PROGNOSIS IN PYELONEPHRITIS : PROMISE OR PROGRESS?

Medical Grand Rounds
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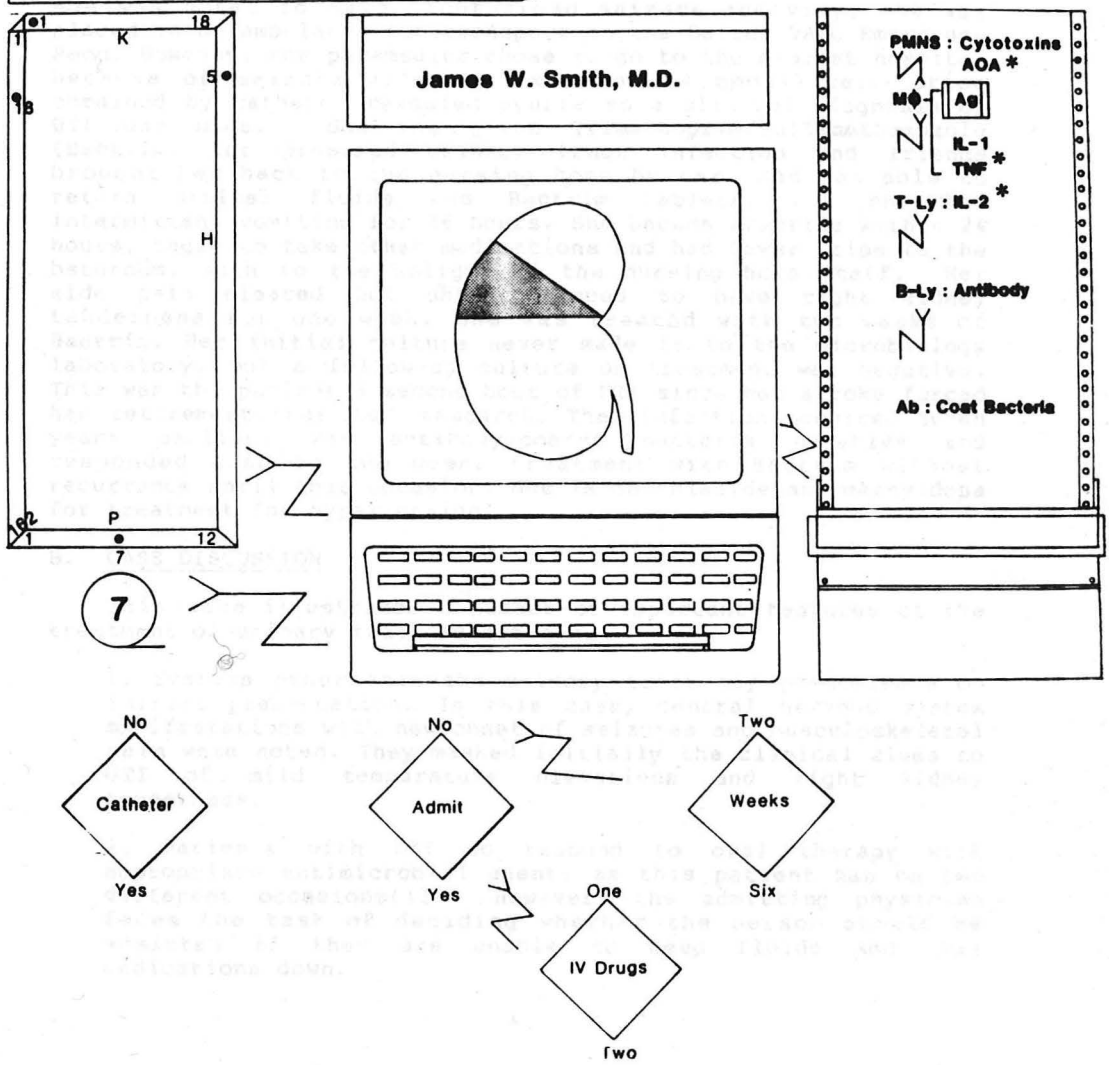


I. URINARY TRACT INFECTION (UTI)
OPUS 11

A. CASE HISTORY

M.J.A., a 73 year old white female veteran who was totally aphasic with a total right hemiparesis, complained of pain in the right neck and shoulder on July 31, 1987 to her nursing home attendants. The pain apparently radiated from her right flank area. Her temperature was noted to be 99.8°F, two degrees above her normal. The next morning she had nausea and vomiting and had to be taken more frequently to the bathroom for urination. When she was noted to have right-sided seizure activity, she was placed in an ambulance for transport to the Dallas VAMC Emergency Room. However, the paramedics chose to go to the nearest hospital because of seizure activity (x2) in the ambulance. Urine obtained by catheter revealed pyuria so a clinical diagnosis of UTI was made. She was given Trimethoprim/Sulfamethoxazole (Bactrim) for presumed urinary tract infection and friends brought her back to the nursing home by car. She was able to retain minimal fluids and Bactrim tablets, but she had intermittent vomiting for 36 hours. She became afebrile within 24 hours, began to take other medications and had fewer trips to the bathroom, much to the delight of the nursing home staff. Her side pain cleared but she continued to have right kidney tenderness for one week. She was treated with two weeks of Bactrim. Her initial culture never made it to the microbiology laboratory, but a follow-up culture on treatment was negative. This was the patient's second bout of UTI since her stroke forced her retirement from VAMC research. That infection occurred seven years earlier, was antibody-coated bacteria negative and responded also to two weeks treatment with Bactrim without recurrence until this occasion. She is on thiazide and methyldopa for treatment for hypertension.

B. CASE DISCUSSION

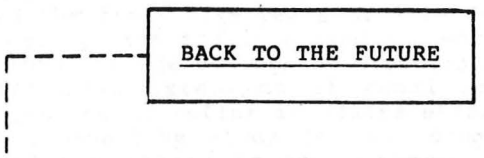
This case illustrates a number of important features of the treatment of urinary tract infections.

1. Systems other than the urinary tract may predominate on initial presentation. In this case, central nervous system manifestations with new onset of seizures and musculoskeletal pain were noted. They masked initially the clinical clues to UTI of mild temperature elevations and right kidney tenderness.

2. Patients with UTI do respond to oral therapy with appropriate antimicrobial agents as this patient has on two different occasions(1). However, the admitting physician faces the task of deciding whether the person should be admitted if they are unable to keep fluids and oral medications down.

3. Patients with recurrent urinary tract infection have slightly increased frequency of hypertension(2,3). This was a hot topic in the 60's, but now is no big deal- Treat both appropriately!

4. Private hospitals can screw up just as well as teaching hospitals in losing specimens, thus making assessment of microbiologic response difficult.



II. Course of Renal Infection

I wish initially to address questions concerning the future course for individuals with urinary tract infection, particularly those with presumed upper tract infection or pyelonephritis, before discussing treatment. Is the prognosis as grave as the textbooks tell us? It was once emphasized that pyelonephritis was progressive and could lead to renal failure and death, providing a bleak future for young females with recurrent urinary tract infection.

A. Do persons with UTI have progressive renal disease?

1. The frequency of renal disease resulting from pyelonephritis is exceedingly low. It has been estimated (since no large prospective study has been done) that the rate is less than 1 per 5,000 persons with bacteriuria per year(4). In fact, the frequency is even less than that. Renal failure has not been detected in women observed a number of decades after having had acute pyelonephritis in pregnancy or in elderly institutionalized men(2,5).

2. Previous reports of progressive renal failure in association with pyelonephritis probably included large numbers of patients who ingested large quantities of the analgesic phenacetin(3). This drug caused interstitial nephritis and papillary necrosis, leading to progressive renal disease with UTI in patients. It has not been available for over 2 decades in U.S., so comingling of cases of UTI with analgesic abuse is less common, plus more physicians are aware of analgesic toxicity (to be discussed in detail by Dr. Henrich soon). Renal failure in persons with recurrent UTI is uncommon; few of these patients now give a history of significant analgesic abuse (>1 kg. lifetime ingestion)(6)

3. Patients with the radiologic diagnosis of chronic pyelonephritis with decreasing glomerular filtration

rates (Table 1) have a higher frequency of hypertension, proteinuria, but a low frequency of bacteriuria and recurrent infections(6). In fact, the presence of radiologic findings on pyelograms in women with urinary tract infection in their 20's and 30's probably represents renal scarring from unrecognized infections in the first five years of life (discussed in 7). This results from the increased susceptibility of the growing kidney to the effects of microorganisms. Adult women do not have extension of renal scarring nor does the presence of reflux in adults effect management (6). In a prospective study in men, progressive renal disease did not relate to persistence of bacteriuria but to presence of other severe underlying disease including obstructive uropathy, renal calculi, or presence of severe hypertension(8).

Table 1.

PYELONEPHRITIS: PROGRESSIVE OR NOT?(6)

	STABLE GFR %	DECREASING GFR %
HYPERTENSION	32	64*
PROTEINURIA	41	86*
RECURRENT UTI	100*	36
INFECTIONS/YEAR	1.0*	0.5

*SIGNIFICANTLY GREATER AT P <0.01

4. Individuals with severe urinary tract infection during pregnancy do not have progressive renal disease symptoms, but rather were found decades later to have recurrent urinary tract infection (2,9). Hence, the major problem with renal infection is that the infection either persists if not treated or recurs at a later date if appropriately treated, as shown in our first case.

CONCLUSION: The prognosis is hopeful with low morbidity and essentially non-existent case fatalities.

B. Does an elderly patient or nursing home patient with bacteriuria have a grave prognosis?

1. Bacteriuria is frequent in the elderly (2-25 percent in men, 8-18 percent in women)(10-11).

a. The frequency is higher in functionally impaired nursing home residents, in those who are demented or confused, in patients with previous history of bacteriuria and in those who have either in-dwelling catheters or external catheters.(10-12)

b. In most studies, there has been no increase in case fatality rate in persons with bacteriuria. An initial study from Greece did show increased case fatality rates with bacteriuria, but recent reports from Canada, Sweden, and the U.S. have failed to confirm this finding (11-13). In one study, men with bacteriuria with cancer had a higher case fatality rate, but when controlled for malignancy, there was no associated case fatality (11).

c. Bacteriuria is highly variable in time with a high rate of turnover of bacterial biotypes and species (10). Persistence of same biotype is more likely if a person has renal bacteriuria but also relates to functional status, (increased in those incontinent of bladder and bowel) (10,12).

d. As institionalized residents deteriorate functionally, many (>70%) became bacteriuric (12). However, febrile episodes attributable to urinary tract infection were infrequent, accounting for 7% all febrile episodes (unlike our experience with some nursing home patients) (5). Pneumonia, skin and soft tissue infections were far more significant causes of fever. Few deaths were directly attributable to urinary infection (12).

e. Treatment of asymptomatic persons is of minimal value. Frequency of infectious episodes per resident per year was not significantly different if antimicrobial therapy had been administered (5).

CONCLUSION: Although bacteriuria is frequent in the elderly, it does not contribute to significant morbidity and mortality in recent studies (Do these studies reflect observer influence on care of patients?).

C. Does presence of an in-dwelling urinary catheter predispose the person to greater complications or is there a "safer" catheter?

1. Case fatality rates do appear to be higher in catheterized patients. This is particularly true for those hospitalized who acquire urinary infection following insertion of in-dwelling catheters(14). In recent surveys of NHCU and Medical Service at the DVAMC, nosocomial urinary tract infection accounted for 25% and 37% of all infections (prevalence of infection of 4 and 2% respectively), was mainly inpatients with condom catheters but was not a significant cause of morbidity or case fatality.

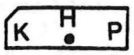
2. The frequency of febrile episodes due to infection in both women and men ranges from approximately 1 per 100 patient days to 1 per 1800 patient days (15,16). The former rate is actually comparable to the rate of such episodes in spinal cord injury patients upon initiating intermittent catheterization (17). However, the severity of infections appears to be lower in intermittently catheterized than in patients with urinary catheters (16,17). I recommend that patients with neurogenic bladder be trained to do intermittent catheterization. Families can be taught to do this procedure for bedfast patients if they have minimal obstruction. The low rate was achieved in DVAMC patients at home who were followed by Hospital Based Home Care (HBHC) Nurses and evaluated by the Infection Control Coordinators. Families can also be trained by nurses to maintain fluids and report early any problems with in-dwelling catheters (15).

3. Most febrile events in catheterized patients are self-limited and patients recover without antimicrobial therapy. These episodes were more commonly associated with nasogastric intubation (16). This could relate to the difficulty in maintaining satisfactory intake and urinary output in those who are intubated, although it also could reflect non-urinary tract causes of fever, such as aspiration pneumonia. Febrile episodes were infrequently associated with catheter obstruction, but catheter obstruction increased the frequency of fever eight-fold (16). Certainly, this is a predisposing event in catheterized patients admitted for possible urosepsis at the DVAMC.

4. Bacteremia and death were significantly associated with temperatures exceeding 38.8°C (102°F) (16). Conversely, febrile events were not associated with catheter obstruction, age, or the presence of decubiti.

CONCLUSION: Safer urinary catheters, like safer sex, are not totally that, but prevention of UTI with former is better if hospital-based home care is provided by DVAMC.

III. WHAT ACCOUNTS FOR LOCALIZATION AND PERSISTENCE OF INFECTION?



"Your zeal is more for experiments than truth, thus you will turn experiments into truths of your own devising." Page 194, Hawksmoor, P. Ackroyd.

Table 2.

O: K: H TYPES FOUND IN PATIENTS WITH PYELONEPHRITIS (18,19)

O	K	H	F(Pili)
1	1	7	11
4	5	5	--
6	2	1	7(P)
7	1	1	--
13	13	1	--
16	K	6	12
18	1 or 5	--	8

A. Renal infection is caused by particular serotypes of E. coli (Table 2) which more frequently have K antigen (capsule), are smooth strains of certain specific O types which produce larger quantities of lipopolysaccharide (LPS) and have fimbriae or pili of certain types (18,19). It has been postulated recently that P. pili (type 7 or mannose-resistant pili), are found on E. coli responsible for upper tract infection(20,21). These strains contain Gal-Gal (A*- D Gal(1-4)-*B-D Gal) adhesin which preferentially binds to globoseries glycolipids on human epithelial cells. Unfortunantly, (Lomberg and Svanborg-Eden in Goteborg, Sweden and O'Hanley and Schoolnik at the Palo Alto VAMC) used clinical criteria as the localizing test for renal infection in their studies. However, clinical criteria cannot be used to categorize all patients with presumed pyelonephritis, since these criteria are notoriously unreliable (7). Rather a critically defined test as the antibody-coated bacteria test must be used(22). Hence, it is uncertain how many of the cases in these reports truly had renal infection; this makes their studies of

"pyelonephrogenic" bacteria somewhat invalid. More recently, Lomberg of Goteberg, Sweden, examined strains from children with renal scarring and Stamm's group in Seattle studied adult women with UTI and urosepsis; only a slight majority (Table 3) had P pili(23,24). Furthermore, the Seattle group formed that persons with upper UTI (positive ACB) with P pili strains were likely to have clinical symptoms of pyelonephritis (60%) (Table 4); conversely, patients with upper UTI with type 1 pili infrequently had symptoms of pyelonephritis (33%) (significant P <0.05)(23). In our own studies of the E. coli from men with upper UTI (positive ACB and persistant bacteriuria), 50% had P or mannose-resistant pili and adherence to kidney tissue whereas another 50% had type 1 pili with mannose-susceptible agglutination and adherence to kidney tissue (25,26). Hydrophobicity of the organism appeared to be a greater determinant of adherence in our studies than the type of pili but hypertonicity and acidic conditions (similar to renal medulla) inhibited adherence (Table 5)(26,27).

Table 3.

FREQUENCY OF P. PILI IN UPPER UTI

	UTI %	CONTROL %
LOMBERG - CH.*	68	25
STAMM AD/F	47	17
SMITH AD/M	50	33
STAMM UROSEPSIS	62	--
LOMBERG CH W/SCARS	59	27

* CLINICAL CRITERIA ONLY

Table 4.

CLINICAL PRESENTATIONS FOR PATIENTS WITH ACB+ BY PILI TYPE (23)

CLINICAL PRESENTATION	TYPE OF PILI P	TYPE 1
PYELONEPHRITIS	8	10
CYSTITIS	5	20

Table 5.

ADHERENCE TO KIDNEY

P PILI AND TYPE 1 ADHERE EQUALLY WELL

HYDROPHOBICITY CRITICAL

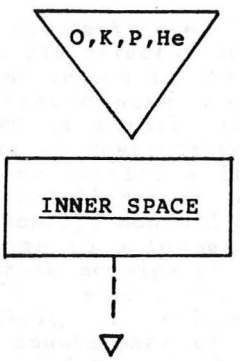
HYPERTONICITY AND ACID INHIBIT,

SO VERY DIFFICULT TO INITIATE

RENAL INFECTION

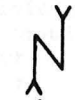
P STRAINS CAUSE MORE RENAL SYMPTOMS

CONCLUSION: Invasion of the kidney does not relate to a single bacterial factor, but rather to colinked ones, including surface factors (hydrophobic conditions and pili) which enhance adherence to kidney epithelial cells, presence of capsule (K types 1-18 in about 50%) which prevent phagocytosis initially, LPS to induce an inflammatory response and stimulate leukocytes and macrophages, and a hemolysin (He) which may injure tissue. Flagella (H) does not appear to be an important factor(18,21,26).



B. A significant cellular response begins promptly upon initiation of infection with the early entrance of phagocytes (within 24 hours).

1. Polymorphonuclear leukocytes (PMNs):



a) necrosis
b) Acyloxyacyl (AOA) hydrolase of LPS *

2. Macrophage (MØ):

a) Process and present antigen to T-lymphocyte

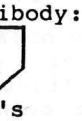
b) produce IL-1 and IL-1 inhibitors,

c) TNF (Cachectin)*

T-Lymphocytes — produce IL-2,*

B-lymphocytes: — antibody synthesis surface release

Antibody: — Coat Bacteria
Enhanced phagocytosis
Decreased inflammation



PMN's

*Theoretical, not proven, highly likely, will await next research study period.

Polymorphonuclear leukocytes (PMNs) at a local inflammatory site have multiple effects. Braude has estimated that up to 90% of the destruction in the pyelonephritic kidney is due to PMN's, although some credence must be given to the effects of LPS as a toxin (26). Rather than seeing the effect of PMNs as destructive, one could compare them to the Park Service setting a fire intentionally to localize an out-of-control "fire" or infection in a specific region of kidney. Recently, Munford and Hall have shown that PMNs and macrophages to a lesser extent may "detoxify" LPS, through an enzyme acyoxyacyl (AOA) hydrolase. Removal of fatty acids from a side chain of the lipid A moiety renders LPS less likely to induce a Schwartzman phenomenon (experimental counterpart of acute signs of inflammation) (30). This detoxification of LPS could operate locally in the kidney, but it is not established as yet. Macrophage activity is prominent early with 10-100 fold increase in macrophages within a day of infection (31). These macrophages are active: they more readily engulf and kill the infecting organism than do normal macrophages, which ingest very few E. coli and do not kill bacteria after ingestion(32). This "activation" may result from activation of complement receptors on the surface of the macrophage (32). Macrophages (MØ) are also doing their usual business by presenting antigen to T-lymphocytes,

(demonstrated in experimental pyelonephritis both with a non-specific antigen as ovalbumin and pili, a protein antigen from the infecting organism). MØ likely also process complex antigens such as LPS and lipoproteins into immunogenic packets. As a consequence, second signals are given, resulting in release of factors such as IL-1 (leukocytic pyrogen) and TNF (tissue necrosis factor or cachectin). The former has been substantiated to be produced by MØ locally in experimental pyelonephritis. (Smith). IL-1 may operate not only as a pyrogen but also as a stimulant which leads to an expansion of immune populations, (Lipsky GR 1986). IL-1 also has been shown to neutralize the activity of LPS (33). Theoretically, it could even neutralize or have negative feedback on LPS generated by bacteria. In addition, inhibitors of IL-1 are also produced locally by macrophages with experimental pyelonephritis (Smith), much as inhibitors have been noted in synovial fluid mononuclear cells from patients with active rheumatoid arthritis (34). This inhibitor activity could account for the diminished responsiveness of T-lymphocytes to non-specific mitigens in the kidney as has been noted in synovial fluid (34-36). This has been interpreted by others (Miller of Auckland, New Zealand) as evidence for suppression of cellular activity in pyelonephritis (37). However, in my laboratory, these macrophages suppress non-specific mitogenic activities of T-lymphocytes but not the response to specific antigens (LPS and lipoproteins from the outer membrane of bacteria) (35-40). There is, furthermore, a rapid expansion in the population of B-lymphocytes, ultimately leading to lymphoid follicles where synthesis and release of immunoglobulin, and antibody principally IgG occurs (35). This antibody "coats" bacteria by day 10 of infection and likely leads to decreased signs of inflammation (41). Miller has shown that ablation of cellular response in experimental animals (polymorphonuclear leukocytes, macrophages, T-lymphocytes, and B-lymphocytes) systemically did not effect the course of pyelonephritis nor was the course different in T-lymphocyte deficient strains of rats (42). However, recently, he has shown that cyclosporin A does materially alter the course of infection with a substantial increase in abscess formation and quantity of bacteria (42). Hence, the important pathophysiologic effects of immune cells may be the mediators they release rather than any direct effect of the cells themselves. It is also likely that macrophage activity leads to release of TNF or cachectin in experimental pyelonephritis (43). LPS is a potent inducer of TNF by macrophages so the factor should be produced in the infected kidney (44). (When case #1 worked as a research laboratory technician at the VA, she chose the animals for experiments on immunity in pyelonephritis by the amount of weight that the rabbits had lost over the first two weeks of infection.) Fortunately, most humans come to medical management before weight loss is a critical

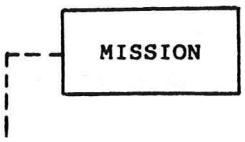
factor, so pyelonephritis is not considered in the differential diagnosis of patients with weight loss along with malignancy and tuberculosis.

KIDNEY SEGMENT

C. Anatomic factors within the kidney operate to localize or halt the spread of the infection to segmental areas (see screen on cover page). Hence, bacteria spread from the medulla toward the cortex, resulting in cortical areas of acute inflammation which ultimately form the pitting the cortical surface, the hallmark pathologically of chronic pyelonephritis. If significant urethral obstruction is present (or bilateral ureteral dilatation from urethral or prostatic obstruction), then the infection spreads to other segments of the kidney as can be reproduced in hematogenous experimental pyelonephritis following transient ureteral obstruction (28). Frequently, local obstruction in a segment leads to intrarenal collections of inflammatory pockets which are slow to heal.

CONCLUSION: An amazing assortment of cellular components are operative at the local site in pyelonephritis. They are not quite adequate to the task generally, so they don't eradicate infection, but rather slow the process to preserve renal function.

D. Our studies have shown that the course of experimental pyelonephritis, just as the clinical course in men with upper tract infection and a significant proportion of women with upper tract infection, is typically characterized by persistence of the infection with frequent relapses if treated. In humans, as stated above, clinical symptoms are unreliable in predicting if infections are kidney in origin (7,23). This was a spur for Jones to utilize the antibody-coated bacteria test (ACB) for delineation of prognosis in pyelonephritis. Men with positive tests are more likely to relapse after short course (2 weeks of therapy) (22). Unfortunately, he also published a single case report of a case of prostatitis with a positive ACB test. This has been widely circulated as a reason to consider the test useless in men [an example of the amazing influence of a single case report in NEJM- but, "so it goes" says Vonnegut]. Later studies validated the test and showed that virtually all men with recurrent infection had upper UTI (22). However, the ACB test is not generally available, so therapy needs to be given based on educated guess of renal infection, otherwise the clinician can recognize renal infection if the patient has a recurrence of infection within 1 month after discontinuation of treatment.(22)



IV. WHAT IS THE TREATMENT OF A PERSON WITH UPPER UTI?

A. If the patient is mildly or moderately symptomatic, able to retain fluids and take medications: the patient can be treated with certain oral antibiotics (TMP/SMX, Norfloxacin) for a two week period of time with the expectation of good clinical response.

APPROACH:

(1) Urine culture and susceptibility tests (5 out of 24 or 20% of patients admitted at DVAMC 6/15-8/15 with possible urosepsis failed to have a urine culture make it to lab).

(2) Large volume of fluids to maintain flow of 1500 cc of urine a day, it is not necessary to specify fluids such as cranberry juice.

(3) Treat with Trimethoprim/ Sulfamethoxazole (TMP/SMX), two BID, or if allergic to this drug or has known resistance, then Norfloxacin 400 mg BID or ciprofloxacin (when released) 750 q BID. Recent studies have indicated two weeks of TMP/SMX is significantly better than ampicillin even when organism is susceptible.(1) (Table 6) A two week course was as effective in treatment of presumed upper urinary tract infection in women as was 6 weeks and had fewer side effects. Ampicillin or oral cephalosporins have lower cure rates in patients likely to have upper tract infection (45). This low clinical efficacy likely relates to low medullary concentration due to active secretion of drugs by the renal tubule.(46)

Table 6.

ACUTE RENAL INFECTION - WOMEN (1)

ACB+ IN 2/3: COURSE SAME + OR -

CURE RATE -	2 WEEKS %	6 WEEKS %
TMP/SMX	90	83
AMPICILLIN 2G.	35	60
SIDE EFFECTS (T/S)	17	20+

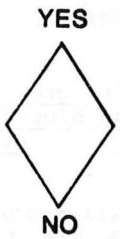
Only 60% of E. coli isolated from urine at the DVAMC are susceptible (Table 6) to ampicillin and only slightly higher rates are seen with 1st generation cephalosporins. Norfloxacin is an acceptable drug, and in my limited experience, it is effective when given for two to three weeks. Ciprofloxacin when approved could be is particularly useful for organisms resistant to all other oral antimicrobial agents.(47) However, it must be remembered that concommitant antacids may reduce serum levels.(47) At DVAMC, 100% of small sample of urine isolates are susceptible to Norfloxacin. Relapses do occur in 40% but usually respond to repeat 3 week courses. Remember with any drug, the cure rate is determined by freedom from bacteriuria at 4-6 weeks after therapy so that is the important followup time. Not all data on Rx of UTI given by drug representatives is acceptable since recent evaluations are based upon followup at 5-9 days (presently permitted by FDA!)

An alternative approach in the emergency room, particulary in febrile patient, would be to give a single treatment of an aminoglycoside IM, such as gentamicin and then send the patient home on the oral drug. This is perfectly acceptable and safe, with low renal toxicity, yet gives persistent intrarenal levels of gentamicin so home treatment with an oral agent might be more acceptable.

(4) Have the patient observe closely temperature and symptoms at home. If neither respond in 2 days, instruct the patient to call back since most upper and even upper urinary tract infections should respond within 48 hours with improvement in symptoms. Drug susceptibilities can be checked

although many patients will improve even with drugs that are not susceptible by usual testing. This relates to the ability of antimicrobial agents to achieve inhibitory concentrations in the urine, especially after obstruction is relieved and fluids are administered. Ultimate recovery from upper UTI with microbiologic cure relates to success in achieving intrarenal levels of appropriate antimicrobial agents.

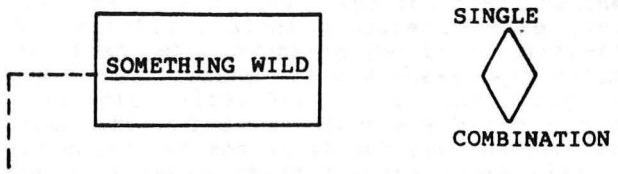
B. Patients should be admitted if:



1) central nervous system changes are present. Meningitis is not common but many patients with urinary tract infection, particularly the elderly, develop mental status changes. They become more difficult to manage and this may interfere with the intake of adequate quantities of fluid and of oral drugs. Conversely, decreased renal output and volume depletion are frequent with UTI; if the patient has underlying CNS disease, then they develop mental status changes.

2) unable to keep medications or fluids down due to nausea and vomiting. With pyelonephritis, these symptoms are quite commonplace. Unless home nursing care with administration of drugs can be arranged promptly, then patients may need few days in the hospital until symptoms ameliorate. If patient develops nausea and vomiting with administered drug, or fail to respond after initiation of therapy, may have to be admitted later.

3) catheterized patient has a temperature > 38.8°C or 102°F. They have increased likelihood of case fatalities and complications in this situation (16). They also should be observed until catheter obstruction is relieved and other symptoms subside. Although bacteremia is more common with high temperatures, it alone is not a significant predictor of outcome in uncatheterized patients unless hypotension or decreased urinary output due to renal failure is present. Up to 40% of persons with urinary tract infection had bacteremia in Bo Sander's study and the course is the same as in those with fever without bacteremia.(48)



C. Therapy for patients admitted to hospital with sepsis and urinary tract infection should be combination therapy of a drug with an aminoglycoside.(46)

1) Antimicrobial therapy is best accomplished with the combination of two drugs that are effective against the organism. (Table 7) In the past, the traditional combination has been IV ampicillin with an aminoglycoside (ampicillin because MIC's are fourfold greater for GNB than with pencillin G just as with enterococci or hemophilus). However, presently fewer than 2/3 of patients with community-acquired UTI have organisms susceptible to ampicillin.(1, Table 7) Furthermore, only 1/2 of VAMC patients admitted with UTI had organisms susceptible to ampicillin. Consequently, other combinations proposed by Bergeron could be used such as TMP/SMX or cephalosporins in combination with aminoglycoside (46). I prefer to use combinations in which either is likely to have 80% chance of being effective.(Table 7) For E. coli, TMP/SMX with gentamicin would be effective. If previously hospitalized with UTI, has catheter or in nursing home (so more likely to have Pseudomonas), may need piperacillin or cefotaxine with gentamicin.

Table 7.

% SUSCEPTIBLE OF URINE ISOLATES DVAMC, JULY, 1987

	AMPICILLIN	CEPHALOTHIN	TMP/SMX	CEFOTAXINE	TICAR	PIPERCILLIN	GENTAMICIN	TOBRAMYCIN	AMI
E. coli	59	78	91	100	66	66	97	97	100
All Entero-bacteriae	43	67	74	98	52	72	86	86	100
Pseudomonas	--	0	7	92	96	96	72	72	96
All Grm Neg	32	50	62	95	63	77	82	82	99

Rationale: Bergeron found that 3 days of gentamicin in combination with another drug, then 7 days of the other drug alone, (if organisms were susceptible), resulted in 100% cure of the infection.(49) Neither TMP/SMX or ampicillin alone produced a cure (49). Three days of an aminoglycoside led to persistently high levels in the kidney for > 2 weeks with mildly enhanced toxicity (49,50). If the drug is discontinued after 3 days, then one can diminish nephrotoxic potential and still achieve benefit from the unique intrarenal pharmacologic properties of the aminoglycoside. If the patient responds and becomes promptly afebrile within 48-72 hours, then they can be switched from parenteral to the appropriate oral drug (TMP/SMX, Norfloxacin) based on susceptibility testing. The only single drugs I consider effective for upper UTI are imipenim (Primaxine) 500 mg q 6 hr ($40) or aztreonam (Azactam) 2 gm q 12 hr ($38/d) given parenterally for 7-10 days; although insufficient followup has been done to be certain of their efficiacy. At the DVAMC, 97% of urine isolates are susceptible to Imipenim and 72% to Aztreonam. Ticarcillin and piperacillin are more effective in vitro than ampicillin but can't be used alone for renal infections. I have no experience with clavulanic acid combinations (timentin), but this agent has been no more effective than ampicillin or ticarcillin- all are associated with high relapse rates (48). I would not use the agent alone, and ticarcillin costs less (Table 8).

Table 8.

PARENTERAL ANTIMICROBIAL AGENTS
FOR UPPER UTI OR UROSEPSIS

DRUG COMBINE WITH AG	DOSAGE	$ DAILY COST $ COST-DVAMC	BENEFIT	RISK
AMPICILLIN	12 G	$25	SAFE, STANDARD	RASH, DIARRHEA, 1/3 RESISTANT
TMP/SMX	480 MG	$42	EFFECTIVE, MODERATELY SAFE	NOT AS EFFECTIVE FOR OTHER THAN E. COLI, PHLEBITIS
CEFAZOLIN	6 G	$23	SAFE	INEFFECTIVE ALONE
CEFOTAXINE	8-12 G	$70	SAFE	EXPENSIVE
TICARCILLIN	24 G	$47	SAFE	REDUCE DOSE IF RENAL FAILURE; PLATELET, POTASSIUM LOSS
TIMENTIN		$60	--	NO BETTER THAN TICARCILLIN SAME SIDE EFFECT, EXPENSIVE
AMINOGLYCOSIDE	5-15 MG/KG	$10-35	EFFECTIVE	NEPHROTOXICITY, IF MORE THAN 7 DAYS
SINGLE DRUG IMIPENIM	2 G	$40	EFFECTIVE, HIGH SUSCEPTIBILTY	INCREASED COST- TOXICITY IN RENAL FAILURE
AZTREONAM	4 G	$38	EFFECTIVE IF SUSCEPTIBLE	RESISTANCE > 20%; NOT GOOD EMPIRIC THERAPY

2. If the patient fails to respond clinically within 3-4 days, then investigations should be initiated for evidence of obstruction, intra-renal inflammation (nephronia) or renal abscess. Perinephric abscess formation occurs more often in the elderly, paraplegic and diabetic patient (5). Generally the patients will have had symptoms greater than 5 days prior to coming into the hospital, and will continue to have fever after antimicrobial agents are began. A more common entity was termed by radiologists focal bacterial nephritis or "nephronia", since it is analogous to lobar pneumonia (52). It refers to a renal mass causing local infection without liquifaction. Patients with nephronia continue to have fever for 11 days compared to the usual 2-3 days with pyelonephritis (53). It can usually be detected with ultrasonography, which shows a sonolucent area with disruption of the normal cortical-medullary architecture. Ultrasound is usually normal in standard pyelonephritis but with nephronia, an area of decreased echogenicity is noted within irregular walls (53). Computed tomography (CT) is highly sensitive in pyelonephritis with hypodense areas or localized renal enlargement on contrast study. In contrast with nephronia, non-contrast studies reveal round areas of decreased density with peripheral rim enhancement with contrast (53). Gallium scan also has been used to locate abscess in or about the kidney but it is somewhat less specific since other lesions may present with such abnormalities (54). Patients with intra-renal abscess or nephronia can be treated successfully with antibiotics alone (55). Again, combination therapy with appropriate beta-lactam or TMP/SMX with aminoglycoside should be used and treatment continued for at least 2 weeks. If the patient responds and becomes afebrile, then an oral antibiotic could be given for an additional 3 weeks, or combination therapy given for a total of 3 weeks. If the patient continues to have fever beyond 2 weeks with appropriate combination therapy, then followup scan should be obtained and if intra-renal collections remain present, then it is reasonable to consider CT directed aspiration or surgical exploration by urologist.

CASE NO. 2:

J.B. was a 62 yr. old white male with a long history of ethanol abuse who was admitted to a referral hospital in May 1987

with left lower extremity cellulitis. He had active liver disease and a left pleural effusion so he was initially treated with cefazolin and metronidazole parentally. Blood cultures were reported positive for Klebsiella pneumoniae, so he was switched to p.o. Trimethoprim/Sulfamethoxazole and cephelexin for the cellulitis. However, he continued to have low grade temperature and was transferred to the D.V.A.M.C. on the 8th day of hospitalization. He had a temperature of 38.3°C on admission, bilateral flank tenderness, and elevated white count of 18,400 with 71% PMNs and 11% bands. He had evidence of active liver disease with bilirubin of 2.7 mg/dl and AST of 90 units. His urine contained 30 WBC and 4-5 RBC per high power field and his chest x-ray showed blunting of the right costophrenic angle. A CT scan showed bilateral multiple areas of lobar nephronia and pleural effusion. He was treated with cefazolin and gentamicin along with total parenteral nutrition, until p.o. intake improved. He slowly responded with slight daily improvement in strength, but continued to have low grade temperature for the first seven days. Since renal sonogram was negative, he had a repeat CT which showed signficant improvement with decrease in the hypodense areas. His serum creatinine rose significantly on the 8th day of treatment, so aminoglycosides were discontinued. The levels returned to normal over the next 3 weeks as Cefazolin was continued for an additional week and then p.o. TMP/SMX for an additional 3 weeks.

> This case showed rather classical radiologic evidence of lobar nephronia. He required parenteral therapy for an extended length of time, but he responded satisfactorily to combination therapy. When renal function impairment was noted, a single parenteral agent was used. Patients can be successfully treated without surgery, but may require prolonged parenteral therapy. The major risk with combination therapy is enhanced nephrotoxicity(50).

D. Non-specific therapy should include fluids to elicit output of 1500 cc, careful monitoring intake and output and relieving obstruction. If a catheter has been in place, reevaluate to determine if patient requires catheter. If patient has neurogenic bladder with increased residual urine, may be candidate for in-and-out catheters q. 8 hours. Family can be trained by nurses to do these. Although frequency of urinary tract infection may be the same, the severity of the infection is not nearly as great. Ronald recommends Trimethroprim/ Sulfmethoxazole as continuous preventive therapy while doing in-and-out catheterizations (56). My own preference is to treat each symptomatic episode when it occurs alternating antimicrobial agents depending upon susceptibility testing. Above all, avoid using in-dwelling catheters or even external catheters unless absolutely necessary.

CASE NO. 3:

J.H. is a 70 year old white male with severe rheumatoid arthritis with leukopenia, splenomegaly and weight loss. He had weight loss attributed to an esophogeal stricture secondary to peptic esophagitis. He was initially treated with pencillamine but was later switched to low dose predisone. A duodenal tube was placed, and he was transferred to a nursing home. Two weeks prior to admission, an indwelling urinary catheter was placed because of decreased ability to void. One week later, he developed a tender right scrotum and was noted to have a necrotic penis. Both surface cultures and urine grew Pseudomonas aeruginosa resistant to gentamicin and netilmycin but susceptible to amikacin, ticarcillin and other ureidopenicillins. On admission to the VA, he was a cachectic white male, who was afebrile with normal blood pressure. He had a conjunctivitis of the right eye, with orbital cellulitis and erythema along the left eye. He had a blackened penile shaft, with eschar and multiple draining areas extending over the perineum. He also had multiple 1 cm. circular necrotic black ulcers in the right groin extending over the thigh. Although he had a WBC of 27,000, this was considered to be ecthyma gangrenosum which was spread by direct contact. He was given Soludrol 125 mg. BID, timentin and amikacin. His temperature was normal. Drainage procedures were performed on multiple occasions by the urology service, with improvement but he was discharged to NHCU with a clean open wound of the penis and perineum.

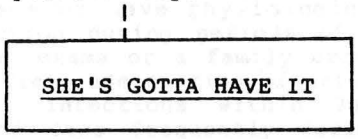
1) This was an unusually severe local pseudomonas infection in an immunosuppressed patient with Pseudomonas aeruginosa. He had local extension with lesions resembling ecthyma gangrenosum with involvement of the eye as well. All this followed the use of urinary catheter in someone who likely carried pseudomonas and had poor leukocyte function due to underlying disease and corticosteroid administration.

2) Surgical debridement was combined with anti-pseudomonas combination therapy for immunosuppressed patient. Normally combination therapy is offered only for those with polymorphonuclear leukocyte < 1000/ mm^3, but in this case, both drugs were given since PMN's weren't functioning normally due to corticosteroid administration.

3) Satisfactory anti-pseudomonas coverage could have been obtained with ticarcillin and amikacin (96% of DVAMC urine

isolates, respectively). Timentin is a commonly used house staff antimicrobial agent with weak justification. It cannot be used alone for pseudomonas infections nor for any infection in an immunocompromised patient and is not indicated as a 1° drug in treatment of UTI since relapse rate is so high (48). Although its empiric use is justified based on its potential of anti-staphylococcal coverage and for beta-lactamase producing organisms, clinical trials show no significant difference with combinations containing ticarcillin alone; its anti-staphylococcal efficiacy is yet to be proved. It is a marketing product whose minor advantage has been exploited by its drug representatives. I've yet to see a case where its use is justified plus more organisms are likely to be susceptible to imipenim or ceftazidine.

V. What can be done preventively?



A. If women have at least two occurrences in 6 months or recur within 1 month after treatment of a previous infection or men who have their recurrence within 1 month; treat with continous low-dose therapy: Either TMP/SMX 1/2 tablet q. OD for women or q D for men, or nitrofuranton 50-100 mg q D.(56-57) It's cost effective if women have three infections per year(58). For women, a six month trial is recommended initially but duration in men is not certain.(56) After discontinuation of the therapy, if symptomatic infection recurs, then the therapy can be reinitiated and continued for up to 2 years. In men, therapy may be required indefinitely to prevent recurrences (very small number require this). My preference is to alternate the two drugs every 6 months since TMP/SMX may cause bone marrow toxicity and nitrofurantoin may cause peripheral neuropathy or pulmonary fibrosis if administered continuously (> 1 year). However, Ronald has claimed low toxicity in treating large numbers of women with TMP/SMX(56). Stamey reported at this Grand Rounds in 1985 of success with low-dose cephelexin and quinilones, but I have little experience with these. In fact, I would specifically recommend using quinilones for treatment of UTI and not suppression since they may be the last remaining oral antimicrobial agent for use in treatment.

ABOUT LAST NIGHT

B. Women with recurrent lower tract infection more than 6 months apart can be preventively treated with intermittent therapy.

1) Acquisition of infection in women clearly relates to carriage of the organism in the urethral area and ascension following intermittent obstruction, as with sexual intercourse (59). Infections also occur in those women who use a diaphragm or have physiologic changes in trigonal (bladder) function during periods of High Anxiety such as graduate school exams or a family crisis(59-61). Nicole has shown the immediate association of urinary infection in women with recurrent infections within 24 hours after sexual intercourse and less frequently during menstruation (59). Stamm's group and others found frequent association of UTI with diaphragm use (60). In fact, they were unable to obtain a control group of diaphragm users who did not have recurrent urinary tract infection for their studies, so they had to use women taking oral contraceptives. The diaphragm has been shown to result in high residual urines, a decrease in the rate of urinary flow, and indirectly increase the intravesical pressure (61).

2) Successful prevention of urinary tract infection has been shown by Vosti with nitrofurantoin 50 mg. or by others with TMP/SMX 1/2 tablet post-sexual intercourse (62-63). The former drug can be taken with the next meal. It is highly successful in clinical practice. If an infection develops while on the drug, then an alternative agent can be used to treat the infection.

C. Urologic evaluation is NOT necessary in individuals with recurrent urinary tract infection.

> Urine: from old French urine, a reshaping of early French **orine**, from Vulgar Latin **aurina**, a "folk" alteration from the Latin **aurum**, gold.

1) Few have urologic defects for which surgery would be indicated (64,65). In these studies, IVP's demonstrated abnormalities but none of these required urologic surgery. As discussed above, these abnormalities in women probably relate to infections as a child when the growing kidney was more susceptible to infection. Cystography occasionally

reveals urethral diverticulum which requires surgery. However, such abnormalities which predispose to urinary tract infection is so infrequently demonstrated by either study that evaluation is rarely indicated. There is no basis for a recent recommendation that invasive tests would be of value in all patients, particularly in determining duration of therapy (66). Few men with recurrent infection have surgical defects since minimal-to-moderate prostatic obstruction is present, evaluation is not necessary initially since few have significant voiding problems (25). Clinical symptoms of prostatism are a better guide to the necessity for urologic evaluation than radiologic studies.

2) Above all, do not use urethral dilatation as therapy unless stricture is present. There is no evidence that urethral dilatation is of any value for women with recurrent infections. It is not only uncomfortable, but also can contribute to recurrent infection or persistent infection with resistant organisms.

CASE NO. 4

R.H. was a 24 year old architectural graduate student with recurrent urinary tract infections in the first year of marriage. She was evaluated with cystoscopy after the third infection, which was negative. Six months later after the fourth infection, she received a bladder irrigation with silver nitrate. Within 2 weeks, she developed urinary tract symptoms and consulted an Infectious Disease specialist. She had Pseudomonas maltophilia resistant to all oral antimicrobial agents, except carbenicillin. She was treated with carbenicillin indanyl sulfate continuously for two months, but had intermittent bouts of dysuria which were treated alternately with TMP/SMX or doxycycline. She continued to have negative cultures on the carbenicillin but at 4 months, she had recurrent urinary tract symptoms and grew E. coli resistant to all oral antimicrobial agents except TMP/SMX. She responded to TMP/SMX when the carbencillin was discontinued, but the Pseudomonas maltophilia recurred. She was seen by the Chief Resident, Urology Service at Parkland Memorial Hospital, who found no evidence of lower tract abnormality. He recommended long term penicillin G therapy (cheaper than carbenicillin) and TMP/SMX 1/2 tablet at bedtime for 6 months. On this combined regimen, she did well and has been followed the last 3 years by a physician at the Oxford University Infirmary, where her husband is pursuing a graduate degree in theology, with no recurrent infections.

1) Recurrent urinary symptoms are quite frequent in young women. Urinary tract organisms are recovered in approximately 1/2 of those with urinary symptoms, so patience is required in handling recurrent symptoms.

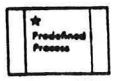
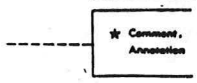
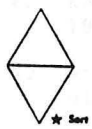
2) Urologic manipulation may be associated with disaster, especially when dilatation and irrigations are employed. Long term therapy with antibiotics achieving high urinary levels eventually will eradicate the organism.

3) Prophylactic therapy may need to be used concurrent to prevent recurrent infections since women with recurrent infections may acquire organisms with varying susceptibilities.

Selected Short Subjects:

"Oh, the anguish one endures
with an infected vesica urinaria.
Such mega misery manifested,
by such microbic bacteria."

H. Gibson-Ausbrook

FLOW CHART SYMBOL	DEFINITION
 PUNCHED CARD MAGNETIC TAPE	MEDIA FOR INPUT/OUTPUT FUNCTIONS
 CORE	A MEDIUM FOR AN ESSENTIAL INPUT/OUTPUT FUNCTION
 PREDEFINED PROCESS	A PROGRAMMED STEP SPECIFIED IN A SUBROUTINE PROCEDURE
 COMMENT, ANNOTATION	ADDITIONAL DESCRIPTIVE CLARIFICATION
MERGE 	COMBINING TWO OR MORE SETS OF ITEMS INTO ONE SET
 SORT	ARRANGING A SET OF ITEMS INTO A SEQUENCE
TERMINAL INTERRUPT 	A TERMINAL POINTING A FLOW CHART; A HALT OR START IN THE SUBROUTINE.
 PREPARATION	INSTRUCTION MODIFICATION TO CHANGE PROGRAM- MODIFY OR INITIALIZE A ROUTINE
DECISION 	A SWITCHING-TYPE OPERATION THAT DETERMINES WHICH ALTERNATIVE PATH TO FOLLOW.
 AUXILIARY OPERATION	OFFLINE PERFORMANCE ON EQUIPMENT NOT UNDER DIRECT CONTROL OF CENTRAL PROCESSING UNIT

THESE SYMBOLS CONFORM TO THE ISO "INFORMATION" PROCESSING- FLOW CHART SYMBOLS

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BIBLIOGRAPHY

1. Stamm WE, McKevitt M, Counts GW: Acute Renal Infection in Women: Treatment with Trimethoprim- sulfamethoxazole or Ampicillin for two or six weeks. Ann Int Med 1987; 106:341-345.

2. Parker J, Kunin C: Pyelonephritis in Young Women. A 10 to 20 year Followup. JAMA 1973; 224(5), 585-590.

3. Gower PE, et al: A prospective study of patients with radiological pyelonephritis, papillary necrosis and obstructive atrophy. Qtrly J Med 1976; 45:315-349.

4. Kass EH: Should Bacteriuria be Treated? Med J Aust Special Suppl 1973,1:38-43.

5. Nicolle LE, Bjornson J, Harding GKM, MacDonnell JA: Bacteriuria in elderly institutionalized men. New Eng J Med 1983, 390;1420-1425.

6. Arze RS, Ramos JM, Owen JP; Morley AR, Elliott RW, Wilkinson R, Ward MK, Kerr DNS: The natural history of chronic pyelonephritis in the adult. Qtrly J Med, 1982; 51:396-410.

7. Holgrem J and Smith JW: Immunological aspects of urinary tract infections. Progr Allergy 1975, 18:289-352.

8. Freeman RB, Smith WM, Richardson JA, Hennelly PJ, Thurm RH, Urner C, Vaillancourt JA, Griep RJ, Bromer L: Long-term therapy for chronic bacteriuria in men. Ann Int Med 1975, 83:133-147.

9. Leigh DA, Gruneberg RN, Brumfitt W: Long-term followup of bacteriuria in pregnancy. Lancet 1968, 1:603-605.

10. Boscia JA, Kobasa WD, Knight RA, Abrutyn E, Levison ME, Kaye D: Epidemiology of bacteriuria in an elderly ambulatory population. Am J Med 1986, 80:208-214.

11. Nordenstam GR, Brandberg CA, Oden AS, Svanborg Eden CM, Svanborg A: Bacteriuria and mortality in an elderly population. New Eng J Med 1986, 314:1152-1156.

12. Nicolle LE, Henderson E, Bjornson J, McIntyre M, Harding GKM, MacDonell JA: The association of bacteriuria with resident characteristics and survival in elderly institutionalized men. Ann Int Med 1987; 106:682-686.

13. Dontas AS, Kasviki-Charvati P, Papanayiotou PA, Marketos SG: Bacteriuria and survival in old age. New Engl J Med 1981, 304:939-943.

14. Platt R, Polk BF, Murdock B, Rosner B: Mortality associated with nosocomial urinary tract infection. New Engl J Med 1982, 307:637-642.

15. Steward DK, Wood GL, Cohen RL, Smith JW, Mackowiak PA: Failure of the urinalysis and quantitative urine culture in diagnosing symptomatic urinary tract infections in patients with long-term urinary catheters. Am J Inf Cont 195, 13: 154-160.

16. Warren JW, Damron D, Tenney JH, Hoopes JM, Deforge B, Muncie HL: Fever, bacteremia, and death as complications of bacteriuria in women with long-term urethral catheters. J Inf Dis 1987, 155: 1151-1158.

17. Rhame FS, Perkash I: Urinary tract infections occurring in recent spinal cord injury patients on intermittent catheterization. J Urology 1979, 122:669-673.

18. Orskov I, Orskov F: Serology of Escherichia coli Fimbriae. Prog Allergy 1983, 33:80-105.

19. Hanson LA, Ahlstedt S, Jodal U, Kauser B, Larsson P, Lidin-Janson G, Lincoln K, Lindberg U,Mattsby I, Olling S, Peterson H, Sohl A: The host-parasite relationship in urinary tract infections. Kidney Int 1975: 8:S28-S34.

20. Lomberg H, Hanson LA, Jacobsson B, Jodal U, Leffler H, Svanborg-Eden C: Correlation of P blood group, vesicoureteral reflux, and bacterial attachment in patients with recurrent pyelonephritis. New Engl J Med 1983; 308:1189-1192.

21. O'Hanley P, Low D, Romero I, Lark D, Vosti K, Falkow S, Schoolnik G: Gal-Gal Binding and hemolysin phenotypes and genotypes associated with uropathogenic Escherichia coli. New Engl J Med 1985, 313:414-420.

22. Jones SR, Smith JW, Sanford JP: Localization of urinary-tract infections by detection of antibody-coated bacteria in urine sediment. New Engl J Med 1974; 290:591-593.

23. Latham RH, Stamm WE: Role of fimbriated Escherichia coli in urinary tract infections in adult women: correlation with localization studies. J Inf Dis 1984, 149:835-840.

24. Johnson JR, Roberts PL, and Stamm WE: P Fimbriae and other virulence factors in Escherichia coli urosepsis: association with patients' characteristics. J Inf Dis 1987, 156:225-228.

25. Smith JW, Jones SR, Reed WP, Tice AD, Deupree RH, Kaijser B: Recurrent urinary tract infections in men. Ann Int Med 1979, 91:554-548.

26. Smith JW, et al: Adherence to kidney tissue of Escherichia coli from humans with urinary tract infection. Current Microbiol 1986; 14:91-94.

27. Smith JW: Microbial and host factors that influence adherence of Escherichia coli to kidney epithelium. Am J Kidney Dis 1986, 7:368-374.

28. Lehmann JD, Smith JW, Miller TE, Barnett JA, Sanford JP: Local immune response in experimental pyelonephritis. J Clin Invest 1968, 47:2541-2550.

29. Williams TW, Lyons JM, Braude AI: In vitro lysis of target cells by rat polymorphonuclear leukocytes isolated from acute pyelonephritic exudates. J Immunol 1977, 119:671-674.

30. Munford RS and Hall CL: Detoxification of bacterial lipopolysaccharides (endotoxins) by a human neutrophil enzyme. Science 1986, 234:203-205.

31. Smith JW, et al: Bactericidal activity of kidney macrophages from animals with experimental pyelonephritis. Rev Inf Dis, 1987 (in press).

32. Wright SD, Griffin FM. Activation of phagocytic cells C3 receptors for phagocytosis. J Leukocyte Biol 1985, 38:327-339.

33. Riveau GR, Novitsky TJ, Roslansky PF, Dinarello CA, Warren HS: Role of Interleukin-1 in augmenting serum neutralization of bacterial lipopolysaccharide. J Clin Microbiol 1987, 25:889-892.

34. Lotz M, Tsoukas CD, Robinson CA, Dinarello CA, Carson DA, Vaughan JH: Basis for defective responses of rheumatoid arthritis synovial fluid lymphocytes to anti-CD3 (T3) antibodies. J Clin Invest 1986, 78:713-721.

35. Smith JW, Adkins MJ, McCreary D: Local immune response in experimental pyelonephritis in the rabbit. I. Morphological and functional features of the lymphocytic infiltrate. Immunology 1975, 29: 1067-1076.

36. Smith JW: Role of suppressor cells in experimental pyelonephritis. J Inf Dis 1980, 142:199-204.

37. Miller T, Scott L, Stewart E, North D: Modification by suppressor cells and serum factors of the cell-mediated immune response in experimental pyelonephritis. J Clin Invest 1978, 61:964-972.

38. Smith JW: Local immune response in experimental pyelonephritis in the rabbit. II. Lymphocyte stimulation by lipopolysaccharide of infecting organism. Immunology 1975, 29:1077-1085.

39. Smith JW, Kaijser B: Local immune response in experimental pyelonephritis in the rabbit. III. Lymphocyte responsiveness to O and K antigens of Escherichia coli. Immunology 1976; 31:233.

40. Smith JW: Local immune response to lipoprotein of the outer membrane of Escherichia coli in experimental pyelonephritis. Infection & Immun 1977; 17:366-370.

41. Smith JW, Jones SR, Kaijser B: Significance of antibody- coated bacteria in urinary sediment in experimental pyelonephritis. J Inf Dis 1977; 135:577-581.

42. Miller T and Findon G: Cellular basis of host defences in pyelonephritis. Rev Int Med (in press).

43. Beutler B and Cerami A: Cachectin: More than a tumor necrosis factor. New Engl J Med 1987, 316:379-385.

44. Sayers TJ, Macher I, Chung J, Kugler E: The production of tumor necrosis factor by mouse bone marrow-derived macrophages in response to bacterial lipopolysaccharide and a chemically synthesized monosaccharide precursor. J Immuno 1987; 138:2935-2940.

45. Ronald AR: Optimal duration of treatment for kidney infection. Ann Int Med 1987, 106:467-468.

46. Bergeron MG, et al: Therapeutic potential of high renal levels of aminoglycosides in pyelonephritis. J Antimicrob Chemother 1985; 15:4-8.

47. Preheim LC, Cuevas TA, Roccaforte JS, Mellencamp MA, Bittner MJ: Oral ciprofloxacin in the treatment of elderly patients with complicated urinary tract infections due to Trimethoprim/Sulfamethoxazole-resistant bacteria. Am J Med 1987; 82(suppl 4A):295-300.

48. Sanders CV, Marier RL, Aldridge KE, Derks FW, Martin DH: Safety and effectiveness of ticarcillin plus clavulanic acid in the treatment of community-acquired acute pyelonephritis in adult women. Am J Med 1985, 79(suppl 5B):96-100.

49. Bergeron MG, Beauchamp D, Poirier A, Bastille A: Continuous vs. intermittent administration of antimicrobial agents: tissue penetration and efficacy in vivo. Rev Inf Dis 1981, 3:84-97.

50. Beauchamp D, Poirier A, Bergeron MG: Increased nephrotoxicity of gentamicin in pyelonephritic rats. Kidney Int 1985; 28:106-113.

51. Thorley JD, Jones SR, Sanford JP: Perinephric abscess. Medicine 1974; 53:441-451.

52. Rosenfield AT, Glickman MG, Taylor KJW, Crade M, Hodson J: Acute focal bacterial nephritis (acute lobar nephronia). Radiology 1979, 132:553-561.

53. June CH, Browning MD, Smith P, Wenzel DJ, Pyatt RS, Checchio LM, Amis Jr ES: Ultrasonography and computed tomography in severe urinary tract infection. Arch Int Med, 1985; 145:841-845.

54. Hampel N, Class RN, Persky L: Clue of ^{67}-Gallium scintigraphy in the diagnosis of localized renal and perirenal inflammation. J Urology 1980, 124:311-314.

55. Hoverman IV, Gentry LO, Jones DW, Guerriero WG: Intrarenal abscess. Report of 14 cases. Arch Int Med 1980; 140:914-916.

56. Sheehan G, Harding GKM, Ronald AR: Advances in the treatment of urinary tract infection. Am J Med, May 15,1984 (suppl); 76:141-146.

57. Kraft JK, Stamey TA: The natural history of symptomatic recurrent bacteriuria in women. Medicine 1977; 56:55-60.

58. Stamm WE, McKevitt M, Counts GW, Wagner KF, Turck M, Holmes KK: Is antimicrobial prophylaxis of urinary tract infections cost effective? Ann Int Med 1981; 94:251-255.

59. Nicolle LE, Harding GKM, Preikasaitis J, Ronald AR: The association of urinary tract infection with sexual intercourse. J Inf Dis 1982; 146:579-583.

60. Fihn SD, Latham RH, Roberts P, Running K, Stamm WE: Association between diaphragm use and urinary tract infection. JAMA 1985; 254:240-245.

61. Gillespie L, et al: The diaphragm: an accomplice in recurrent urinary tract infections. Urology 1984; 24:25-30.

62. Vosti KL, et al: Recurrent urinary tract infections. Prevention by prophylactic antibiotics after sexual intercourse. JAMA 1975; 231:934-940.

63. Ronald AR, Harding GKM: Urinary infection prophylaxis in women. Ann Int Med 1981; 94:268-270.

64. Engel G, Schaeffer AJ, Grayhackk JT, Wendel EF: The role of excretory urography and cystoscopy in the evaluation and management of women with recurrent urinary tract infections. J Urology 1980; 123:190-191.

65. Fowler JE, Pulaski ET: Excretory urography, cystography, and cystoscopy in the evaluation of women with urinary-tract infection. New Engl J Med 1981; 344:462-465.

66. Tolkoff-Rubin NE, Rubin RH: New approaches to the treatment of urinary tract infection. Am J Med 1987; 82(suppl 4A): 270-277.