Original Article

Ventilator-associated pneumonia in Iranian intensive care units

Aziz Japoni[1], Afsanah Vazin[2], Mohammad Ali Davarpanah[3], Mohammad Afkhami Ardakani[2], Abdolvahab Alborzi [1], Sara Japoni[1], Noradin Rafaatpour[1]

[1]*Professor Alborzi Clinical Microbiology Research Center, Nemazee Hospital, Shiraz University of Medical Sciences, Shiraz, Iran*
[2]*Department of Clinical Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran*
[3]*Gastroentrohepatology Research Center and Internal Medicine ward, Shiraz University of Medical Sciences, Shiraz, Iran*

Abstract

Introduction: Nosocomial pneumonia (NP) and ventilator associated pneumonia (VAP) occur most frequently in intensive care units (ICU). This study seeks to determine the etiological agents of NP and VAP along with their antibacterial susceptibility patterns, and to evaluate the factors contributing to patient mortality. The impact of appropriate therapy in terms of three parameters (body temperature, PaO2/FiO2 ratio and leukocyte count) was also assessed.

Methodology: This study involved 836 adult patients admitted to ICUs at the Nemazee Hospital, Shiraz, Iran, over nine months during 2008 and 2009. The inclusion criterion was the commencement of infection at least 48 hours following hospital admission. Clinical parameters including core temperature, leukocyte count. and PaO2/FiO2 ratio were evaluated. Antibiotic sensitivities of the isolated bacteria to a panel of antibiotics were determined using E-test.

Results: Of 836 cases, only 58 (6.9 %) cases of NP were diagnosed, of which 42 (72 %) were VAP. *A. baumannii*, MRSA, *P. aeruginosa* and MSSA were the most prevalent bacteria. Significant correlations between previous antibiotic therapy ($p = 0.04$), use of corticosteroids ($p = 0.02$) and attributable mortality were found. A strong correlation between fever abatement and the ratio of PaO2/FiO2 with responses to treatment and outcomes was also evident.

Conclusions: Combined treatment with meropenem/imipenem, ciprofloxacin and vancomycin seems to be appropriate and could cover all possible infective agents. To reduce mortality rate, reasonable prescription of antibiotics and corticosteroids could be effective. Furthermore, adopting a strategy to reduce body temperature and PaO2/FiO2 ratio could be beneficial in patients' outcomes.

Key words: ICUs; ventilator-associated pneumonia; PaO2/FiO2 ratio; empiric antibiotic therapy

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Introduction

According to recent American Thoracic Society (ATS) guidelines, nosocomial pneumonia (NP), also known as hospital-acquired pneumonia (HAP) or health care-associated pneumonia (HCAP), is defined as the pneumonia that occurs more than 48 hours after a patient's admission to hospital but that was not incubating at the time of admission. Ventilator-associated pneumonia (VAP) is defined as the pneumonia that occurs after 48 to 72 hours after endotracheal intubation [1]. Nosocomial pneumonia is the second most common nosocomial infection and is usually bacterial in origin [2-4]. Both VAP and NP add significantly to the cost of hospital care and to the length of hospital stays. VAP is commonly classified as either early onset (occurring within 96 hours of the start of mechanical ventilation) or late onset (occurring later than 96 hours after the start of mechanical ventilation). VAP occurs in 9–27% of all intubated patients [2]. The incidence of VAP increases with the duration of ventilation. The risk of VAP is estimated to be 3% per day, during the first five days of ventilation, 2% per day during days 5 to 10 of ventilation, and 1% per day after 10 days [3]. VAP is most commonly caused by exogenous normal flora found in the hospital environment. Following urinary tract infections, hospital-acquired pneumonia (HAP) is the second common cause of nosocomial infections, and its prevalence is 15-20% of the total number [2-4]. It is the most common cause of death among nosocomial infections, while in intensive care units it is the primary cause of death [2,4,5]. Various

factors affecting the outcome of patients with VAP have been suggested [4,5], including poor response to antibiotic therapy [6,7], old age [8] and hospital stay [6,9] among others.

Few reports in the literature are available regarding the clinical and microbiological aspects of NP and VAP in Iran; therefore, the present investigation studied the etiological agents of nosocomial infections and their antibiotic susceptibility patterns. Additionally, factors contributing to the mortality of patients and alternation of a few clinical parameters (body temperature, PaO2/PiO2, leukocyte count) in outcomes of patients were also determined.

Methodology

Criteria for patients enrolled in the study

In total, 836 adult patients hospitalized in five ICUs of Nemazee Hospital (1,000 beds), affiliated with the Shiraz University of Medical Sciences, were enrolled in the study between June 2008 and March 2009. The inclusion criterion for VAP was pulmonary infection observed at least 48 hours post ventilator administration, while for NP the criterion was pulmonary infection with no intubation, at least 48 hours following admission. Patients enrolled in the study did not exhibit any signs of lung infection upon admission to the ICU wards. Further inclusion criteria for patients enrolled in the study were progressive infiltration visible by X-ray imaging, and at least two clinical signs of pneumonia (purulent sputum; fever > 38°C; or leuckocytosis, *i.e.*, WBC > 10,000/ml) [10]. The only difference in criteria for VAP or NP was that the VAP patients were intubated at the time of admission, while NP patients were not. Depending upon the underlying disorders requiring intensive care, patients were admitted to five specific adult ICUs as follows: adult surgical I (six-bed unit), neurosurgical I (nine-bed unit), internal medical (11-bed unit), adult surgical II (five-bed unit) and neurosurgical II (four-bed unit). All necessary information including demographic data, history of antibiotic therapy, duration of stay, vital clinical parameters, risk factors and mortality rate were collected.

Ethical consideration

Written informed consent was obtained from all patients enrolled in the study, and approved by the ethics board of Shiraz University of Medical Sciences.

Microbiological cultures

Samples collected from sputum and aspirated in the tip of the endotracheal tube were cultured directly on blood, chocolate and eosin methylene blue media and incubated overnight at 37°C aerobically. Bacterial growth on the media was identified based on Gram staining and standard biochemical tests.

Antibacterial susceptibility testing

Susceptibility of the isolated strains to 15 antibacterial agents was analyzed with the E-test (AB Biodisk, Solna, Sweden), and minimum inhibitory concentration (MIC) breakpoints for each antibiotic were determined according to the manufacturer's recommendations. American Typing Culture Collection isolates of *Escherichia coli* (ATCC 25922) and *Staphylococcus aureus* (ATCC 25923) were used as controls for MIC determination. Sets of antibiotics including colistin, amikacin, gentamicin, imipenem, meropenem, cefepime, ceftriaxone, ceftazidime, cefazolin, ciprofloxacin, oxacillin, linezolid, vancomycin, quinupristin/dalfopristin and piperacillin/tazobactam were used to evaluate the *in vitro* susceptibility of the bacterial isolates.

Statistical analysis

To compare appropriate and inappropriate empiric antibiotic therapies in terms of a patient's outcome and changes in clinical parameters, or association between risk factors and development of VAP, we used the chi-square test. Mean ± standard deviation (SD) was calculated for continuous variables such as age and APACHE IV score. The significance level was defined as $p < 0.05$.

Results

Demographic data

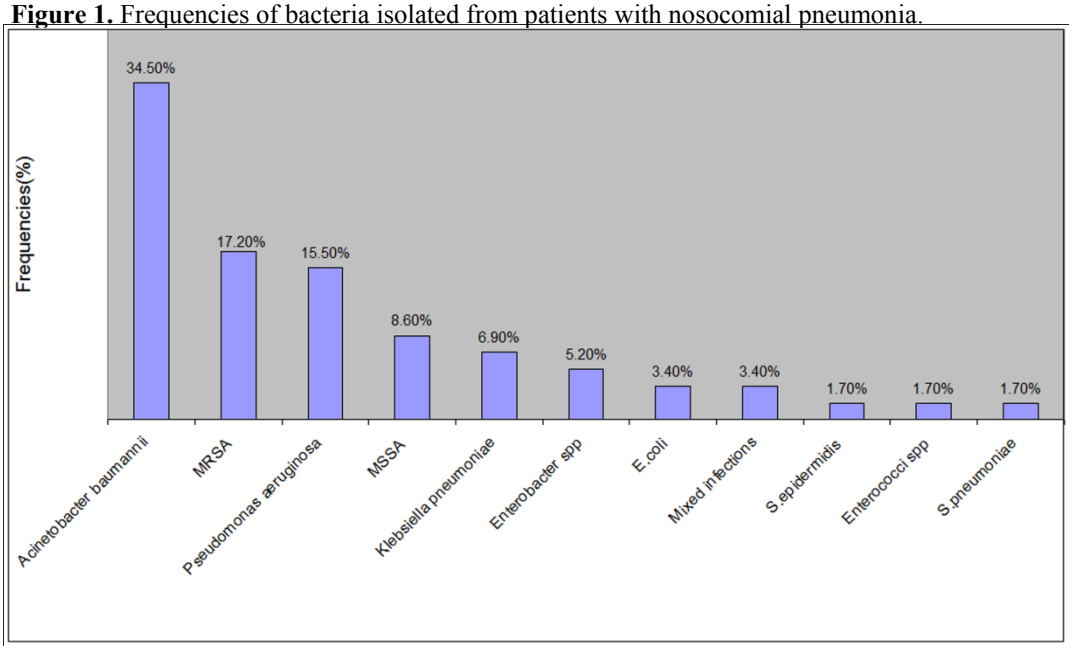
During the nine-month study, 58 admitted patients (6.9 %) suffered from nosocomial pneumonia of which 42 (72 %) were VAP. Four hundred ten patients (49 %) were on ventilators, 42 (10.2 %) of whom developed VAP. Acute Physiology and Chronic Health Evaluation (APACHE) IV scores for the patients treated successfully were 75.1 ± 18.2, while this figure was 94 ± 15.7 for those who died in ICUs ($p = 0.11$). The ratio of male to female patients with nosocomial pneumonia was 42:16 and the patients predominately (44.8 %) suffered from neurological disorders. These data are presented in Table 1.

Table 1. Patients' demographic data and reason for admission (N = 58).

Parameter	Values (range or %)
Male/female	42/16
Mean age, (year range)	39 (14-80)
APACHE IV score, mean ± SD	78.4 ± 18.9
ICU length of stay, mean (range)	18.8 (5-56)
Neurological disorder	26 (44.8 %)
Post operative care	12 (20.7 %)
Head/chest trauma	11 (19 %)
Respiratory (pulmonary edema, pulmonary emboli)	5 (8.6 %)
Others[1]	4 (6.9 %)

1- Parkinson's; Status epilepticus; Guillain Barre Syndrome

Figure 1. Frequencies of bacteria isolated from patients with nosocomial pneumonia.



Microbial patterns

The three pathogenic bacteria most frequently isolated from the patients were *Acinetobacter baumannii* (20; 34.5%), MRSA (methicillin resistant *Staphylococcus aureus*) (10; 17.2%) and *Pseudomonas aeruginosa* (9; 15.5%). These data are illustrated in Figure 1.

Factors contributing to the mortality of patients with nosocomial pneumonia/VAP

Evaluation of risk factors including age, gender, cardiac ischemia, mental insufficiency, renal disorders, chronic obstructive pulmonary disease (COPD), diabetes, coma, dialysis, tracheostomy, smoking, corticosteroid therapy, application of nasogastric tube, previous hospitalization, head trauma, IV drug abuse and previous antibiotic therapy, and their association with mortality rate was performed. It was revealed that of the 42 patients with VAP, 19 (45.2%) patients previously received antibiotics and 23 (54.8%) did not receive antibiotics. Of the 19 patients, 6 (31.6%) died, while of the 23 patients, 2 (8.7%) patients died (p = 0.04). Similarly, of the 15 (35.7%) patients who received corticosteroids, 6 (40 %) died, while from the 27 (64.3%) patients who did not receive this drug, only 2 (7.4%) died (p = 0.02).

Effect of appropriate therapy on three clinical parameters and mortality

The impact of appropriate and inappropriate antibiotic therapies on mortality rate, when patients empirically received antibiotics, was determined. According to the recorded data, the highest mortality rates were in the patients infected with

Table 2. Mortality rates in patients with nosocomial infections associated with appropriate and inappropriate empiric antibiotic therapies (N = 58).

Mortality (%)		Number of patients		Microorganisms
Appropriate treatment	Inappropriate treatment	Appropriate treatment	Inappropriate treatment	
14	46	7	13	*Acinetobacter baumanii*
0	33	1	9	MRSA
0	100	8	1	*Pseudomonas aeruginosa*
0	0	5	0	MSSA
0	0	3	1	*Klebsiella pneumoniae*
0	0	3	0	*Enterobacter* spp.
50	0	2	0	*E. coli*
0	100	1	1	Mixed infection
0	0	0	1	*Staphylococcus epidermidis*
0	0	1	0	*Enterococci* spp.
0	0	1	0	*Streptococcus pneumoniae*

MRSA: methicillin resistant *Staphylococcus aureus*; MSSA: methicillin sensitive *Staphylococcus aureus*

Table 3. Association between appropriate and inappropriate empiric antibiotic therapies, and three clinical parameters, 72 hours after treatment initiation.

Parameter	PaO2/FiO2 (mmHg)		Body temperature °C		Leucocytes/ml	
	> 250	< 250	≥ 38	< 38	> 12000	< 12000
Patients with inappropriate treatment	2	24	21	5	17	9
Patients with appropriate treatment	25	7	5	27	20	12
P value	< 0.001		< 0.001		0.58	

Pseudomonas aeruginosa or had mixed infection (100%), who received inappropriate antibiotic therapies (Table 2). Meanwhile, three vital clinical parameters from the patients were evaluated 72 hours following both appropriate and inappropriate antibiotic therapies. Significant statistical differences between the PaO2/FiO2 ratio and body temperature (fever) were found (Table 3).

Antimicrobial susceptibility patterns

The sensitivity of Gram negative bacteria to the ten antibiotics commonly used in clinics was determined using the E-test method. Colistin, meropenem, and imipenem with 96.6 %, 86.8 % and 84.3 % respective efficacy were the most effective antibacterial agents, while gentamicin and ceftriaxone with 21 % and 13.8 % efficacy were the least effective antibiotics, respectively (Table 4). Determination of the sensitivities of the Gram positive bacteria to seven antibiotics showed that linezolid and vancomycin had the highest *in vitro* activities against the bacteria with 100 % and 94.1 % sensitivity rates, respectively (Table 5). *A. baumannii* were resistant to the most tested antibiotics (Table 4). To more precisely determine the resistance patterns of *A. baumannii* to the tested antibiotics, cross-resistance was calculated (Table 6). High cross-resistance of these organisms to nine tested antibiotics was observed. *A. baumannii* was highly sensitive (100%) to colistin only.

Discussion

Tracheal intubation is performed usually as an emergency procedure to protect the airway from aspiration in unconscious or conscious but critically ill patients, and to facilitate the application of mechanical ventilation. VAP patients are frequently infected with oral and nasopharyngeal flora, mainly from their inability to adequately handle copious secretions. According to the presented data, 58 (6.9 %) of the hospitalized patients in ICU wards developed nosocomial pneumonia and 42 (10.2 %) out of 410 patients on ventilators developed VAP. A higher rate of VAP has been reported from Iran for adult patients suffering from respiratory distress syndrome [11], and similar rates were seen in Latin America, Asia, Africa and the United States [12,13]. Furthermore, another report from Iran has shown that additional hospital stays of patients could attribute to nosocomial infection [14]. Therefore, the

Table 4. Sensitivity patterns of the Gram negative bacteria isolated from patients, to the tested antibiotics.

Total n (%)	*E. coli* n (%)	*Enterobacter* spp n (%)	*Klebsiella* spp n (%)	*Pseudomonas* spp n (%)	*Acinetobacter* spp n (%)	Sensitivity	Antibiotic
28 (96.6)	0	0	0	8 (88.9)	20 (100)	S	Colistin
1 (3.4)	0	0	0	1 (11.1)	0	I	
0	0	0	0	0	0	R	
33 (86.8)	2 (100)	3 (100)	4 (100)	9 (100)	15 (75)	S	Meropenem
1 (2.6)	0	0	0	0	1(5)	I	
4 (10.6)	0	0	0	0	4 (20)	R	
32 (84.3)	2 (100)	3 (100)	4 (100)	8 (88.9)	15 (75)	S	Imipenem
2 (5.1)	0	0	0	1 (11.1)	1 (5)	I	
4 (10.6)	0	0	0	0	4 (20)	R	
17 (44.7)	1 (50)	3 (100)	2 (50)	8 (88.9)	3 (15)	S	Ciprofloxacin
0	0	0	0	0	0	I	
21 (52.5)	1 (50)	0	2 (50)	1 (11.1)	17 (85)	R	
16 (40)	1 (50)	1 (33.3)	2 (50)	8 (88.9)	4 (20)	S	Piperacillin/tazobactam
3 (7.5)	1 (50)	1 (33.3)	0	0	1 (5)	I	
19 (50)	0	1 (33.3)	2 (50)	1 (11.1)	15 (75)	R	
14 (36.8)	1 (50)	1 (33.3)	2 (50)	8 (88.9)	2 (10)	S	Cefepime
4 (10.6)	0	1 (33.3)	0	0	3 (15)	I	
20 (52.6)	1 (50)	1 (33.3)	2 (50)	1 (11.1)	15 (75)	R	
13 (34.2)	1 (50)	0	2 (50)	7 (77.8)	3 (15)	S	Cefazidime
3 (7.9)	0	1 (33.3)	0	1 (11.1)	1 (5)	I	
22 (57.9)	1 (50)	2 (66.7)	2 (50)	1 (11.1)	16 (80)	R	
13 (34.2)	1 (50)	1 (33.3)	2 (50)	6 (66.7)	3 (15)	S	Amikacin
1 (2.6)	1 (50)	0	0	0	0	I	
24 (63.2)	0	2 (66.7)	2 (50)	3 (33.3)	17 (85)	R	
8 (21)	1 (50)	0	2 (50)	2 (22.2)	3 (15)	S	Gentamicin
0	0	0	0	0	0	I	
30 (79)	1 (50)	3 (100)	2 (50)	7 (77.8)	17 (85)	R	
4 (13.8)	1 (50)	0	2 (50)	0	1 (5)	S	Ceftriaxone
2 (6.9)	0	0	0	0	2 (10)	I	
23 (79)	1 (50)	3 (100)	2 (50)	0	17 (85)	R	

S: sensitive, I: intermediate, R: resistant

Table 5. Sensitivity patterns of the Gram positive bacteria isolated to the tested antibiotics.

Antibiotic	Sensitivity	*S. aureus* N (%)	*S. epidermidis* N (%)	Enterococci spp N (%)	Total N (%)
Linezolid	S	15 (100)	1 (100)	1 (100)	17 (100)
	I	0	0	0	0
	R	0	0	0	0
Vancomycin	S	14 (92.3)	1 (100)	1 (100)	16 (94.1)
	I	1 (6.7)	0	0	1 (5.9)
	R	0	0	0	0
Quinupristin/ Dalfopristin	S	14 (93.3)	1 (100)	0	15 (88.2)
	R	1 (6.7)	0	1 (100)	2 (11.8)
Oxacillin	S	5 (33.3)	0	0	5 (31.3)
	R	10 (66.7)	1 (100)	0	11 (68.7)
Cefazolin	S	3 (20)	0	0	3 (18.8)
	I	1 (6.7)	0	0	1 (6.2)
	R	11 (73.3)	1(100)	0	12 (75)

S: sensitive; I: intermediate; R: resistant

Table 6. Cross-resistance of *Acinetobacter baumannii* to the tested antibiotics

Antibiotic	Number of isolates (percent) resistant to									
		PTC	GM	CIP	AK	IP	MP	PM	TX	TZ
PTC	15*		14 (93)	15 (100)	14 (93)	4 (26)	4 (26)	13 (87)	15 (100)	15 (100)
GM	17	14 (82)		16(94)	16 (94)	4 (23)	4 (23)	14 (82)	16 (94)	15 (88)
CIP	17	15 (88)	16 (94)		16 (94)	4 (23)	4 (23)	15 (88)	16 (94)	16 (94)
AK	17	14 (82)	16 (94)	16 (94)		4 (23)	4 (23)	14 (82)	16 (94)	15 (88)
IP	4	4 (100)	4 (100)	4 (100)	4 (100)		4 (100)	4 (100)	4 (100)	4 (100)
MP	4	4 (100)	4 (100)	4 (100)	4 (100)	4 (100)		4 (100)	4 (100)	4 (100)
PM	15	13 (87)	14(93)	15 (100)	14 (93)	4 (26)	4 (26)		14 (93)	14 (93)
TX	17	15 (88)	16 (94)	16 (94)	16 (94)	4 (23)	4 (23)	14 (82)		16 (94)
TZ	16	15 (94)	15 (94)	16 (100)	15 (94)	4 (25)	4 (25)	14 (88)	16 (100)	

Abbreviations: PTC: Piperacillin/tazobactam; GM: Gentamicin; CIP: Ciprofloxacin; AK: Amikacin; IP: Imipenem; MP: Meropenem; PM: Cefepime, TX: Ceftriaxone; TZ: Cefazidime.
*Total number of isolates resistant to the 9 antibiotics

development of strategies to reduce the incidence of nosocomial infections could be cost-effective and warranted.

The APACHE IV score for hospitalized patients was higher in the patients who died in ICUs, compared to those who were treated successfully. This data can serve as a warning to health-care [15,16].

A great number of nosocomial pneumonia cases (26; 44.8 %), were admitted to ICUs because of neurological disorders. High rates of neurological disorders were also previously reported in the region [17,18]. Most of them were purportedly referred to ICUs as a result of car or motorbike accidents A significant correlation between normalization of the PaO2/FiO2 ratio and body temperature (fever) 72

hours after the initiation of appropriate antibiotic therapy was observed, indicating the significance of appropriate treatment to the prognosis of the patients and consequently their survival and the cost effectiveness of the treatment [19-21]. This condition is more prominente when the patients are infected with antibiotic resistant bacteria such as *A. baumannii*, MRSA and *P. aeruginosa* (Table 2).

This survey showed an association between two predisposing factors, namely, previous antibiotic and corticosteroid therapies with VAP. When patients have previously received courses of antibiotics, resistant bacteria can survive and multiplication of antibiotic resistant bacteria continues despite empiric antibiotic therapy [22-24]. Therefore, determination of antibiotic sensitivity patterns alongside the administration of appropriate empiric antibiotic therapy could be mandatory in such cases [17,22]. Additionally, administration of corticosteroids could down-regulate specific and nonspecific immune system responses. To reduce the risk of infections in patients on ventilators, adjustment and reduction of therapeutic doses of such drugs are recommended [24,25].

The Gram negative bacteria in this study were highly sensitive to colistin, meropenem, and imipenem. Despite complete sensitivity of *A. baumannii* to colistin, its use should be restricted to only life-threatening conditions because of possible serious adverse neurological and renal effects [26-28]. Three antibiotics including linezolid, vancomycin, and quinupristin/dalfopristin showed high coverage in Gram positive bacteria. Unfortunately, linezolid, with the highest coverage rate (100%) in Gram positive bacteria, is not yet included in the list of routinely prescribed drugs in Iran, except in some rare life-threatening conditions for which the drug is purchased from abroad. It is well-known that *A. baumannii* is multidrug resistant, and that prevalence has been recently increasing in ICUs [29-31]. It is generally accepted that antibiotic resistance in *Acinetobacter* mainly develops due to the acquisition of a highly efficient resistance system, known as an integron [32-34]. To alleviate the situation, strict control measures and appropriate effective antibiotic therapy should be adopted. Furthermore, the majority of the isolated *Acinetobacter* exhibited cross-resistance to the tested antibiotics (Table 6), which limits the application of effective antibiotics whenever empiric therapy should be considered or alternative therapy is indicated.

In conclusion, because of the high possibility of transfer of the antibiotic resistance determinants through a variety of transmissible elements such as plasmids, transposons and especially integrons, the prevalence of multidrug resistant bacteria in ICUs must be reduced. Furthermore, comprehensive control measures must be taken and rational prescription of appropriate antibiotics must be practiced to help promote the patients' survival, reduce their time spent in hospital, and save on costs. Additionally, timely and wise prescription of corticosteroids and adopting a strategy to reduce body temperature and PaO2/FiO2 ratio could be beneficial in patients' outcomes and consequently reduce the mortality rate.

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Corresponding author

Dr. Aziz Japoni
Professor Alborzi Clinical Microbiology Research Center
Nemazee Hospital
Shiraz University of Medical Sciences
Shiraz, 71037-11351, Iran
Telephone: +98-711-6474264 Fax: +98-711- 6474303
Email: Japonia@hotmail.com

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