset.



Death within 4 weeks of fever presentation occurred in 28 (15.85) of the 177 residents in whom CRP was analyzed. Compared to survivors, residents who died within 4 weeks of fever presentation were signficantly more likely to be male gender ($p = 0.002$), bowel incontinent ($p = 0.03$), and to have a longer duration of fever (3.5 ± 3.9 versus 9.6 ± 7.1 days, $p < 0.001$). Comparison of survivors and non-survivors demonstrated no significant difference in mean age, number of medications, number of type of underlying chronic disease, degree of mobility, mental status, urinary continence, presence of indwelling urinary catheter, or bacteriuria.

The mean acute CRP level was significantly higher in febrile episodes resulting in death within 4 weeks (Figure 3), compared to febrile episodes which did not result in death [(180.1 ($\pm$ 138.3 SD) versus 78.2 ($\pm$ 74.3 SD), $p < 0.001$)]. CRP did not vary significantly with infectious versus non-infectious causes of death ($p = 0.1$). Of the 28 episodes resulting in death within 4 weeks of fever onset, 18 (64%) were associated with a CRP $\geq$ 100 mg/L, compared to 91 (29%) of 319 episodes which did not result in death (OR = 4.51, 95% CI 1.89, 10.96, $p = 0.0002$). Although the negative predictive value for death within 4 weeks was 95.7% for a CRP < 100 mg/L, the positive predictive value of CRP $\geq$ 100 mg/L was only 16.5% in this population.

Analysis by multiple linear regression (Table 9) revealed age ($p = 0.004$) and outcome ($p = 0.013$) to be independently and significantly associated with CRP. The correlation of fever duration with CRP was no longer significant after controlling for outcome and age.

Table 9. Multiple Linear Regression of CRP (Dependent Variable)

Independent Variables	Full Model (r^2 = 0.06) Coefficient	p	Final Model (r^2 = 0.06) Coefficient	p
Age	0.01	0.27	0.01	0.004
Fever duration	0.02	0.14	0.01	0.125
Outcome	0.31	0.70	-0.29	0.013
Outcome x age	-0.01	0.54		
Outcome x fever duration	-0.01	0.39		

4.4 Bacteriuria

Significant bacteriuria was identified in initial urine cultures for 179 (50%) of 356 episodes where urine cultures were obtained and evaluable (Table 7) . Episodes without indwelling catheters and with urine specimens obtained prior to initiation of antimicrobial therapy were associated with bacteriuria in 55(51%) of 108 women and 60(34%) of 179 men. The prevalence of bacteriuria for women was similar at both institutions. At facility two, men were more frequently bacteriuric, with 59% of episodes in bacteriuric men compared to 21% at facility one ($p<0.001$).

The prevalence of bacteriuria in non-catheterized residents with urine specimens obtained prior to antimicrobial therapy varied with different clinical presentations of fever, from 28% of episodes of respiratory infection to 73% of febrile episodes due to gastrointestinal infection. By definition 100% of episodes due to urinary infection were associated with bacteriuria. The prevalence of bacteriuria was similar for episodes of respiratory source at the two facilities [9 (25%) of 36 episodes at facility one and 8 (33%) of 24 at facility two]. For episodes of unknown source, however, the prevalence of bacteriuria was 16 (31%) of 52 episodes at facility one and 30 (77%) of 39 episodes at facility two ($p<0.001$). The positive predictive value of bacteriuria for clinical genitourinary infection was only 11% (95% CI 4%,18%) for all patients; the individual positive predictive values for facilities 1 and 2 were 15% and 7% respectively. Evaluable urine specimens were obtained four weeks following the onset of fever in 323 episodes (Table 7). Antimicrobial therapy had been given for 252 (73%) of these episodes. For 67 (81%) of 73 episodes with antimicrobial susceptibility available, the infecting urinary pathogen pretherapy was susceptible to the antimicrobial prescribed. The prevalence of bacteriuria at 4 weeks for different sources of fever was similar to the prevalence at onset, with the exception of febrile

Figure 4. Acute (A) and convalescent (C) ELISA antibody titres (optical density) to E. coli MOMP (•-•) or to formalin inactivated whole cell (o-o) in febrile residents with clinical genitourinary infection.

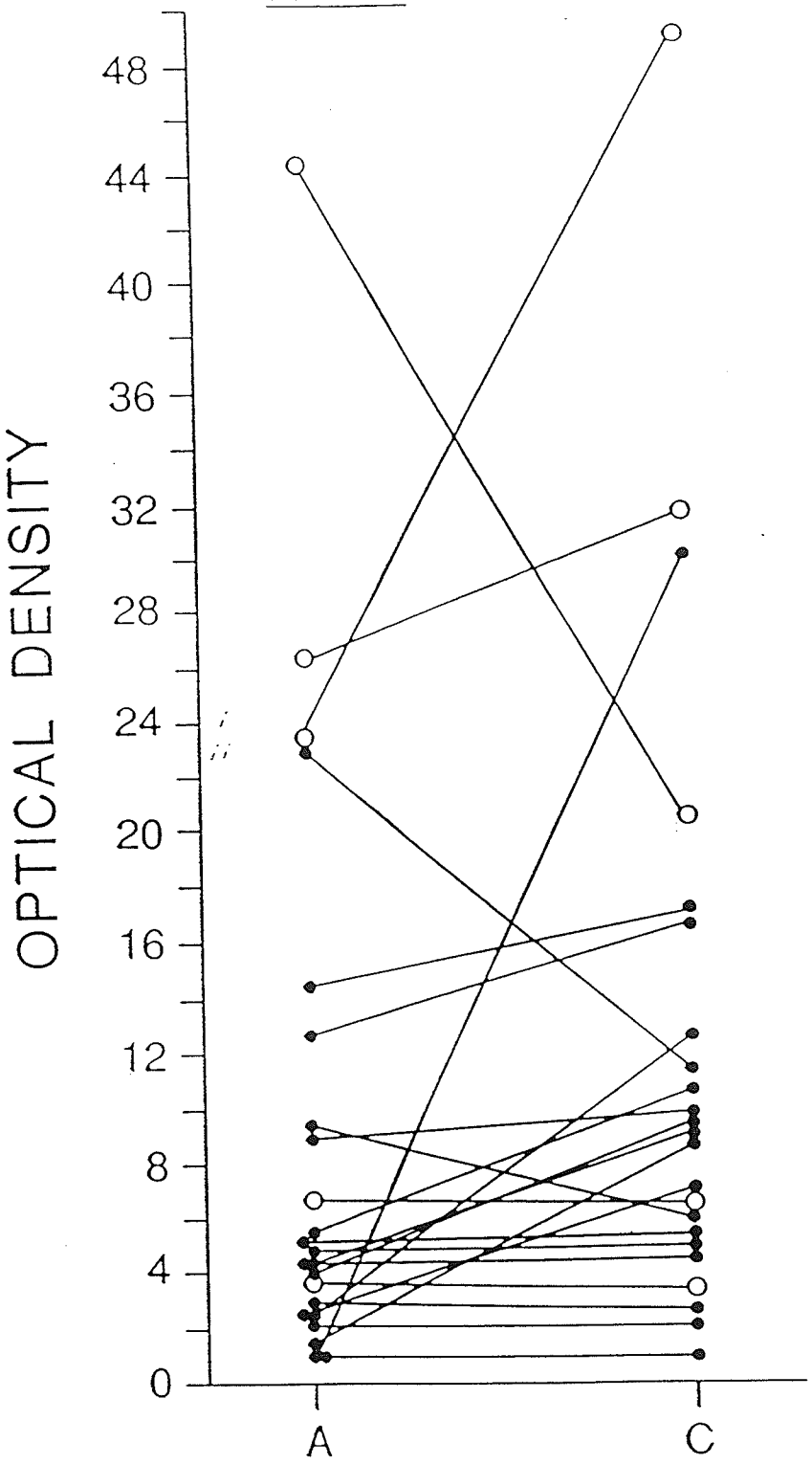
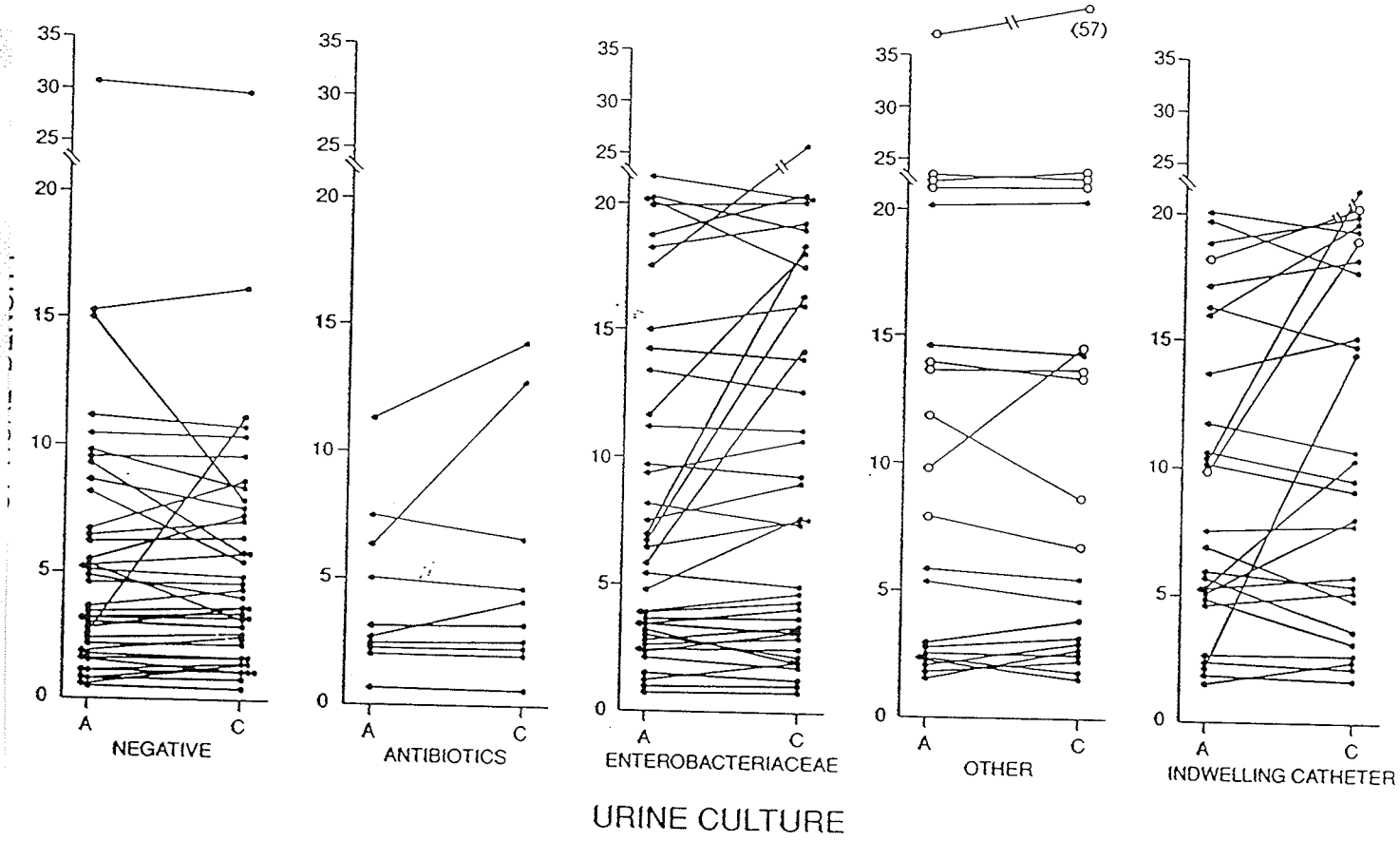


Figure 5. Acute (A) and convalescent (C) ELISA antibody titres (optical density) in residents with an unknown source of fever, according to initial urine culture, antibiotic therapy or catheter status.



episodes identified clinically as genitourinary infection; the prevalence of bacteriuria in these cases decreased significantly ($p = 0.017$).

4.5 Serologic evidence for invasive urinary infection

Acute and convalescent sera were available for 315 episodes (85% of those enrolled) in 162 subjects. There were 19 episodes in 17 subjects with an increase in MOMP antibody consistent with invasive urinary infection. Significant increases occurred in 7 (29%) of 24 episodes of genitourinary source with paired sera (Figure 4), 11 (8.3%) of 132 unknown (Figure 5), 0 of 12 cutaneous, 1 (4%) of 25 gastrointestinal infections, and 0 of 122 respiratory infections. Three additional episodes had antibody increases. Two clinical gastrointestinal episodes, one source with a negative urine culture and symptoms consistent with acute cholecystitis, and an episode with a right lower quadrant mass not investigated prior to death, were considered of non-urinary origin. One subject with antibody rise with two consecutive febrile episodes of unknown source had the second episode prior to obtaining convalescent sera for the first episode; the increase in titre seen during the first febrile episode was therefore judged to be spurious.

Three episodes had a significant antibody decline (ratio of ELISA optical density <0.58); one of these episodes was of unknown source with negative urine cultures and two were genitourinary episodes in residents with indwelling catheters. These latter two were considered to represent invasive urinary infection. High sustained antibody titres to MOMP (an initial titre greater than 10, and ratio between 0.58 and 1.46), were associated with bacteriuria, occurring in 4 (9.8%) of 41 episodes with negative cultures obtained prior to antimicrobial therapy, 5(17%) of 30 episodes with negative urine cultures obtained after initiation of potentially effective antibiotics and 42(31%) of 135 episodes with positive urine cultures ($p=0.0115$). The proportion of episodes with high sustained titres did not, however,

differ for genitourinary [2(13%) of 15], respiratory [26(19%) of 136], gastrointestinal [6(27%) of 22], skin [1(7.7%) of 13], or unknown fever source [27(23%) of 118] (p=0.51). These episodes with high sustained antibody titres were not considered consistent with acute invasive urinary infection.

Five (11%) of 47 fever episodes with non-enterobacteriaceae urinary infection had an antibody increase between acute and convalescent sera in the formalin-inactivated assay. The ratios of convalescent to acute antibody titres for these five ranged from 1.47 to 3.57. The mean ± SD of the ratio for the other 42 episodes was 1.02 ± 0.14. These five episodes in four subjects were associated with urinary infection with P. aeruginosa in four, and E. faecalis in one. The episodes had been clinically categorized as genitourinary (n=1), respiratory (n=1), and unknown (n = 3).

Antibody changes consistent with invasive urinary infection were therefore identified for 10 (43%) of 23 episodes identified clinically as genitourinary in origin, 14 (11%) of 132 unknown source episodes, 1 (4%) of 25 gastrointestinal and 1 (.8%) of 122 respiratory origin. Twelve (13%) of 95 episodes with positive urine cultures designated clinically as unknown source met serologic criteria for invasive urinary infection (Figure 5). Six (16%) of 38 unknown episodes in subjects with Enterobactereaceae bacteriuria had antibody changes consistent with invasive infection, compared to 1 (2.4%) of 42 episodes of respiratory, gastrointestinal, or skin origin (p = 0.04). Four (15%) of 27 unknown episodes in residents with indwelling catheters had serologic evidence of invasive infection compared with 0 of 22 catheterized residents with non-genitourinary sources identified (p=0.08). The positive predictive value of bacteriuria for serologic evidence of invasive urinary infection was 12% (22 of 184 episodes, 95% CI 7%, 17%). If only episodes identified clinically as genitourinary or unknown source are considered, the positive predictive value of bacteriuria

for serologic evidence of invasive urinary infection is 20% (20 of 107, 95% CI 12%, 27%).

Clinical characteristics of residents and episodes with and without serologic evidence of invasive urinary infection were compared. The 23 residents with serologic evidence of urinary infection had fewer chronic diseases [3.0±1.2 vs 3.7±1.4; p=0.02], less frequent diagnosis of cardiovascular disease [5(22%) vs 76(54%); p=0.007] or gastrointestinal disease [0 vs 29(21%); p=0.01], and more frequent past history of urinary infection [19(83%) vs 62(44%); p=0.001] compared with 140 residents without invasive urinary infection. When only episodes of unknown source are considered, subjects with invasive urinary infection had significantly fewer chronic diseases (2.9±1.0 vs 4.0±1.6; p=0.02) and more frequently a history of prior urinary infection (11 of 12 vs 23 of 45; p=0.01). There were no differences in age, sex, duration of institutionalization, presence of specific other chronic diseases including diabetes, presence of known structural genitourinary abnormalities, or history of previous genitourinary intervention, number of medications, or functional status.

4.6 Estimates of incidence of febrile urinary infection

Estimates of the proportional contribution of urinary infection to febrile morbidity, and of the incidence of invasive urinary infection, are summarized in Table 10. With either clinical or serologic criteria, less than 10% of episodes of fever were attributable to invasive urinary infection. The estimated incidence was similar for the two institutions for subjects without indwelling catheters. For facility one, invasive urinary infection occurred 18 times more frequently by clinical criteria, and 9.6 times more frequently by serologic criteria, in subjects with long term indwelling catheters.

The observation that no residents with indwelling catheters at facility two were identified with invasive urinary infection by either clinical or serologic criteria was unexpected, leading to a review of resident characteristics at the two institutions. At facility

Table 10. Proportion of episodes of fever estimated to be due to invasive urinary infection, and estimated rate of febrile invasive infection

	All Episodes		Indwelling catheter		No indwelling catheter	
	Number (%)	Rate/10,000*	Number (%)	Rate/10,000*	Number (%)	Rate/10,000*
Clinical diagnosis	26(6.9)	0.93	13(17)	6.39	13(4.3)	0.50
Facility one	20(8.9)	1.42	13(25)	9.90	7(3.6)	0.55
Facility two	6(4.1)	0.47	0	0	6(4.5)	0.49
Serologic criteria**:	26(8.2)	1.09	8/59(14)	4.63	18(7.0)	0.82
Facility one	15(8.2)	1.26	8/45(18)	7.09	7(5.0)	0.74
Facility two	11(8.4)	0.96	0	0	11(9.4)	1.04

* Incidence per 10,000 residents days. Adjusted for 24% of episodes not enrolled for specimen and data collection, 13% at facility one and 37% at facility two.

** Incidence for serologic criteria further adjusted for 16% of episodes at facility one and 11% at facility two without paired sera available.

two, 16 episodes of fever occurred in 6 subjects with indwelling catheters; 3 were female and the median age was 58.5 years (37-92 years). Twelve of these episodes occurred in 5 subjects with quadriplegia due to multiple sclerosis. At facility one, 53 episodes of fever occurred in 16 subjects with long term catheters; 13 were male and the median age was 76 years (45-93 years). Underlying illnesses necessitating institutional care and indwelling catheters in these subjects were cerebrovascular disease (n=7), dementia (n=2), cerebral hemorrhage (n=2), multiple sclerosis (n=2), and one each with hydrocephalus and myotonic dystrophy. Thus, residents with chronic indwelling catheters at the two facilities were substantially different populations, potentially explaining the institutional variation in invasive urinary infection in these subjects.

Some episodes clinically designated as of unknown origin were likely due to urinary infection. An alternate method of estimating the occurence of invasive urinary infection can be calculated based on the excess prevalence of bacteriuria in episodes of unknown source compared with non-genitourinary sources. The prevalence of bacteriuria for episodes identified in non-catheterized residents with specimen collection prior to antimicrobials was 51% for unknown source, compared with 36% for all other non-genitourinary episodes. This latter prevalence is similar to the 36% of bacteriuric subjects with influenza and 32% with radiologically documented pneumonia. The excess prevalence of bacteriuria in episodes of unknown source suggests 33 (11%) unknown episodes may be urinary infection, an incidence of 1.18/10,000 resident days. This excess prevalence of bacteriuria for unknown episodes was, however, only observed for facility two. In addition, if all febrile episodes of unknown source occurring in subjects with indwelling catheters were assumed to be due to invasive urinary infection, 33 (70%) of 70 episodes of fever in subjects with indwelling catheters (25.1/10,000 catheterized resident days) at facility one and 8 (44%) of 16 (9.5/10,000

catheterized resident days) at facility two would be attributable to invasive urinary infection.

5. DISCUSSION AND CONCLUSIONS

5.0 Fever in Residents of LTC Facilities

The results of this study confirm the clinical imprecision in the diagnosis of fever source in an institutionalized, predominantly elderly, population. The failure to identify a source for almost 50% of clinically significant episodes of fever, or to identify clinical variables associated with serologic evidence of urinary infection in episodes of unknown etiology, demonstrates the limitations of current diagnostic approaches in this population. Clinical criteria for the diagnosis of infection reflect observations drawn from studies of younger, less impaired populations. The validity of these criteria in the functionally impaired elderly with communication difficulties and multiple comorbidities is uncertain. The clinical criteria proposed for the elderly institutionalized population and used in this study have not been validated (98). The limitations in access to, and use of, diagnostic laboratory and radiologic facilities observed in this study and reported in other institutions (100, 101) contribute to the diagnostic imprecision. Additionally, certain microbiologic studies, such as sputum (38, 102) and urine cultures (6), when obtained, have limited utility in an elderly institutionalized population.

Methodologic issues which were raised in designing this study include possible biases introduced by the choice of study site, and the non-interventional nature of the study. The choice of two study sites allowed for the inclusion of two types of LTC facilities based on differing availability of physician and laboratory resources. The separate analyses by institution allows for comparisons of the two populations. The non-interventional study design, based on an analysis of observations and treatment initiated by health care workers

not associated with the study, increases the applicability of the results to institutions with similar populations and resources.

The identification of patients with fever provides one example of the dilemma for the researcher in choosing between an interventional study, which may allow for more accurate data collection, versus a non-interventional study which more closely reflects the "real life" situations of clinical care. "Routine" temperature monitoring is not usually performed at LTC facilities in Manitoba, and was not performed at the two institutions used in this study. Temperatures are obtained when an alteration in a resident's clinical status is noted. In accepting this standard of care, fever occurring in residents without evidence of clinical alteration would not have been identified in this study. The clinical relevance of such episodes of undetected fever, however, is questionable. Similarly, episodes of clinical deterioration due to infection, which may not have been associated with fever, were not identified in this study. The observations in this study, therefore, are valid only for febrile LTC residents with observed alteration of clinical status.

5.1 Urinary Tract Infection

The remarkable prevalence of bacteriuria in our populations is consistent with previous published studies (6). A high proportion of episodes of fever of any clinical source occurred in subjects with bacteriuria. Not only was bacteriuria common at onset of the fever, but intensive interval antimicrobial exposure had negligible impact on the prevalence of bacteriuria 4 weeks after onset of fever. Invasive urinary infection contributed to less than 10% of episodes of febrile morbidity. In addition, mortality attributable to urinary infection was not identified in these two large institutional populations during the two year study period. Thus, urinary infection had a limited contribution to febrile morbidity or mortality in these populations with a high prevalence and incidence of bacteriuria.

Only 43% of febrile episodes identified clinically as urinary infection were associated with serologic changes consistent with invasive urinary infection. The secondary immune response is relatively conserved in elderly subjects (103), and invasive urinary infection should be associated with an antibody rise to the infecting uropathogen (104). Compared to serology, the clinical criteria used in this study showed a sensitivity and specificity for invasive urinary infection of 38% and 92% respectively (positive and negative predictive values were 43% and 91%). Criteria such as as change in character of the urine, or increased confusion, are unreliable and insensitive. The positive predictive value of bacteriuria for invasive urinary infection was low using either clinical or serologic criteria. Thus, while a negative urine culture may exclude a urinary source for infection in this population, a positive urine culture cannot differentiate genitourinary from other sources of fever.

The diagnostic uncertainty in the evaluation of fever in the institutionalized elderly, and the high prevalence of bacteriuria in this population, results in the diagnosis of and treatment for invasive urinary infection when the urine culture is positive and no other source is apparent. Following this approach, approximately 30% of episodes of fever in our populations would be attributed to a urinary source. Despite the limited morbidity or mortality reported here and in previous studies, urinary infection is the most frequent diagnosis for which antimicrobials are prescribed in nursing homes (105-107). Some of this use reflects therapy for symptomatic infection without fever, but it seems likely substantial usage is for asymptomatic bacteriuria or for episodes of fever in bacteriuric residents presumed to have a urinary source.

The serologic criteria in this study allow an objective measure of the incidence of invasive genitourinary infection. An antibody increase to the MOMP antigen would also be

anticipated, however, with Enterobactereaceae infection at non-urinary sites, such as the episode noted in this study which was clinically compatible with acute cholecystitis. Antibody changes consistent with invasive urinary infection were not observed for episodes of skin and soft tissue infection and only one episode, with antibody rise to P. aeruginosa, was identified for episodes of respiratory source. This suggests that Enterobacteriaceae are infrequent causes of skin or lower respiratory infection in these two institutions, despite previously documented extensive oropharyngeal colonization with Enterobacteriaceae in facility one (102).

It has been previously reported that urinary infection in the elderly may present with non-classical symptoms such as nausea and vomiting (108). In this study only one febrile patient presenting with primary gastrointestinal symptoms and signs had serologic evidence consistent with invasive urinary infection. Thus invasive urinary infection presenting with predominant gastrointestinal manifestations occurred infrequently in our study. The majority of episodes of invasive urinary infection identified serologically were designated clinically as being of unknown source. Only 10% of all unknown episodes, however, and 16% of unknown episodes with Enterobactereaceae bacteriuria, were attributable to invasive urinary infection by serologic criteria. Resident or episode characteristics associated with these episodes were not identified.

In addition to the previously discussed methodologic difficulties in identifying LTC residents with fever, the definition of fever may be problematic in this population. Elderly subjects have a lower temperature response to an infectious stimulus than younger subjects (3). In addition, some elderly subjects have a low baseline temperature (109) and fever may not be identified because the measured temperature remains below "standard" definitions for fever, although elevated for the individual. There is, however, no accepted standard to

define fever in older populations. The temperature of 38° C used here in most episodes is consistent with current definitions for fever and with previous studies (99).

Limited previous reports describe the frequency and origin of fever in residents of long term care institutions. Warren et al (48) reported an incidence of fever of 1.7/100 patient days of long term catheterization and 0.6/100 patient days for non-catheterized female residents of two chronic care hospitals in Maryland, with rates of 1.1/100 catheterized days and 0.4/100 non-catheterized resident days for episodes of "possible urinary source". This frequency of fever and the proportion of episodes attributed to a urinary source are substantially higher than those reported in this study. The differences may reflect a more impaired resident population with a higher incidence of fever in the Maryland study, but are more likely explained by differences in definitions of, and surveillance for, temperature. Warren et al obtained temperatures at least once daily 5 days a week, whether or not the resident was clinically ill, and 37.7° C was defined as the upper limit of normal. Thus, clinically inapparent fever was more likely identified in that study.

Ouslander et al (110) reported the incidence of "symptomatic urinary tract infection", usually febrile, was 69/10,000 resident days for male nursing home residents with indwelling catheters. The definition of symptomatic infection in that study was broad and encompassed what we considered fever of unknown source. As not all their episodes were associated with fever, the reported rate may be comparable to the incidence of 25/10,000 resident days for catheterized residents reported in this study in our facility one, if all febrile episodes of unknown source in residents with long term indwelling catheters are considered to be due to urinary infection.

5.2 C-Reactive Protein

In the clinical evaluation of our patients, CRP was not helpful in distinguishing fever source. However, the observation of a significant linear increase in CRP in institutionalized individuals $\leq$ 80 years old who experienced febrile episodes, and a significant negative correlation in those over 80 years of age, was of considerable interest. The association was independent of illness severity as measured by fever duration and mortality.

Normal values for CRP in the elderly have not been established. Variations in CRP levels have been noted in normal individuals, and while some studies have noted small increases in mean CRP with age (90), others have not (91). Recent observations of altered regulation of cytokine production in the elderly may shed new light on the relationship between acute phase reactants and age. Age related increases in IL-6 production have been demonstrated in healthy elderly individuals as well as mice (111,112). In the aged mouse model, elevated IL-6 production has been prevented and/or reversed by dietary supplementation with dehydroepiandrosterone sulfate, an adrenal hormone whose production decreases with age in mice as well as humans (111). Thus it is possible that increases in CRP levels with age may reflect altered regulation of IL-6 production associated with declining adrenal function. However, the reversal of the trend in CRP levels in those over 80 years old which we observed in our study remains unexplained. Further elucidation of the pathophysiology of hepatocyte response to IL-6, including the mode of action of IL-6 on the hepatic receptor, regulation of receptor synthesis, and intracellular signal transduction mechanisms, may help in this regard.

The association between elevated CRP levels and mortality, independent of age, in this population of febrile elderly individuals supports the findings of Cox et al (9), and may also be related to elevated IL-6 levels in those with severe illness. In a recent study of

critically ill patients admitted to hospital with sepsis, IL-6 levels were significantly correlated with mortality (113). However the prognostic value of CRP for individual patients was limited in our study. Although an acute CRP < 100 mg/L had a high negative predictive value for mortality within four weeks of fever onset, the positive predictive value for CRP $\geq$ 100 mg/L was poor.

Although CRP was of limited usefulness as a laboratory tool, in the diagnostic and prognostic evaluation of our study population it may prove valuable as a marker for host immune response in prospective studies of patients with infection or inflammation. Future studies are indicated to determine the correlation, if any, of CRP with IL-6 in these patients. Normal mean CRP levels in healthy institutionalized and non-institutionalized elderly individuals should also be established. At the cellular level, clarification of the immunoregulation mechanisms of cytokine production in the young and old, as well as the pathophysiology of hepatocyte response, may aid in our understanding of the significance of CRP in host defense.

5.3 Febrile Urinary Infection: From Descriptive Epidemiology to Prevention Strategies

As the utilization of LTC facilities increases steadily in Canada (16), the attention of both care givers and researchers must focus on primary, secondary and tertiary prevention of morbidity and mortality in this population. Recent declines in coronary heart disease and cerebrovascular disease in the United States have suggested that many chronic diseases can be differentiated from the primary aging process, and may be at least partially preventable (114). Infections have been replaced by chronic diseases as the leading causes of death among the elderly in North America. However, infectious diseases remain important in terms of the burden of illness for which they are responsible, particularly in LTC facilities, and their "susceptibility" to prevention.

Advances in our understanding of the epidemiology of urinary tract infection in the elderly have aided the development of primary, secondary and tertiary prevention strategies. Avoidance of catheterization when possible, and strict attention to infection control procedures in those requiring short or long term catheterization, are important for the primary prevention of infection. Through a program for continence training in a geriatric facility, Nordquist and co-workers succeeded in removing catheters in 94% of 124 patients. Antibiotic costs were reduced by 90%, and savings were also noted in the costs for laundry and incontinence aids (115). In those with bacteriuria, antibiotic therapy prior to invasive urinary procedures may be used as a preventive strategy (116). When catherization is required the use of sterile technique for catheter insertion and the maintenance of closed drainage systems, are necessary for the prevention of catheter-associated infection in individuals and the control of transmission within facilities. The use of silver ion-coated catheters in women, although expensive, have been shown to decrease the incidence of catheter-associated infection (117). For women >65 years who undergo short term catheterization, antibiotic therapy after catheter removal can prevent infection, but the optimal duration of treatment is presently unknown (118). Other preventive strategies which attempt to interrrupt the attachment of bacteria to the periurethral area, and subsequent migration to the bladder and kidney have been less successful. Prospective randomized controlled trials have not shown any protective efficacy of bladder installation of antiseptic solutions, or topical antiseptics or antibiotics for urethral meatal cleansing (119-121).

Preventive strategies for urinary tract infection in the institutionalized elderly have focused on catheterization issues because of the prevalence of catheters in this population, and the success of education, infection control and targeted treatment programs in reducing the morbidity and mortality attributable to them. In the non-catheterized elderly population,

however, effective methods to prevent urinary tract colonization and infection have not been developed. For this population, attention has turned to the indications for antibiotic therapy in order to reduce unnecessary costs, prevent toxicity and the development of antimicrobial resistance, and improve the outcome of those for whom treatment is truly required.

In 1988-89, the total expenditure for antibiotics in Manitoba personal care homes was $114,059; 46.9% of all PCH residents received at least one antibiotic prescription during that period (122). Antibiotic costs in this population rose by 19% between 1987 and 1989. Although data regarding the indications for therapy are not available, it is possible that a proportion of these costs were due to unnecessary treatment of asymptomatic bacteriuria in otherwise well patients, or in those with fever mistakenly attributed to urinary tract infection. In the former group, treatment results not only in unnecessary expense, but also exposes the patient to the risks of drug toxicity, drug interactions and microbial resistance. In the latter group, antibiotic therapy may be unnecessary in those with fever due to undiagnosed viral infection, or inappropriate if the antibiotic prescribed for a presumed urinary infection is ineffective in treating the true source of infection. In a study of antibiotic therapy for 120 infections occuring over a three month period in two Oregon nursing homes, Jones et al found that 42% of prescriptions were inappropriate, and 9% were unjustified (107).

Date on the indications, type, duration and toxicity of antibiotic therapy in Manitoba personal care homes would assist in the development of programs to promote the rational use of these agents. Education strategies, pharmacy monitoring programs and the implementation of formularies have been helpful in improving the prescribing habits of physicians and reducing costs (122 - 124). Avoidance of unnecessary antibiotic therapy, and the prudent choice of medication when required, result in savings not only in drug costs but

also in personnel and supply costs. The development of new antibiotics such as ciprofloxacin and ceftriaxone, which achieve blood levels through oral or intramuscular administration routes that are comparable to those achieved through intravenous therapy, has allowed treatment of some residents in their own facility and thus prevented transfers to hospitals (125). However, in addition to the monetary savings suggested here, we must acknowledge the non-monetary benefits, such as patient satisfaction and improved sense of well-being, which may be achieved through rational antibiotic use which prevents drug toxicity and hospital transfers, and leads to more effective therapy. These "savings" have not been well studied in the medical literature, despite their importance to the patient as well as physician.

The rationalization of antibiotic therapy for the elderly patient with fever, however, is difficult given the diagnostic difficulties described in this study:

1. Despite the high prevalence of bacteriuria in the study population, less than 10% of febrile episodes were attributable, by clinical or serologic criteria, to genitourinary infection.
2. The source of fever remained unknown in 43% of febrile episodes.
3. Neither bacteriuria or CRP were predictive of fever source.
4. When compared to serology, the clinical criteria which were used in the study demonstrated poor sensitivity for invasive genitourinary infection. Alternatively, serology is not an available or useful laboratory tool for the evaluation of febrile patients in clinical, as opposed to research, settings.

What information from this study can assist with current clinical care of residents of LTC facilities? The observation that clinical presentations consistent with respiratory, gastrointestinal, or skin and soft tissue infections are unlikely to be atypical manifestations of invasive urinary infection, may prove to be useful in patient management. When clinical

evidence for these infections is present, obtaining urine cultures or treating bacteriuria is likely not appropriate. Forty-three percent of cases fulfilling the relatively restrictive clinical criteria for genitourinary infection used in this study will be attributable to invasive urinary infection, but only 11% of febrile episodes without localizing symptoms or signs of a source will be due to invasive urinary infection. For both clinicians and researchers involved in health care for the elderly, the following observations and recommendations can be made:

1. The present approach of empiric management of selected clinical presentations of fever, which is used in the majority of LTC facilities, requires prospective evaluation.
2. Such studies should also assess the optimal use of laboratory and radiologic investigation in these institutions.
3. Until such studies are done, it is unclear whether increased provision of "on site" technology and/or physician services would result in diminished morbidity and mortality in this patient population.
4. Antimicrobial management of infection in this population is hampered by the diagnostic uncertainties which have been described. Nevertheless, treatment protocols may be devised which maximize drug effectiveness and minimize associated monetary and non-monetary "costs".
5. While improvements in our ability to diagnose invasive urinary infection may promote the secondary prevention of disease progression, and tertiary prevention of morbidity and mortality, primary prevention must remain the cornerstone of our approach to this important condition in elderly LTC residents.

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