CHAPTER 4

RESULTS

A. In Vitro Study

Table 6 shows the activity of aztreonam against gram negative bacteria in cumulative percentage of MICs (μg/ml). At concentration of 1 μg/ml, aztreonam inhibited more than 70% of Enterobacteriaceae. For other gram negative bacteria, Aeromonas spp. (30 isolates), Pseudomonas aeruginosa (29 isolates) and Acinetobacter spp. (22 isolates) were 100% inhibited at 0.5, 16 and 128 μg/ml, respectively.

Figure 8-17 show the relationship between the cumulative percentage of the inhibited organisms and log MIC values. By interpolating to the minimum inhibitory concentrations of 50 and 90 cumulative percentage inhibited, the MIC_{50} and MIC_{90} were obtained. The overall geometric means and ranges of MICs of aztreonam to gram negative bacteria from various sources are shown in table 7.

Table 6 Cumulative percentage of gram negative bacteria to MIC (μg/ml) of aztreonam.

Organism	No of strains	Cumulative percentage of isolated strains Inhibited at concentrations (μg/ml) of													
		⩽0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	>128
Acinetobacter spp.	22										23	27	82	100	
Aeromonas spp.	30	77	87	90	93	100									
Enterobacter spp.	53	9	21	47	60	75	75	75	87	88	92	92	94	98	100
Escherichia coli	66		42	93	100										
Klebsiella spp.	52	4	52	88	96	96	98	100							
Proteus spp.	19	74	95	95	95	95	95	100							
P. aeruginosa	29									76	100				
Salmonella spp.	28		46	86	86	86	86	100							
Serratia spp.	20		20	40	50	75	100								
Shigella spp.	32	25	53	69	69	84	84	94	100						

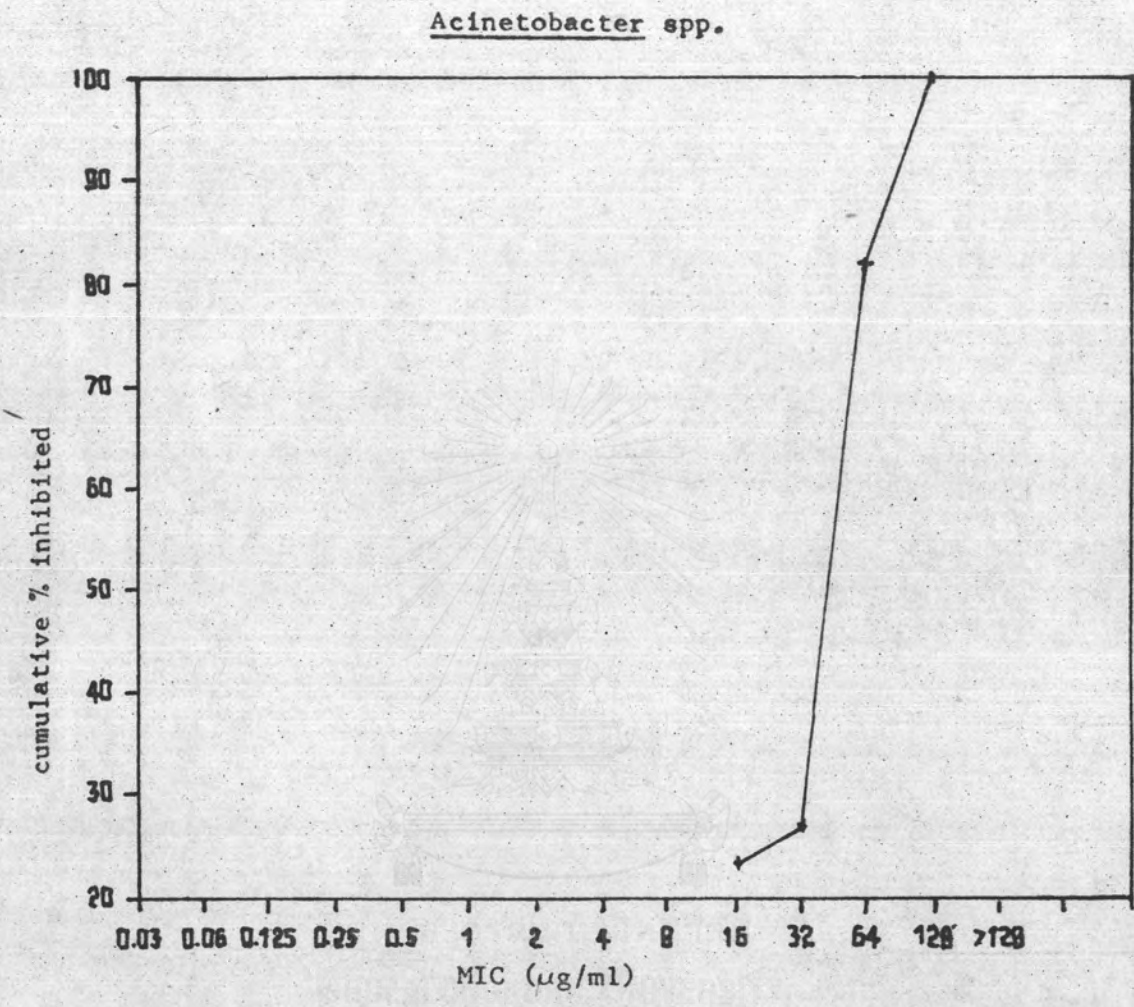

Figure 8 The activity of aztreonam against Acinetobacter spp.

(22 isolates)

Aeromonas spp.

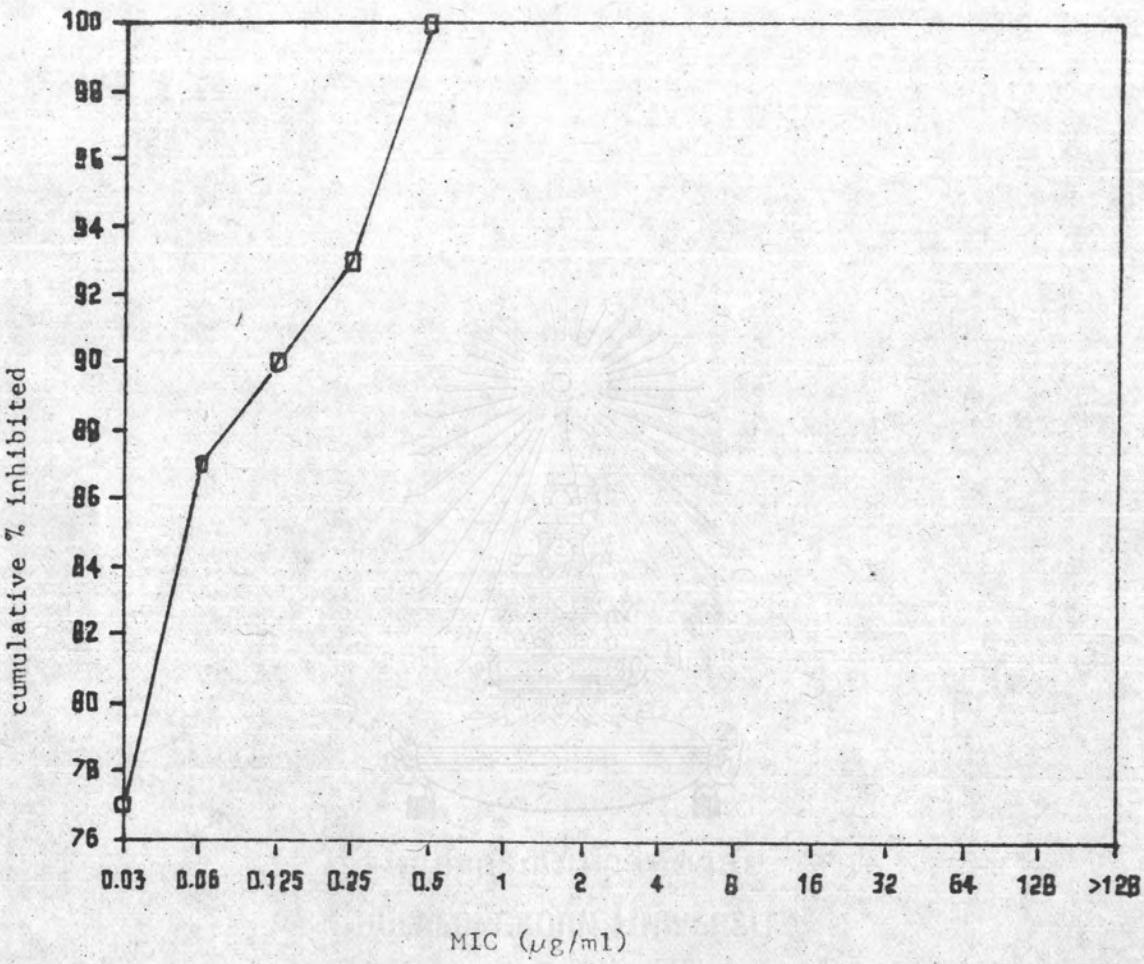

Figure 9 The activity of aztreonam against Aeromonas spp.

(30 isolates)

E. coli

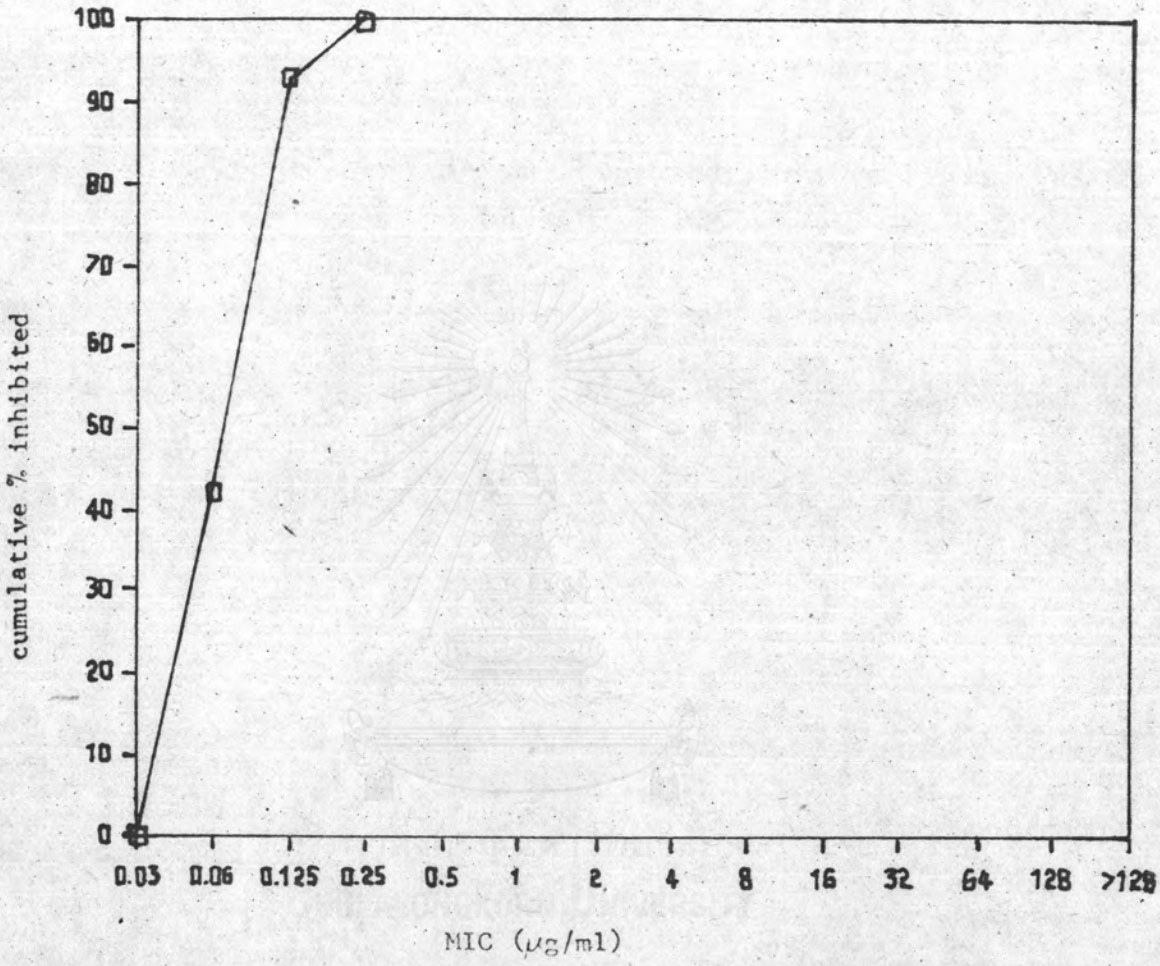

Figure 10 The activity of aztreonam against E. coli (53 isolates)

Enterobacter spp.

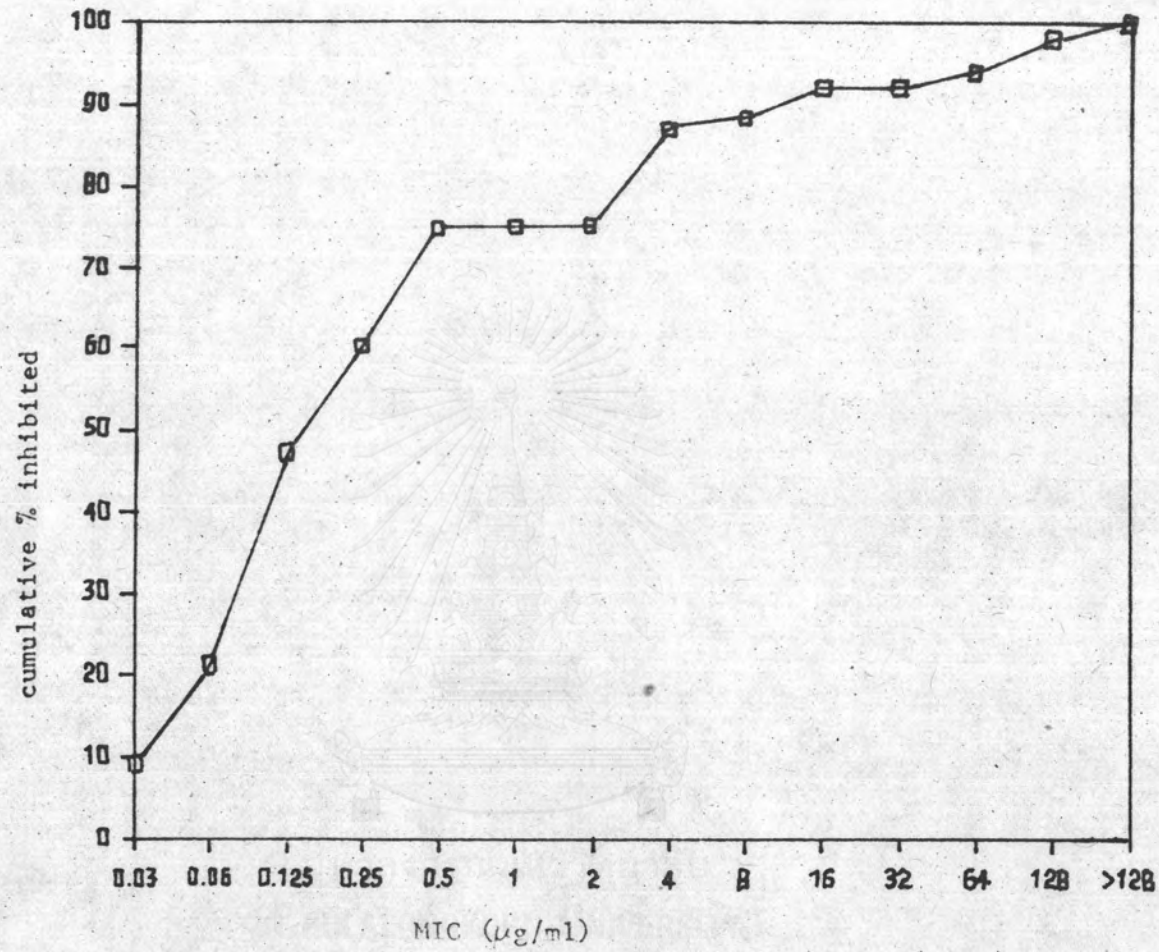

Figure 11 The activity of aztreonam against Enterobacter spp.

(66 isolats)

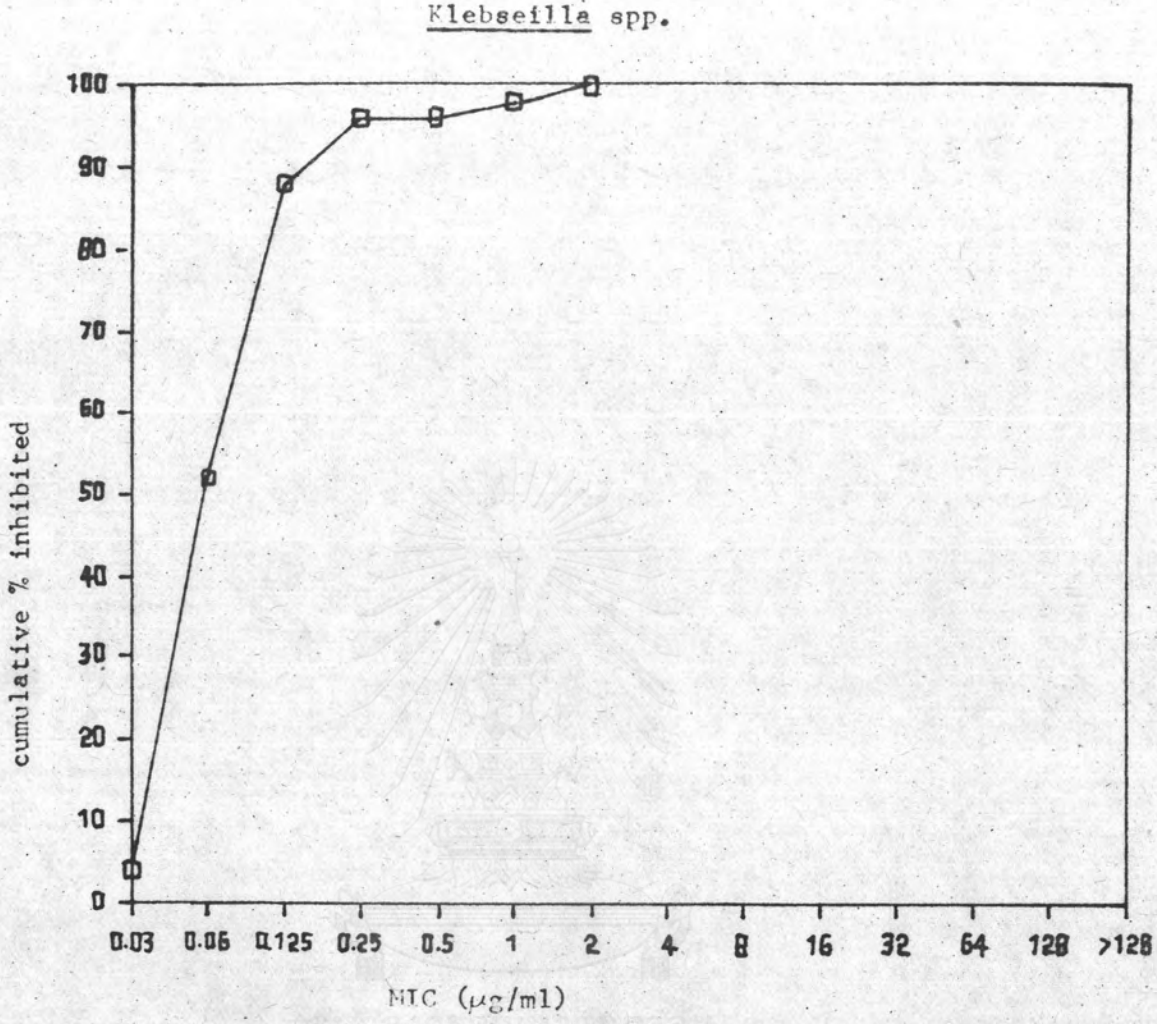

Figure 12 The activity of aztreonam against Klebsiella spp. (52 isolates)

P. aeruginosa

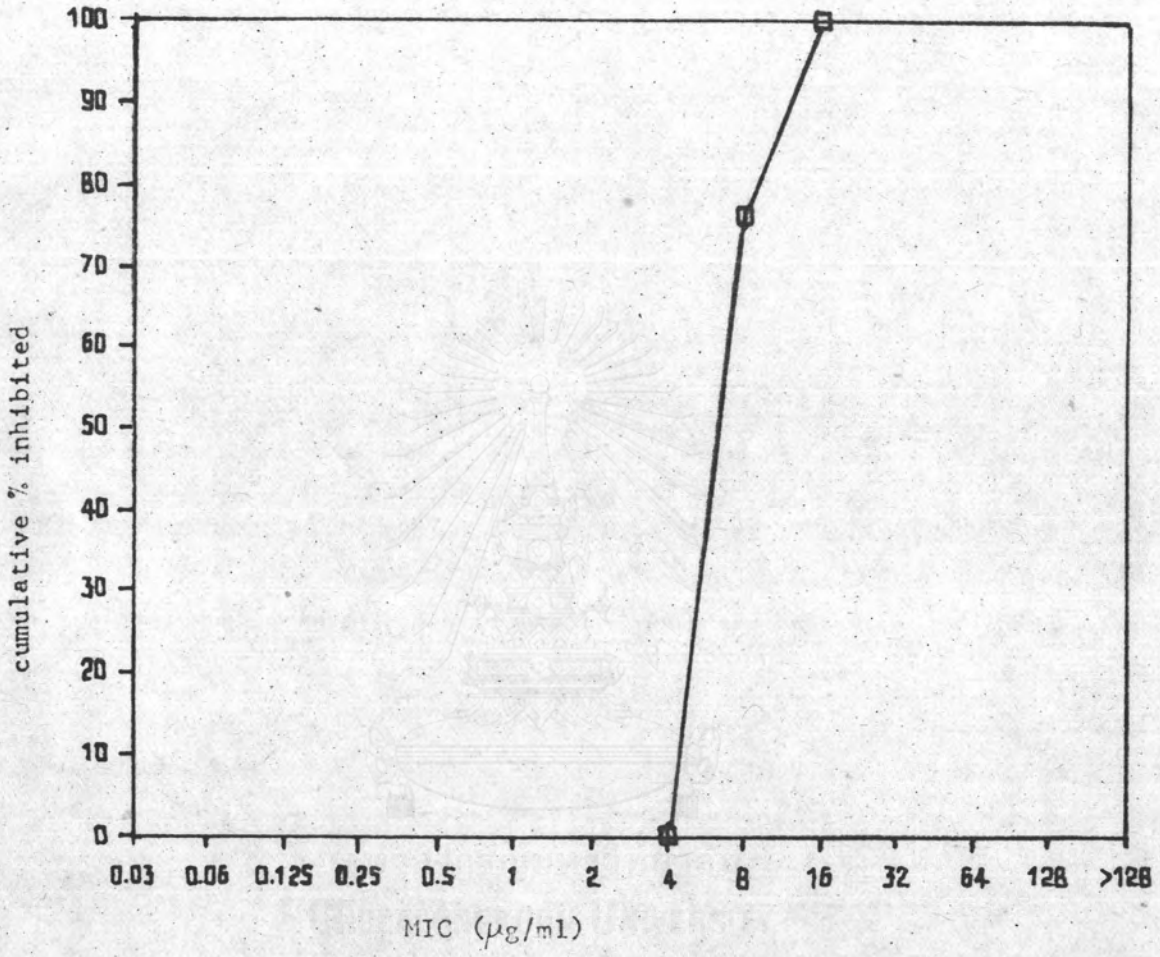

Figure 13 The activity of aztreonam against P. aeruginosa (29 isolates)

Proteus spp.

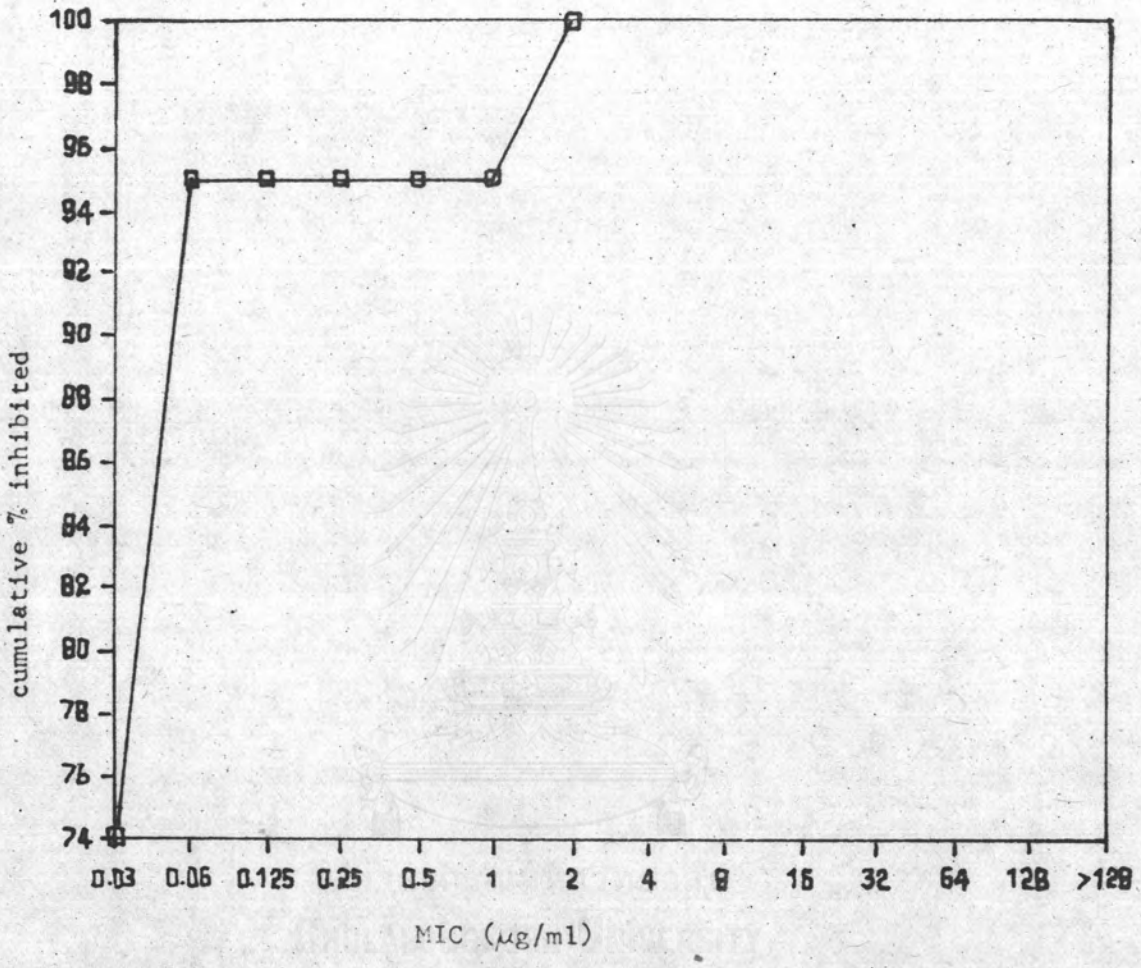

Figure 14 The activity of aztreonam against Proteus spp.

(19 isolates)

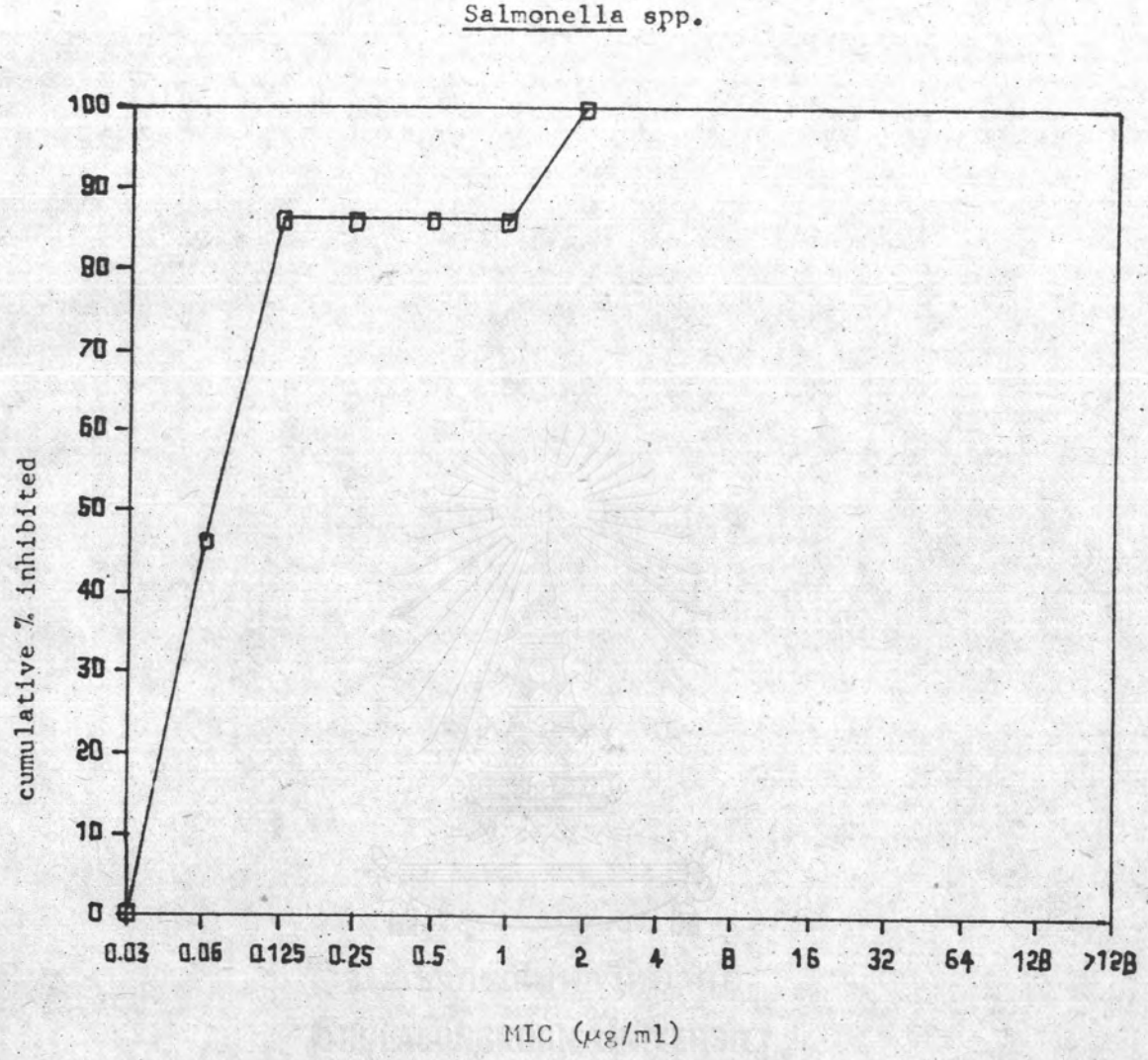

Figure 15 The activity of aztreonam against Salmonella spp. (28 isolates)

Serratia spp.

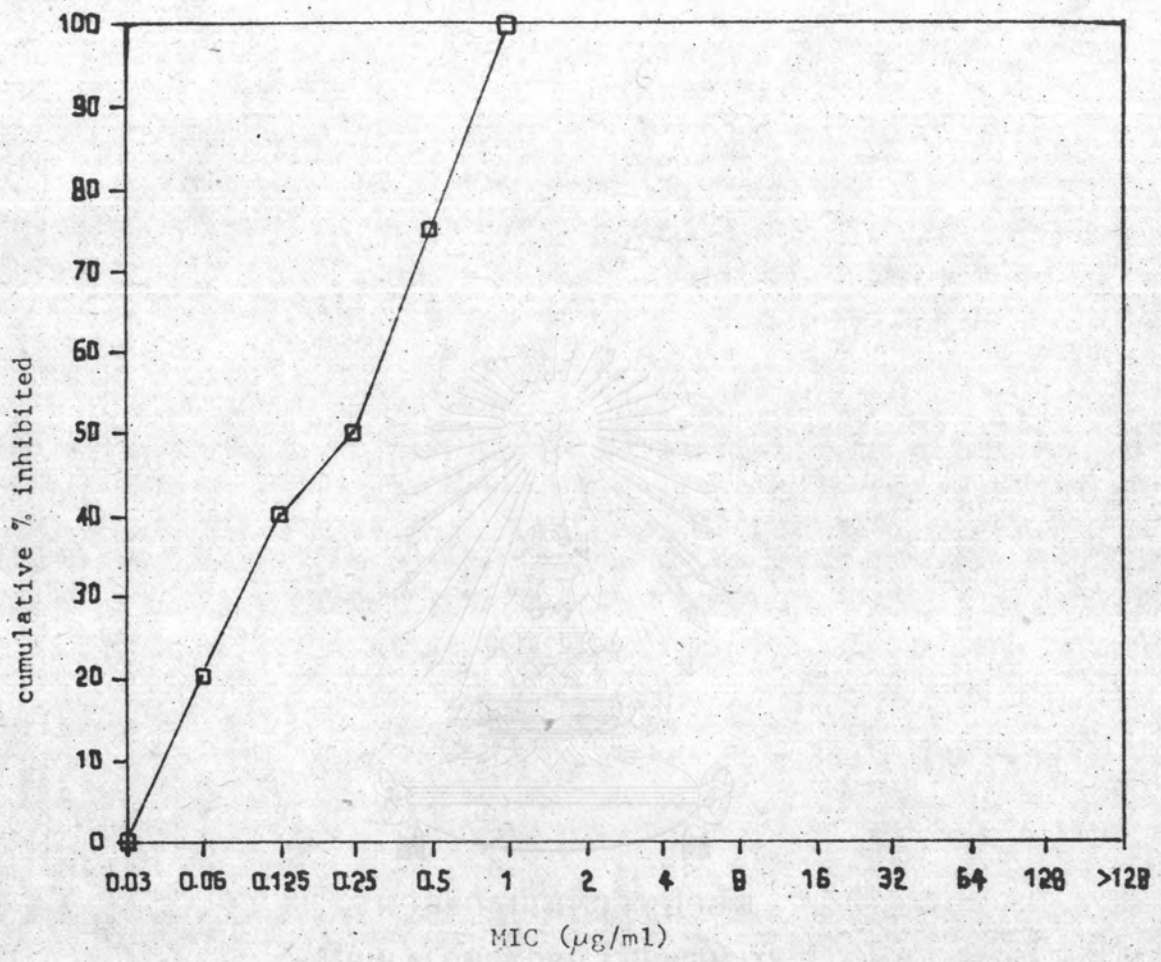

Figure 16 The activity of aztreonam against Serratia spp.

(20 isolates)

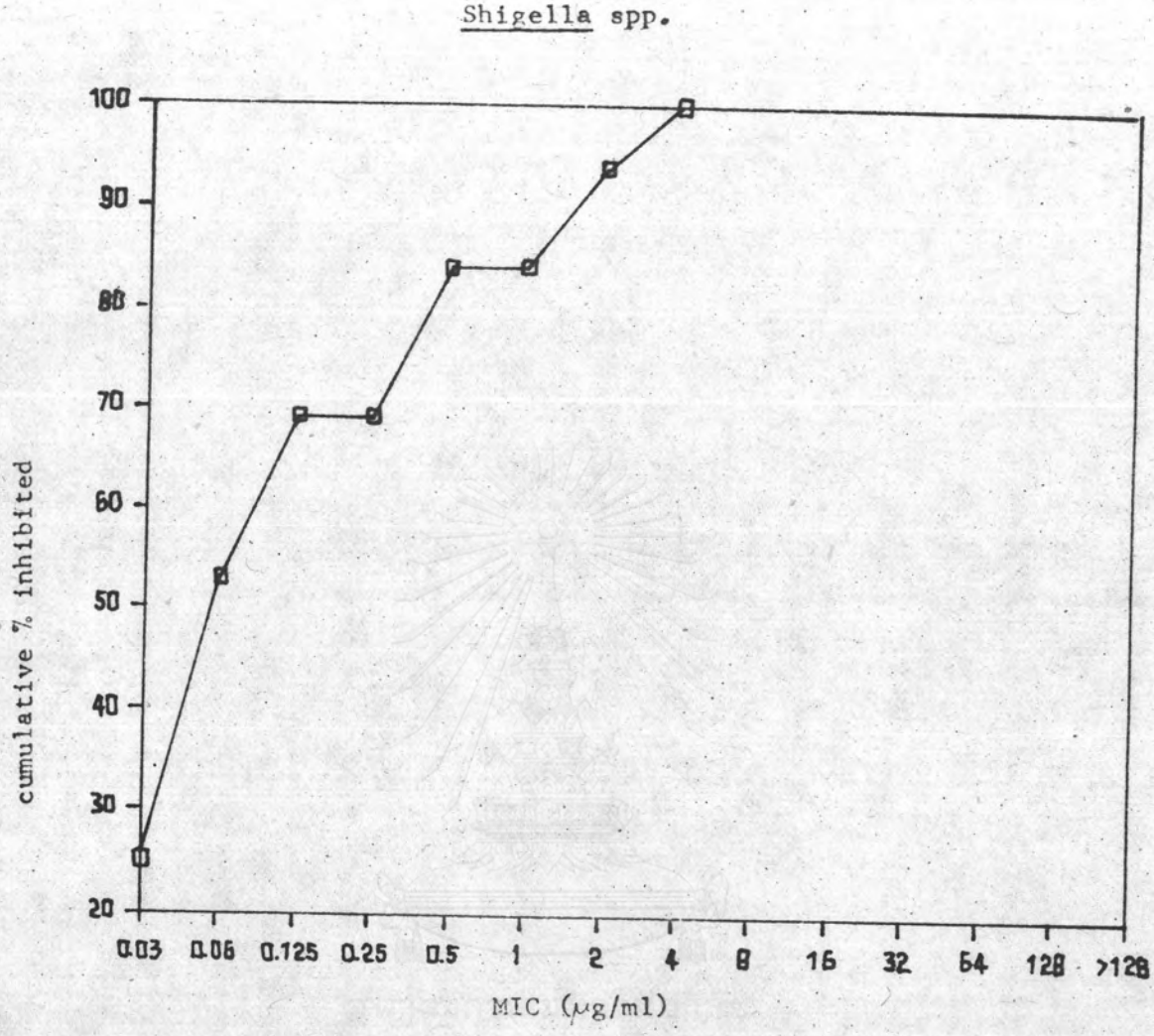

Figure 17 The activity of aztreonam against Shigella spp.

(32 isolates)

Table 7 The overall geometric means and ranges of MICs of aztreonam to gram negative bacteria from various sources.

Organism	Source	No. of Strains	MIC Range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
Acinetobacter spp	R	22	16-128	42	86
Aeromonas spp	R	30	0.03-0.5	0.03	0.13
Enterobacter spp	C	29	0.06-128	0.17	6.93
	R	3	0.06-4	0.13	1.35
	S	21	0.03-128	0.06	33.8
	Total	53	0.03-128	0.15	10
Escherichia coli	MS	66	0.06-0.25	0.07	0.11
Klebsiella spp	R	52	0.03-2	0.06	0.17
P. aeruginosa	R	29	8-16	6	11.9
Proteus spp	R	19	0.03-0.06	0.03	0.05
Salmonella spp	R	28	0.06-2	0.07	1.6
Shigella spp	R	32	0.03-4	0.06	1.5
Serratia spp	S	20	0.06-1	0.25	0.77

C = Chulalongkorn Hospital

MS = Medical Sciences

R = Ramathibodi Hospital

S = Siriraj Hospital

B. Clinical Study

Table 8 and 9 show the overall collected data of aztreonam. Children's age were varied from 3 months- 14 years with the ratio of the male to female is 5 : 5. Most of patients received drug intravenously, except case No. 6 who received drug by intramuscular. Causative bacteria were known such as Escherichia coli and other gram negative bacteria.

From 10 patients treated with aztreonam, 9 patients suffered from urinary tract infection, the rest suffered from skin infection. Most of the patients, except case No.10, had other associated diseases. They were obstructive nephropathy (3 cases),neurogenic bladder (3 cases),lymphoma (1 case), pneumonia with apnea (1 case) and Systemic Lupus Erythrematosus (1 case). Patient No. 8 also suffered from renal insufficiency.

Dose of aztreonam varied from 53 mg/kg/day to 100 mg/kg/day. The duration of aztreonam therapy varied from 5 days to 14 days with the average of 10.6 ± 2.65 days. All of the patients were treated with aztreonam alone.

Table 9 show serum level of aztreonam. The serum aztreonam concentrations from all of the patients , at $\frac{1}{2}$- 1 hour after the injection were ranged from 40.8 μg/ml to 85.4 μg/ml with the average of 67.86 ± 12.68 μg/ml. In addition, serum level of aztreonam at 6 or 8 hours after injection were range from 0.93 μg/ml to 30.2 μg/ml.

Adverse effect occurred in 2 patients (patient No.1 and 10). Phlebitis occured in patient No. 1 who received the drug by bolus injection as well as pain at the injection site in patient No. 10 who also received the drug by the same method.

Table 8 Sex, age, weight, diagnosis, causative organism, site of infection, bacteriological response, clinical response of pediatric patients treated with aztreonam.

Case No.	Sex	Age (yr)	Weight (kg)	Diagnosis	Causative organism	Site of infection	Bacteriological response	Clinical response
1	M	5/12	4.3	- Urinary tract infection - Obstructive nephropathy	K. pneumoniae	Urinary tract	colonization with C. albican, Streptococcus group D	improvement
2	M	5	19.4	- Urinary tract infection - Obstructive nephropathy	P. aeruginosa	Urinay tract	elimination	improvement
3	M	13	27	- Infected wound - Lymphoma	P. aeruginosa	Skin	colonization with E. cloacae	improvement
4	F	12	26	- Urinary tract infection - Leukemia with neurogenic bladder	E. coli	Urinary tract	superinfection with Streptococcus group D	failure

Table 8 cont.

Case No.	Sex	Age (yr)	Weight (kg)	Diagnosis	Causative organism	Site of infection	Bacteriological response	Clinical response
5	F	3/12	3.1	- Urinary tract infection - Pneumonia with apnea	P. mirabilis	Urinary tract	elimination	improvement
6	M	1	9.3	- Urinary tract infection - obstructive nephropathy	E. coli	Urinary tract	colonization with Streptococcus group D	improvement
7	F	2	9.6	- Urinary tract infection - neurogenic bladder	E. coli	Urinary tract	elimination	improvement
8	F	14	28.5	- Urinary tract infection - SLE	E. coli P. mirabilis	Urinary tract	colonization with C. albican	improvement

Table 8 cont.

Case No.	Sex	Age (yr)	Weight (kg)	Diagnosis	Causative organism	Site of infection	Bacteriological response	Clinical response
9	M	5/12	4.3	- Urinary tract infection - neurogenic bladder	E. cloacae	Urinary tract	colonization with C. albican	improvement
10	F	8	21.5	- Urinary tract infection	E. coli	Urinary tract	elimination	cure

Table 9 Dosing interval, route of administration, serum level, duration of treatment in children treated with aztreonam.

Case No.	Aztreonam dose (mg/kg/day)	Dosing interval (hr)	Route of administration	Duration of treatment (days)	Serum level (μg/ml)	
					$\frac{1}{2}$ - 1 hr. after injection	6 or 8 hr. after injection
1	80	8	IV	10	67.9	2.14
2	80	6	IV	14	58.8	21.2
3	76.9	6	IV	14	40.8	8.2
4	75	8	IV	10	85.4	1.08
5	80	8	IV	9	70.0	1.2
6	90	8	IM	10	59.5	0.93
7	80	8	IV	10	66.85	2.0
8	53	8	IV	10	80.5	30.2
9	80	8	IV	14	75.68	9.8
10	100	6	IV	5	73.2	1.04

Bacteriological results

A total of 11 causative organisms were obtained from 10 patients. All of them were gram negative bacteria included E. coli (5 isolates), P. aeruginosa (2 isolates), K. pneumoniae (1 isolate), P. mirabilis (2 isolates) and E. cloacae (1 isolate). Only one isolate of K. pneumoniae, showed resistance against aztreonam.

Determination of bacteriological response was also performed. All the initial pathogens were eliminated. However, one patient developed superinfection with Streptococcus group D. Colonization of the urine also occurred with Candida albican (2 cases), Streptococcus group D (1 case), E. cloacae (1 case), and both Candida albican and Streptococcus group D (1 case). The overall bacteriological responses are shown in table 10.

Table 10 In vitro activity of aztreonam against causative organisms compared to bacteriological response.

Case No.	Causative organism	In vitro result	Bacteriological response
1	K. pneumoniae	R	colonization with C. albicans Streptococcus group D
2	P. aeruginosa	S	elimination
3	P. aeruginosa	S	colonization with E. cloacae
4	E. coli	S	superinfection with Streptococcus group D
5	P. mirabilis	S	elimination
6	E. coli	S	colonization with Streptococcus group D
7	E. coli	S	elimination
8	E. coli P. mirabilis	S S	} colonization with C. albicans
9	E. cloacae	S	colonization with C. albicans
10	E. coli	S	elimination

R = resistance S = sensitive

Clinical responses were also evaluated. A complete clinical resolution of infection occurred in 1 case and the other 8 cases resulted in a marked clinical improvement. A favorable clinical response occured in 9 cases (90%), while unfavorable clinical response (failure) occurred in 1 case (10%) (table 11).

The overall responses for specific infections were evaluated. All sites of infection, both clinical and bacteriological responses were observed. The relationship of clinical and bacteriological responses to site of infection were as follow :

Urinary tract : Eight out of the nine of urinary tract infection treated with aztreonam had the satisfactory clinical and bacteriological responses. However, 5 out of these 8 cases developed colonization with C. albicans (2 cases) Streptococcus group D (1 case), E. cloacae (1 case) and C. albican with Streptococcus group D (1 case). The treatment failure was found in patient No. 4 who developed a superinfection with Streptococcus group D.

Skin : Skin and soft tissue infections comprised in one case, satisfied clinical response was obtained but colonization with E. cloacae was appeared.

The overall clinical and bacteriological responses for specific infections are shown in table 12.

Table 11 The overall clinical responses.

Clinical responses	No. of cases
Cure	1
Improvement	8
Failure	1

Table 12 The overall responses for specific infections.

Response	No. of patients	
	Skin infection	Urinary tract infection
Clinical response		
Cure		1
Improvement	1	7
Failure		1
Bacteriological response		
elimination		4
relapse		
reinfection		
superinfection		1
colonization	1	4