



Pay Attention to Valvular Disease in the Presence of Atopic Dermatitis

Naoto Fukunaga, MD; Yukikatsu Okada, MD, PhD; Yasunobu Konishi, MD;
Takashi Murashita, MD; Tadaaki Koyama, MD, PhD

Background: Atopic dermatitis (AD) is a common skin condition in which *Staphylococcus (S.) aureus* can cause native valve destruction in patients with infective endocarditis (IE). The aim of this study was to determine the early and late outcomes of IE and AD.

Methods and Results: The medical records of patients with IE and AD who presented between January 1997 and September 2010 were analyzed retrospectively. IE and AD patients were compared with those with IE without AD. The mean follow-up period was 5.5 ± 3.4 years. The incidence of AD among IE patients was 6.7% and they were significantly younger than those without AD (28.4 years vs. 53.7 years; $P < 0.0001$). Methicillin-sensitive *S. aureus* and *Streptococcus* species were more prevalent in IE with AD ($P < 0.0001$) and without AD ($P = 0.0259$), respectively. One developed postoperative mediastinitis caused by methicillin-resistant *S. aureus* despite preoperative skin care. None of the patients died in hospital or had IE recurrence. Freedom from recurrent IE or prosthetic valve endocarditis at 5 years was $100 \pm 0.0\%$.

Conclusions: Patients with IE must be checked for AD and history of AD because AD patients have a high incidence of staphylococcal colonization in their skin lesion.

Key Words: Atopic dermatitis; Infective endocarditis; *Staphylococcus aureus*; Valvular disease

Infective endocarditis (IE) is a microbial infection of the endocardial surface of the heart. It most commonly occurs at the heart valves, but it may also occur at the site of a septal defect, on the chordae tendineae, or mural endocardium.¹

Editorial p ????

Atopic dermatitis (AD) is a common skin condition colonized by aggressive *Staphylococcus (S.) aureus* that causes valve destruction or neurological complications in IE patients. These entities appear unrelated, although a few case reports have described IE in the presence of AD.²⁻⁶

We reviewed our experience of 8 patients with IE and AD at Kobe City Medical Center General Hospital and determined the early and late outcomes.

Methods

We performed 4111 cardiovascular surgeries involving cardiopulmonary bypass (CPB) between January 1997 and September 2010.

Eight patients (0.19%) who were preoperatively diagnosed

with IE and AD and 112 with IE but without AD were retrospectively analyzed. The incidence of AD among the IE patients was 6.7% (8/120).

Tables 1,2 list the clinical characteristics of the IE patients vs. the presence of AD.

Complete information was obtained from the 8 patients with IE and AD over a mean follow-up period of 5.5 ± 3.4 years.

Definition of AD

We used the definition and diagnostic criteria for AD formulated by the Japanese Dermatological Association that require the presence of pruritus, typical morphology and distribution and a chronic or chronically relapsing course irrespective of AD severity.⁷ Patients with AD not meeting these criteria should be evaluated based on age and clinical course for a tentative diagnosis of acute or chronic, non-specific eczema. Other diagnostic criteria are also shown.⁷

Patients with a history of AD were also included in this study because the underlying mechanism was *S. aureus* infection. Even when the skin appeared clear, it can be presumed that any skin breach would induce *S. aureus* infection in this cohort.

Received November 6, 2012; revised manuscript received January 29, 2013; accepted February 14, 2013; released online March 27, 2013 Time for primary review: 15 days

Department of Cardiovascular Surgery, Kobe City Medical Center General Hospital, Kobe, Japan

Mailing address: Naoto Fukunaga, MD, Department of Cardiovascular Surgery, Kobe City Medical Center General Hospital, 2-1-1 Minatojima-minamimachi, Chuo-ku, Kobe 650-0047, Japan. E-mail: naotowakimachi@hotmail.co.jp

ISSN-1346-9843 doi:10.1253/circj.CJ-12-1371

All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp

Table 1. Clinical Characteristics of IE Patients vs. Presence of AD

	IE with AD (n=8)	IE without AD (n=112)	P-value
Mean age (years)	28.4±7.7	53.7±16.8	<0.0001
Male	6 (75)	72 (64)	0.7116
Hypertension	1 (13)	34 (30)	0.4348
Hyperlipidemia	0 (0)	13 (11)	0.5966
Diabetes mellitus	0 (0)	15 (13)	0.5937
COPD	0 (0)	2 (2)	0.7031
Stroke	6 (75)	37 (33)	0.0244
CAD	0 (0)	4 (4)	0.5867
Liver cirrhosis	0 (0)	8 (7)	0.4339
Creatinine (mg/dl)	0.93±0.34	1.30±1.23	0.4094
Hemodialysis	0 (0)	5 (4)	0.5416
PAD	0 (0)	5 (4)	0.5416
LVEF (%)			
≥60	4 (50)	71 (63)	0.4713
40–60	4 (50)	27 (24)	0.2022
≤40	0 (0)	1 (1)	0.7884
NYHA functional class			
I	3 (38)	3 (3)	0.0036
II	2 (25)	62 (55)	0.1439
III	2 (25)	24 (21)	0.6833
IV	1 (13)	23 (21)	0.5630
Urgency of surgery			
Elective	4 (50)	77 (69)	0.4351
Emergency/Urgent	4 (50)	35 (31)	0.4351

Data given as n (%) or mean±SD. AD, atopic dermatitis; BSA, body surface area; CAD, coronary artery diseases; COPD, chronic obstructive pulmonary disease; IE, infective endocarditis; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAD, peripheral artery disease.

Managements of Skin Care in AD

Based on our experience, the patients are placed under routine skin care for AD before surgery. **Table 3** summarizes the skin conditions of the present 8 patients. Seven of them were under skin care directed by dermatologists. We analyzed the use of steroid/non-steroid ointment, moisturizing and anti-allergic agents. Skin conditions in patients 2 and 8 were better than that in the others, and 6 patients had some preoperative skin problems that were appropriately managed.

Statistical Analysis

Data were statistically analyzed using StatView version 5.0 (SAS Institute, Cary, NC, USA). Categorical variables are pre-

Table 2. Clinical Characteristics of IE vs. Presence of AD

	IE with AD (n=8)	IE without AD (n=112)	P-value
Valve involved			
Mitral	6 (75)	53 (47)	0.1303
Aortic	0 (0)	26 (23)	0.1236
Mitral and Aortic	1 (13)	19 (17)	0.7434
Others	1 (13)	14 (13)	–
Blood organism			
MSSA	6 (75)	12 (11)	<0.0001
MRSA	1 (13)	2 (2)	0.0608
Other <i>Staphylococcus</i>	0 (0)	1 (1)	0.7884
<i>Streptococcus pneumoniae</i>	0 (0)	4 (4)	0.5867
<i>Streptococcus viridans</i>	1 (13)	2 (2)	0.0608
<i>Streptococcus mitis</i>	0 (0)	7 (6)	0.4662
Other <i>Streptococcus</i>	0 (0)	44 (39)	0.0259
<i>Enterococcus faecalis</i>	0 (0)	5 (4)	0.5416
Other <i>Enterococcus</i>	0 (0)	1 (1)	0.7884
Others	0 (0)	5 (4)	0.5416
Culture negative	0 (0)	26 (23)	0.1236

Data given as n (%). MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*. Other abbreviations as in Table 1.

sented as total numbers.

Continuous variables are expressed as mean±SD and were compared using an unpaired t-test. P<0.05 was considered to indicate statistical significance.

Results

Table 1 lists the characteristics of the IE patients with or without AD. Most demographic variables did not significantly differ. IE patients with AD were statistically much younger than those without AD (28.4 years vs. 53.7 years; P<0.0001). More IE patients without AD had underlying diseases such as hypertension, hyperlipidemia and diabetes mellitus than those with AD, but the difference did not reach statistical significance. More patients with AD had New York Heart Association (NYHA) functional class I than those without AD. The total number of patients with NYHA functional classes I and II, however, was similar between the 2 groups.

Preoperative stroke was more prevalent among IE patients with, than without, AD (P=0.0244).

Table 2 lists details of IE including location and causative organisms in the 2 groups. Involved valves did not significantly

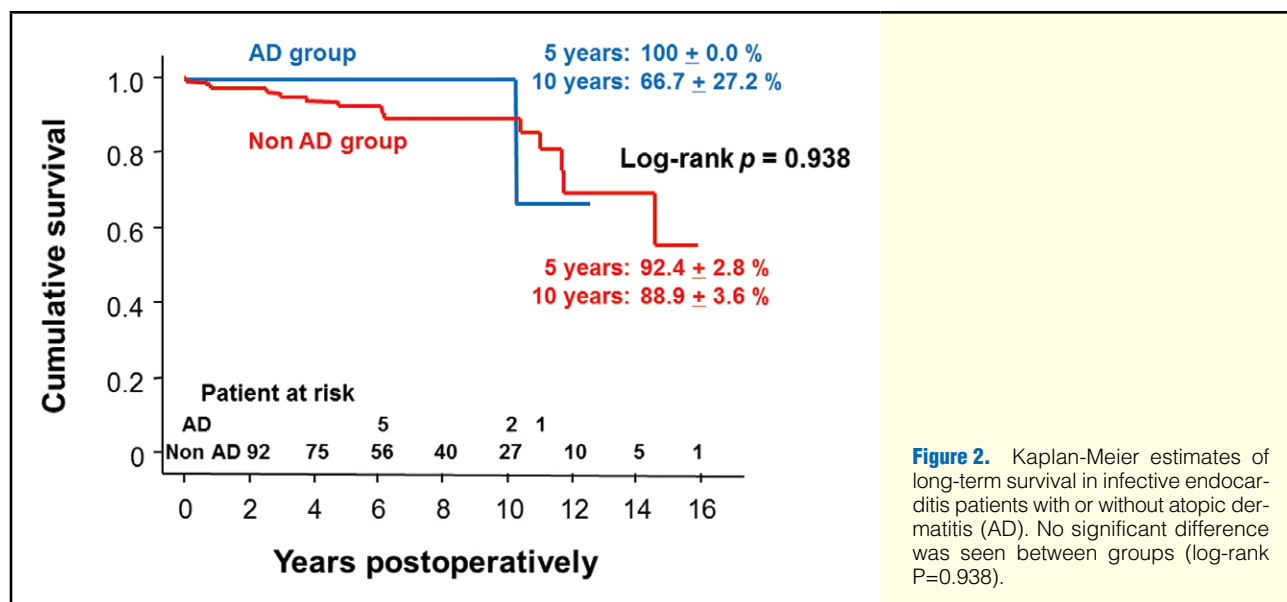
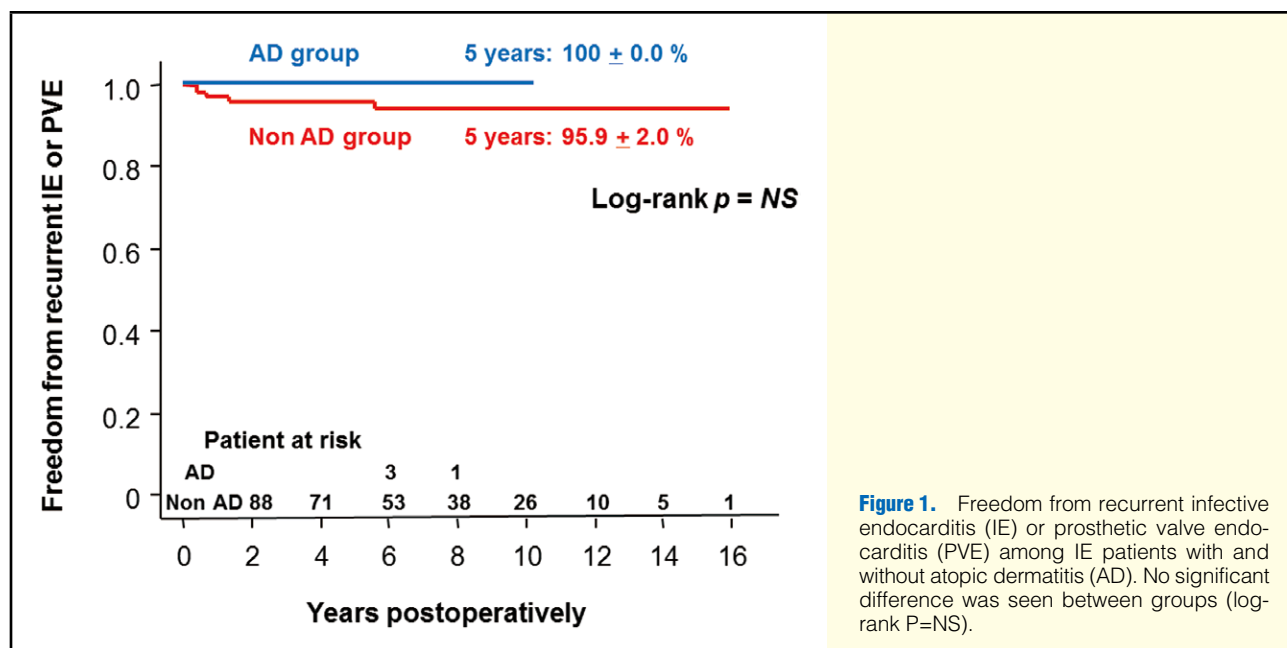
Table 3. Atopic Dermatitis Management

Patient	Age (years)/Sex	Skin condition	Management
1	20/M	Dry skin	Non-steroid ointment, oral anti-allergic agent
2	20/F	Clear	No
3	37/M	Dry skin	Non-steroid ointment
4	31/M	Systemic erythema	Steroid ointment
5	40/M	Dry skin, erythema	Steroid ointment, moisturizing agent
6	21/F	Systemic erythema	Steroid/non-steroid ointment
7	28/M	Dry skin	Steroid ointment, anti-allergic agent
8	30/M	Clear	Moisturizing agent

Table 4. Details of Eight Patients With IE and AD

Patient	Type of surgery	Heart disease	Organism	Complications	Surgery	Approach
1	EL	MR	MSSA	Brain abscess, CI, BM	MVP	Sternotomy
2	EM	TR	MRSA	PI	TVP	Sternotomy
3	EM	MR	MSSA	CI, RI, SI	MVP	Sternotomy
4	EL	MR	MSSA	CI	MVP	Sternotomy
5	EL	MR, ASD	MSSA	CI	MVP + ASD closure	Thoracotomy
6	UR	MR	<i>Streptococcus viridans</i>	No	MVP	Thoracotomy
7	EL	MR	MSSA	Brain abscess, CI, RI, SI	MVP	Thoracotomy
8	EM	AR, MR	MSSA	Brain abscess, CI	AVR + MVP	Sternotomy

AR, aortic valve regurgitation; ASD, atrial septal defect; AVR, aortic valve replacement; BM, bacterial meningitis; CI, cerebral infarction; EM, emergency surgery; EL, elective surgery; MR, mitral valve regurgitation; MVP, mitral valve plasty; PI, pulmonary infarction; RI, renal infarction; SI, splenic infarction; TR, tricuspid valve regurgitation; TVP, tricuspid valve plasty; UR, urgent surgery. Other abbreviations as in Tables 1,2.



differ between the 2 groups. The mitral valve was the most frequently affected in both groups, but the aortic valve was also affected in the IE group without AD. Methicillin-sensitive and -resistant *S. aureus* spp. (MSSA and MRSA, respectively) were the most prevalent organisms in IE with AD ($P<0.0001$ and $P=0.0608$, respectively), whereas *Streptococcus* spp. were the most prevalent in those without AD ($P=0.0259$).

Eight patients with AD underwent open-heart surgery for IE on CPB. Table 4 summarizes the details of IE in eight patients. Patients 8 and 4 had a history of hypertension and antiphospholipid syndrome, respectively. None of the eight patients had potential risk factors for IE such as dental cavities or oral procedures before IE occurred.

Eight patients had pre-existing heart valve diseases including mitral (MR), aortic (AR) and tricuspid valve (TR) regurgitation. Preoperative left ventricular ejection fraction and NYHA functional class were $58.6\pm9.3\%$ and 2.1 ± 1.1 , respectively.

The status of three patients (2, 3 and 8) at NYHA functional classes III or IV was emergency and that of one (patient 6) at NYHA functional class I was urgent. The main causative organism of IE was *S. aureus*. Except the patient with IE caused by *Streptococcus viridans*, seven patients with IE induced by *S. aureus* had IE-related complications and 6 had preoperative stroke. The incidence rate of stroke was much higher in IE with, than without AD ($P=0.0244$). All eight patients underwent open-heart surgery. A 30-year old male patient (patient 8) underwent double valve surgery consisting of aortic valve replacement with a prosthesis and mitral valve plasty (MVP). Others underwent reparative single valve surgery such as MVP and tricuspid valve plasty (TVP). Open-heart surgery proceeded via a right thoracotomy and conventional median sternotomy in patients 5, 6 and 7, and remaining 5 patients.

The surgical approach was selected based on the surgeons' preference, the nature of the surgical procedure and the condition of patients' skin at the time. Because we previously reported a higher incidence of postoperative mediastinitis in patients with AD undergoing median sternotomy than thoracotomy,⁸ we selected thoracotomy whenever possible.

The CPB duration was 166.2 ± 48.2 min and 89.3 ± 16.9 min for the sternotomy and thoracotomy groups, respectively, and aortic clamp duration was 117.6 ± 47.8 min and 56.7 ± 14.6 min, respectively.

After surgery, antibiotics appropriate to the causative organism were prescribed to all patients for a few weeks based on our experience and the guidelines for the prevention and treatment of IE reported by the Japan Circulation Society.

The duration of i.v. antibiotic treatment was approximately 2 weeks if the IE was cured, and 4–6 weeks if IE remained active, but we considered changing the antibiotics when fever persisted or if laboratory data did not improve.

Postoperative mediastinitis that occurred in patient 1, who had MRSA despite preoperative skin care, was successfully treated by further surgical and medical approaches. IE did not recur in any patient while in hospital.

None of the patients died in hospital, and all were discharged in good health.

During an average follow-up period of 5.5 years, a 20-year-old woman (patient 2) who underwent TVP for IE caused by MRSA died of heart failure. A 20-year-old man (patient 1) developed postoperative recurrent mediastinitis that was surgically and medically managed. Freedom from recurrent IE or prosthetic valve endocarditis (PVE) did not significantly differ between the IE patients with or without AD (Figure 1; log-rank $P=NS$). Long-term survival rates did not significantly

differ between the 2 groups (Figure 2; log-rank test, $P=0.938$). The NYHA functional class at final follow-up was 1.4 ± 1.1 .

Discussion

We examined the early and late outcomes of IE with AD, which is not generally considered sufficiently important to warrant particular attention. Although some authors have published single case reports describing such patients, they did not warn cardiac surgeons or cardiologists about the danger of this association.^{2–6}

AD is a common skin condition that affects 1–3% of the population, and *S. aureus* is often the underlying mechanism of colonization in such patients.² A deficiency in the expression of inflammation-induced antimicrobial, antifungal, and antiviral peptides known as cathelicidins (LL-37) and β -defensin 2 (HBD-2) plays a role in increasing the susceptibility of patients with AD to colonization with *S. aureus*.⁹ Therefore, the skin of patients with AD provides a favorable environment for colonization, proliferation and invasion by *S. aureus*.² Carriers of *S. aureus* are at high risk for invasive *S. aureus* infections of the bloodstream when the skin is breached. A skin breach could thus lead easily to IE in patients with AD who have valvular disease. AD-related IE, however, has probably remained unrecognized by cardiac surgeons and cardiologists, which would explain the paucity of literature describing a link. Such patients might be encountered quite frequently in routine practice because AD is very common. The incidence of AD among IE patients in the present study was 6.7%.

Recently, *S. aureus* has become the most common cause of IE,¹ characterized by extensive tissue destruction, abscess formation and annular infection or fistula formation requiring surgical management in addition to medical therapy. Neurologic complications of IE, particularly embolic events, are also likely to be higher with *S. aureus*. *Streptococcus* spp. are relatively common in adults ≥ 60 years of age.¹ The higher prevalence of *Streptococcus* spp. in the IE patients without AD, who had a mean age of 54 years, was reasonable.

The present findings support the notion that *S. aureus* is extremely aggressive because seven patients with IE caused by this organism had devastating preoperative complications such as brain abscesses, cerebral and multi-organ infarction. The incidence of preoperative stroke was much higher in the IE patients with AD, which might reflect the nature of the causative organism. The IE patients without AD were more often infected with *Streptococcus* spp., which are less invasive than *S. aureus*. The present findings indicated that complicated IE caused by aggressive *S. aureus* was more likely to develop in patients with than without AD.

Three of the seven patients infected with *S. aureus* presented at emergency due to progressive heart failure. In contrast, IE caused by *Streptococcus viridans*, which is an established cause of IE,¹ was not preoperatively complicated. None of the present patients died in hospital.

Skin care is important for preventing IE in the presence of valvular and other heart diseases. According to the guidelines for AD management, skin care for dry skin or slight skin eruption is recommended to prevent the recurrence of inflammation and reduce symptoms.⁷ We have introduced preoperative skin care by dermatologists for AD patients at Kobe City Medical Center General Hospital.⁸ Most of the present patients had some skin trouble, although the skin appeared clear in two of them. The barrier function, however, is decreased in the skin of patients with AD, and thus, all patients must undergo skin care to prevent infection with *S. aureus* irrespective of require-

ments for cardiac surgery.

We selected 2 surgical approaches to address the management of IE. A median sternotomy is the standard approach to achieve an optimal operative field for cardiac surgery, but thoracotomy is also useful for minimally invasive cardiac surgery such as minimally invasive MVP and aortic valve replacement.¹⁰ Therefore, minimally invasive valve replacement surgery is very useful to avoid PVE, which has high mortality rates. Transcatheter closure of atrial septal defect, which was approved in 2005 in Japan, has excellent mid-term outcomes.¹¹ This technique may be an optional strategy in patients with AD.

Median sternotomy requires sternal division, whereas thoracotomy preserves sternal stability. This difference is very important in the context of AD, because the skin of such patients is colonized with *S. aureus* that can invade the bloodstream via exposed bone marrow during sternotomy, leading to postoperative mediastinitis.¹² We previously reported the clinical outcomes of patients with AD who underwent open-heart surgery.⁸ In that study, 3 patients who underwent open-heart surgery via conventional median sternotomy developed postoperative mediastinitis caused by MRSA. Wound infection never occurred after thoracotomy. The incidence rate of mediastinitis was 15%, which was much higher than that in the general population (1–2%).¹³ Based on this experience, we prefer to use thoracotomy in patients with AD as much as possible.

Compared with the thoracotomy group, the duration of operation was longer for the sternotomy group, possibly because their condition was relatively more complicated and sternotomy was considered safer.

With regard to long-term outcome, the incidences of freedom from recurrent IE or PVE and survival at 5 years in the IE with AD group were both 100±0.0%, which was not significantly different from that for the IE group without AD. Although special care must be taken to avoid postoperative mediastinitis in AD patients, freedom from recurrent IE or PVE and survival were favorable even in these patients.

The present study is limited by the fact that it is retrospective in nature and the case series was small. Therefore, we cannot objectively assume an association between IE and AD.

To our knowledge, however, this is the first institutional review of IE in the presence of AD. We believe that the present study has important implications for cardiac surgeons and

cardiologists who encounter patients with AD.

Conclusion

Patients with IE must be checked for current AD and a history of AD because the incidence of staphylococcal colonization in AD skin lesions is high. Preoperative skin care should be introduced for such patients to prevent *S. aureus* infection arising after open-heart surgery for IE.

References

1. Mylonakis E, Calderwood SB. Infective endocarditis in adults. *N Engl J Med* 2001; **345**: 1318–1330.
2. Benenson S, Ziimhony O, Dahan D, Solomon M, Raveh D, Schlesinger Y, et al. Atopic dermatitis: A risk factor for invasive *Staphylococcus aureus* infections: Two cases and review. *Am J Med* 2005; **118**: 1048–1051.
3. Onoda K, Mizutan H, Komada T, Kanematsu S, Shimono T, Shimpō H, et al. Atopic dermatitis as a risk factor acute valve endocarditis. *J Heart Valve Dis* 2000; **9**: 469–471.
4. Mohiyiddeen G, Brett I, Jude E. Infective endocarditis caused by *Staphylococcus aureus* in a patient with atopic dermatitis: A case report. *J Med Case Rep* 2008; **2**: 143.
5. Grabczynska SA, Cerio R. Infective endocarditis associated with atopic eczema. *Br J Dermatol* 1999; **140**: 1193–1194.
6. Oike MG, Warner JO. Atopic dermatitis complicated by acute bacterial endocarditis. *Acta Paediatr Scand* 1989; **78**: 463–464.
7. Saeki H, Furue M, Furukawa F, Hide M, Ohtsuki M, Katayama I, et al. Guidelines for management of atopic dermatitis. *J Dermatol* 2009; **36**: 563–577.
8. Fukunaga N, Yuzaki M, Shomura Y, Fujiwara H, Nasu M, Okada Y. Clinical outcomes of open-heart surgery in patients with atopic dermatitis. *Asian Cardiovasc Thorac Ann* 2012; **20**: 137–140.
9. Ong PY, Ohtake T, Brant C, Strickland I, Boguniewicz M, Ganz T, et al. Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Med* 2002; **347**: 1151–1160.
10. Hiraoka A, Kuinose M, Chikazawa G, Totsugawa T, Katayama K, Yoshitaka H. Minimally invasive aortic valve replacement surgery: Comparison of port-access and conventional standard approach. *Circ J* 2011; **75**: 1656–1660.
11. Ueda H, Yanagi S, Nakamura H, Ueno K, Gatayama R, Asou T, et al. Device closure of atrial septal defect: Immediate and mid-term results. *Circ J* 2012; **76**: 1229–1234.
12. Schimmer C, Reents W, Bernerder S, Eigel P, Sezer O, Scheld H, et al. Prevention of sternal dehiscence and infection in high-risk patients: A prospective randomized multicenter trial. *Ann Thorac Surg* 2008; **86**: 1897–1904.
13. Basket RJF, MacDougall CE, Ross DB. Is mediastinitis a preventable complication? A 10-year review. *Ann Thorac Surg* 1999; **67**: 462–465.