THE JOURNAL OF DERMATOLOGY

doi: 10.1111/j.1346-8138.2012.01639.x

Journal of Dermatology 2013; **40**: 2–14

GUIDELINE

Guidelines for the management of cutaneous lymphomas (2011): A consensus statement by the Japanese Skin Cancer Society – Lymphoma Study Group

Makoto SUGAYA,[1] Toshihisa HAMADA,[2] Kazuhiro KAWAI,[3] Kentaro YONEKURA,[4] Mikio OHTSUKA,[5] Takatoshi SHIMAUCHI,[6] Yoshiki TOKURA,[6] Koji NOZAKI,[7] Koji IZUTSU,[8] Ritsuro SUZUKI,[9] Mitsuru SETOYAMA,[10] Tetsuo NAGATANI,[11] Hiroshi KOGA,[12] Mamori TANI,[13] Keiji IWATSUKI[2]

[1]*Department of Dermatology, Faculty of Medicine, University of Tokyo, Tokyo,* [2]*Department of Dermatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama,* [3]*Department of Dermatology, Kagoshima University Graduate School of Medical and Dental Sciences,* [4]*Department of Dermatology, Imamura Bun-in Hospital, Kagoshima,* [5]*Department of Dermatology, Fukushima Medical University School of Medicine, Fukushima,* [6]*Department of Dermatology, Hamamatsu University School of Medicine, Hamamatsu,* [7]*Department of Gastrointestinal, Breast and Endocrine Surgery, The University of Tokyo Hospital,* [8]*Department of Hematology, Toranomon Hostapital, Tokyo,* [9]*Department of Hematopoietic Stem Cell Transplantation Data Management/Biostatistics, Nagoya University Graduate School of Medicine, Nagoya,* [10]*Department of Dermatology, Faculty of Medicine, University of Miyazaki, Miyazaki,* [11]*Department of Dermatology, Tokyo Medical University Hachioji Medical Center, Tokyo,* [12]*Department of Dermatology, School of Medicine, Shinshu University, Matsumoto, and* [13]*Department of Dermatology, Graduate School of Medicine, Osaka University, Osaka, Japan*

ABSTRACT

In 2010, the first Japanese edition of guidelines for the management of cutaneous lymphoma was published jointly by the Japanese Dermatological Association (JDA) and the Japanese Skin Cancer Society (JSCS) – Lymphoma Study Group. Because the guidelines were revised in 2011 based on the most recent data, we summarized the revised guidelines in English for two reasons: (i) to inform overseas clinicians about our way of managing common types of cutaneous lymphomas such as mycosis fungoides/Sézary syndrome; and (ii) to introduce Japanese guidelines for lymphomas peculiar to Asia, such as adult T-cell leukemia/lymphoma and extranodal natural killer/T-cell lymphoma, nasal type. References that provide scientific evidence for these guidelines have been selected by the JSCS – Lymphoma Study Group. These guidelines, together with the degrees of recommendation, have been made in the context of limited medical treatment resources, and standard medical practice within the framework of the Japanese National Health Insurance system.

Key words: adult T-cell leukemia/lymphoma, cutaneous lymphoma, guideline, mycosis fungoides, Sézary syndrome.

INTRODUCTION

A number of guidelines on the management of cutaneous lymphoma have already been published in Europe and North America. However, the prevalence and clinical types of cutaneous lymphoma vary among different ethnic groups, and medical systems vary from country to country. As a result, the unmodified European/US guidelines may not be well-suited for use in Japan. We wanted to provide a "best treatment" consensus on clinical practice guidelines for cutaneous lymphoma, based on the actual situation in Japan.

In these guidelines, the diagnosis of cutaneous lymphoma is based on classifications from the World Health Organization (WHO) and European Organization for Research and Treatment of Cancer, Cutaneous Lymphomas Task Force (EORTC),[1] and on the 4th edition of the WHO classification published in 2008.[2] The staging and classification of mycosis fungoides (MF)/Sézary syndrome (SS) are based on the tumor

Correspondence: Keiji Iwatsuki, M.D., Ph.D., Department of Dermatology, Okayama University Graduate School of Medicine, Dentistry and Pharmoceutical Sciences, Okayama, 700-8558, Japan. Email: keijiiwa@cc.okayama-u.ac.jp

Conflict of interest: none

Received 22 June 2012; accepted 26 June 2012.

–node–metastasis (TNM) staging from the International Society for Cutaneous Lymphomas (ISCL) group.[3] For cutaneous lymphomas other than MF/SS, we decided to use the TNM staging system proposed by the ISCL[4] rather than the conventional Ann Arbor classification system.

The British group,[5] EORTC[6] and European Society for Medical Oncology (ESMO)[7] each issued treatment guidelines for MF/SS. In 2009, using published work and overseas guidelines for references, we published the first edition of guidelines based on the actual situation of cutaneous lymphoma in Japan.[8] Because the guidelines were revised in 2011 based on the most recent data, we summarized the revised guidelines in English for two reasons: (i) to inform overseas clinicians about our way of managing common types of cutaneous lymphomas such as MF/SS; and (ii) to introduce Japanese guidelines for lymphomas peculiar to Asia, such as adult T-cell leukemia/lymphoma and extranodal natural killer (NK)/T-cell lymphoma (ENKL), nasal type. References that provide scientific evidence for these guidelines have been selected by the Japanese Skin Cancer Society (JSCS) – Lymphoma Study Group. These guidelines, together with the degrees of recommendation, have been made in the context of limited medical treatment resources, and standard medical practice within the framework of the Japanese National Health Insurance system. The evidence level and degree of recommendation used for the current version are shown in Table 1.

BASIS FOR THE CURRENT GUIDELINES

The cutaneous lymphomas listed in the present guidelines are basically in accordance with the WHO–EORTC classification (2005),[1] but it is difficult to precisely define "primary cutaneous" lymphoma. Ordinarily, a condition is defined as "primary cutaneous" lymphoma if appropriate procedures show no extracutaneous lesions at the time of diagnosis. The present guidelines include lymphomas and hematopoietic malignancies with marked affinity for the skin (Fig. 1, Table 2). The diagnostic nomenclature follows the 4th edition of the WHO classification (2008).[2]

To describe the skin lesions of cutaneous lymphoma, typically MF/SS, uniform terminology is needed. Without consistent terminology, accurate disease staging is impossible, and inconsistencies may develop in prognostic analysis. The ISCL/EORTC group has defined terminology for MF/SS.[9] Those definitions are adopted in the present guidelines (Table S1), and representative clinicopathological findings of various types of cutaneous lymphoma are provided in supporting information (Figs S1–S7).

STAGING

Staging for MF/SS (ISCL/EORTC 2007, modified in 2011)

For the staging of MF/SS, we previously used the categories developed by Bunn *et al.*[10] and Sausville *et al.*[11] In 2007, a new staging system was proposed by the ISCL/EORTC group,[3] which was modified in 2011 (Tables S2 and S3).[12]

In the ISCL/EORTC staging system, peripheral blood findings are classified into three categories: B_0 (atypical lymphocytes accounting for $\leq 5\%$ of peripheral blood lymphocytes), B_1 (atypical lymphocytes accounting for >5% of peripheral blood lymphocytes, but <1000/μL), and B_2 (atypical lymphocyte

Table 1. Standards for the determination of evidence level and degree of recommendation

Classification of evidence level	
I	Systematic review and/or meta-analysis Staging/classification proposal and treatment recommendation or consensus paper from WHO, EORTC and ISCL
II	One or more randomized comparative studies
III	Non-randomized comparative studies
IV	Analytical epidemiology studies (cohort research and case–control studies) Case series studies (≥ 5 cases)
V	Descriptive studies (case reports and case series studies [<5 cases])
VI	Opinions of expert committee and individual specialists*
Degree of recommendation classification†	
A	Strongly recommended for implementation (efficacy shown by at least 1 report providing level I or high-quality level II evidence)
B	Recommended for implementation (efficacy shown by ≥ 1 reports providing low-quality level II, high-quality level III, or very high-quality level IV evidence)
B-C1	Recommended for implementation, but less strongly supported than B
C1	Implementation can be considered, but evidence‡ is insufficient (low-quality III–IV, high-quality multiple V, or committee-approved VI evidence)
C2	No evidence‡; cannot be recommended (no evidence of effectiveness, or evidence available of ineffectiveness)
D	Recommended not to implement (high-quality evidence of ineffectiveness or harmfulness)

*Data from basic research and theories derived from such data are placed at this level. †Some of the "degree of recommendation" statements in these guidelines are not in complete agreement with the above table. ‡"Evidence" refers to knowledge from clinical trials and epidemiological research. This is because these "degree of recommendation" grades were based on a consensus among the committee members, taking feasibility into account. This consensus was reached after due consideration of the shortage of evidence internationally on the treatment of skin cancer and the fact that the evidence from overseas is not directly applicable in Japan.

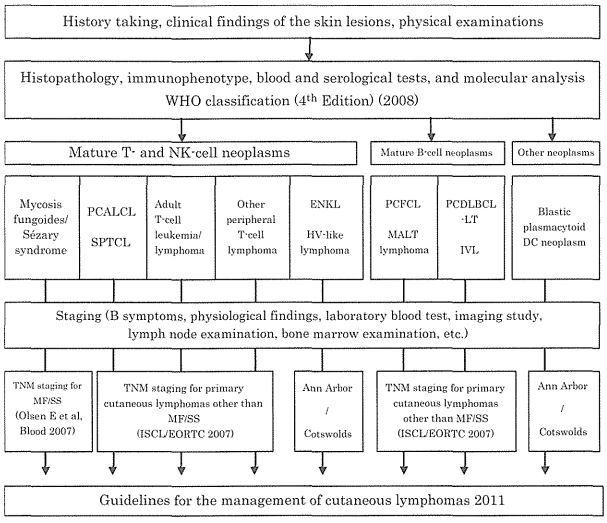

Figure 1. Diagnostic and staging algorithm for cutaneous lymphomas. DC, dendritic cell; ENKL, extranodal T/NK-cell lymphoma, nasal type; HV, hydroa vacciniforme; IVL, intravascular large B-cell lymphoma; MALT lymphoma, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue type; MF/SS, mycosis fungoides/Sézary syndrome; PCALCL, primary cutaneous anaplastic large cell lymphoma; PCDLBCL-LT, primary cutaneous diffuse large B-cell lymphoma, leg type; PCFCL, primary cutaneous follicle center lymphoma; SPTCL, subcutaneous panniculitis-like T-cell lymphoma; TNM, tumor–node–metastasis; WHO, World Health Organization.

count of $\geq$1000/μL with a positive clone). Additional parameters that meet the B_2 criteria include the following: CD4/CD8 ratio of 10 or more, $CD4^+CD7^-$ of 40% or more, and $CD4^+CD26^-$ of 30% or more.[3,12,13] Cases with erythroderma who meet the B_2 criteria are defined as SS, or stage IVA_1 (Table S3 and Fig. S1). Erythrodermic MF of the B_0 or B_1 category is classified as stage IIIA or IIIB.

If lymphoma cells replace all or large portions of the lymph node structure, the condition is diagnosed as N_3 and is classified as stage IV_2 (Table S3). Even if the lymph node is infiltrated by atypical cells, a diagnosis of N_3 is not made as long as the foci are small and nodal architecture is preserved.[3,12]

TNM classification of cutaneous lymphoma other than MF/SS (ISCL/EORTC 2007)

No TNM classification appropriate for the evaluation of cutaneous lesions was available for primary cutaneous lymphoma categories other than MF/SS. In 2007, the ISCL and EORTC proposed a new TNM classification system (Table S4).[4] Although the TNM classification reflect the extent of lesions, an adequate staging system has not been established yet. Moreover, the classification does not indicate prognoses for some disease types.[14] The category of "non-MF/SS" covers many types of cutaneous lymphoma, and new staging systems are needed for each disease type, based on the collected clinical data and prognostic analysis.

Table 2. Classification of cutaneous lymphomas

Cutaneous T/NK cell lymphoma
Mycosis fungoides: MF
Variants
Folliculotropic MF
Pagetoid reticulosis
Granulomatous slack skin
Sézary syndrome: SS
Adult T-cell leukemia/lymphoma
Primary cutaneous $CD30^+$ T-cell lymphoproliferative disorders
Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Hydroa vacciniforme-like lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous $CD8^+$ aggressive epidermotropic cytotoxic T-cell lymphoma*
Primary cutaneous $CD4^+$ small/medium T-cell lymphoma*
Peripheral T-cell lymphoma, not otherwise specified
Cutaneous B-cell lymphomas
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue
Primary cutaneous follicle center lymphoma
Primary cutaneous diffuse large B-cell lymphoma, leg type
Intravascular large B-cell lymphoma
Hematological precursor cell neoplasm
Blastic plasmacytoid dendritic cell neoplasm

*Provisional. Representative clinicopathological features of MF/SS, anaplastic large cell lymphoma, adult T-cell leukemia/lymphoma, subcutaneous panniculitis-like T-cell lymphoma, extranodal NK/T cell lymphoma, hydroa vacciniforme-like lymphoma, blastic plasmacytoid dendritic cell neoplasm have been shown in Figs S1–S7.

Staging of other cutaneous lymphomas and hematopoietic malignancies

Shimoyama and colleagues have provided a widely-used classification of adult T-cell leukemia/lymphoma (ATLL): acute, lymphoma, chronic and smoldering types.[15] According to Shimoyama's criteria, ATLL patients with cutaneous lesions only are usually classified into the smoldering group. It is not appropriate to stage ATLL patients with the TNM system proposed by Kim *et al.*[4] because of the presence of minimal hematological disease. Furthermore, for other hematological malignancies such as ENKL, nasal type, and blastic plasmacytoid dendritic cell neoplasm, the Ann Arbor or Cotswolds staging (Table S5)[16] has been widely adopted in Japan because of hematological and extracutaneous spreading of the illness.

EPIDEMIOLOGY OF CUTANEOUS LYMPHOMA

In line with the WHO classification (3rd edn), the incidence of all types of lymphomas was reported by pathologists in Japan.[17] The data were distinct from those in Western countries and similar in several ways to other data from Asia, although the relatively high rate of ATLL was attributed to the geographical difference in the etiologic factor, human T-lymphotropic virus

type 1 (HTLV-1). The JSCS – Lymphoma Study Group has conducted a nationwide survey of cutaneous lymphoma annually since 2007 (www.okayama-hihuka.jp/pdf/kekka2010.pdf). MF/SS account for approximately 51% of all cutaneous lymphomas, followed by ALCL and ATLL at approximately 9–8% each. B-cell lymphoma accounts for approximately 15% of all cutaneous lymphoma in Japan, so it is less frequent than in Europe or North America. ENLK, nasal type, accounts for only approximately 2%, which is nearly always associated with Epstein–Barr virus (EBV) infection. The NK-cell type is dominant in Japan.

PROGNOSTIC ANALYSIS

Prognostic analyses of patients with cutaneous lymphoma are limited.[18–21] In the present guidelines, we have highlighted the prognoses of MF/SS, ATLL, and ENLK, nasal type, the latter two of which preferentially occur in Japan. For the other types of cutaneous lymphoma, we have used reports from other countries (Table 3).[22–26]

MF/SS

Previous researchers already contributed to disease staging and prognostic analysis for MF/SS.[27] Since the new staging was advocated in 2007, prognostic analyses have been reported from Japan and the UK (Table 3).[18,22] The survival rates of Japanese patients with MF/SS were similar to those shown in previous studies conducted in the USA and Europe. The prognoses of patients with skin tumor (stage IIB) and extracutaneous involvement (stage IV) were significantly worse than those of patients with early-stage disease (stages IA–IIA). Erythrodermic MF patients without blood involvement (stage IIIA) showed excellent survival. Independent prognostic factors in multivariate analyses were higher age and the presence of either skin tumor or extracutaneous disease.[18] Although findings in Japan showed the prognosis for stage IIIA to be quite favorable, a British analysis indicated that it was similar to the prognosis for stage IIb,[22] this may have occurred because the two reports did not use the same diagnostic criteria for erythrodermic lymphoma, resulting in differences in patient characteristics.

ATLL

A recent observation in Japan indicated that the patch and plaque types of ATLL were associated with better survival rates.[19] Multivariate analysis demonstrated that the hazard ratios of the erythrodermic and nodulotumoral types were significantly higher than that of the patch type, and that the eruption type is an independent prognostic factor for ATLL. The overall survival worsened as the T stage became more advanced: the multipapular type and T2 were comparable, and the purpuric type had a significantly poorer prognosis than T1 (Fig. S3).[19]

ENKL

Suzuki *et al.*[20] have reported the prognosis of a total 150 patients with ENKL, nasal type, consisting of 123 nasal and 27 extranasal (16 cutaneous, nine hepatosplenic, one intestinal and one nodal) lymphomas. We focused on patients with the cutaneous type of ENKL, and re-examined their prognoses. Patients with stage I disease (determined by the Ann Arbor staging system) showed a favorable prognosis in 5-year overall survival of 75%, but the prognoses deteriorated in the advanced stages (Table 3). Unlike a previous study on $CD56^+$ hematological neoplasms with or without EBV infection in Europe,[28] our data highlighted that ENKL is usually associated with EBV infection, and assessed the prognoses of "nasal" and "cutaneous" ENKL separately.

TREATMENT GUIDELINES

Treatment guidelines for MF/SS

Mycosis fungoides/Sézary syndrome is the oldest defined form of cutaneous lymphoma, and is more common than other primary cutaneous lymphomas (Tables 4–11). At present, no treatment based on high-level evidence is available for this condition. In many cases, the clinical course may extend for 10 years or more. Therefore, the success or failure of therapeutic intervention may be difficult to determine. Moreover, ethical issues may complicate the implementation of randomized placebo-controlled studies. Only four randomized studies have compared the effectiveness of different treatment methods[29–32] and only one randomized placebo-controlled study has been conducted.[33] These guidelines give substantial weight to consensus among the committee members. The "B" recommendation level has been given to first-line therapies for daily clinical practice.

An additional problem is that far fewer treatment options are available for MF/SS in Japan than in Western countries. In the present guidelines, we have included information on treatment modalities that have not been approved by the Japanese National Health Insurance system. Experimental therapies not yet approved overseas or in Japan have been omitted from these guidelines.

CQ1: Is monitoring the clinical course without treatment recommended for MF?
Degree of recommendation: C1 (stage IA only), C2 (other than stage IA).
Recommendation: In stage IA of MF, one acceptable option is to monitor the clinical course without treatment. For stages beyond IA, monitoring the clinical course without treatment is generally not recommended (Data S1).

CQ2: Are topical steroids recommended for MF/SS?
Degree of recommendation: B.
Recommendation: Topical steroid therapy is recommended at all stages of MF/SS (Data S1).

CQ3: Is topical chemotherapy recommended for MF/SS?
Degree of recommendation: C1.
Recommendation: Mechlorethamine/nitrogen mustard (HN2) or carmustine (BCNU) topical chemotherapy is currently used in Europe and North America, and is recommended for early-stage MF (stage IA through IIA). These agents are not yet approved or available in Japan. Nimustine hydrochloride (ACNU) is currently used topically in some facilities in Japan,

Table 3. Survival rates of various cutaneous lymphomas and hematological neoplasms

Disease	Stage	5y-OS	5y-DSS	Median survival time (months)	References
MF/SS	IA	94–100	98–100	426	18, 22
	IB	84–89	89–95	258	
	IIA	78–87	87–89	190	
	IIB	47–73	56–88	56–78	
	IIIA	47–100	54–100	56	
	IIIB	40	48	41	
	IVA1	0–37	0–41	23–46	
	IVA2	18–33	23–50	25–46	
	IVB	0–18	0–18	13–17	
ATLL	T1	82.5	82.5	192.6*	19, 23
	T2	27.3	27.3	47.9	
	T3	0	0	17.3	
	T4	0	0	3	
	Multi-papular type	42.1	47.1		
	Purpuric type	40.0	40.0		
ALCL	T1	85	93		24
	T2	81	93		
	T3	63	77		
	Leg (−)	86	100		
	Leg (+)	53	67		
SPTCL	HPS (−)	91			25
	HPS (+)	45			
		Total 82			
Nasal ENKL	I	55 (4 years)		59.8	20
	II	33 (4 years)		11.2	
	III	31 (4 years)		33.1	
	IV	10 (4 years)		5.3	
		Total 36 (4 years)		Total 12.9	
Cutaneous extranasal ENKL	I	75 (2 years)		Not reached	20
	II	0 (2 years)		6.2	
	III	Not reached†		75.5†	
	IV	14 (2 years)		4	
		Total 33 (2 years)		Total 6.8	
BNKL	BM/blood (−)	0	25.3 (2 years)	17.1	21
	BM/blood (+)	19.6	46.4 (2 years)	20.4	
	Skin (−)	0	21 (2 years)	24.2	
	Skin (+)	20	48 (2 years)	22.2	
Extranodal MZL of MALT		94–97			26, 27
PCFCL		87–96			
PCDLBCL		37–73			

*Mean survival time. †One case. ALCL, anaplastic large cell lymphoma; ATLL, adult T cell leukemia/lymphoma; BM, bone marrow; BNKL, blastic NK-cell lymphoma; DSS, disease-specific survival; ENKL, extranodal NK/T-cell lymphoma; HPS, hemophagocytic syndrome; MF, mycosis fungoides; MZL of MALT, marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue; OS, overall survival; PCDLBCL, primary cutaneous diffuse large B-cell lymphoma; PCFCL, primary cutaneous follicle center lymphoma; SPTCL, subcutaneous panniculitis-like T-cell lymphoma; SS, Sezary syndrome.

and can be considered for small skin lesions or for short-term use (Data S1).

CQ4: Is ultraviolet (UV) light therapy recommended for MF/SS?
Degree of recommendation: B.
Recommendation: Oral psoralen plus UV-A therapy (PUVA) therapy or narrow-band UV-B therapy is recommended for early-stage MF (stage IA through IIA) (Data S1).

CQ5: Is PUVA therapy with concomitant retinoid or interferon (IFN) therapy recommended for MF/SS?
Degree of recommendation: B.
Recommendation: PUVA with concomitant oral etretinate (RePUVA) or PUVA with concomitant IFN is recommended for MF/SS (Data S1).

CQ6: Is radiation therapy recommended for MF/SS?
Degree of recommendation: B.
Recommendation: Localized radiation therapy is recommended as a palliative treatment for skin lesions in MF, regardless of disease stage. Total skin electron beam therapy is recommended for MF (stage IB through IIA) (Data S1).

CQ7: Are oral retinoids recommended for MF/SS?
Degree of recommendation: B-C1.

Table 4. Summary of clinical questions and degree of recommendation for mycosis fungoides/Sézary syndrome

Clinical question	Degree of recommendation
CQ1: Is monitoring the clinical course without treatment recommended for mycosis fungoides?	C1 (stage IA) C2 (other than stage IA)
CQ2: Are topical steroids recommended for mycosis fungoides/Sézary syndrome?	B
CQ3: Is topical chemotherapy recommended for mycosis fungoides/Sézary syndrome?	C1
CQ4: Is ultraviolet light therapy recommended for mycosis fungoides/Sézary syndrome?	B
CQ5: Is psoralen plus ultraviolet A therapy with concomitant retinoid or interferon therapy recommended for mycosis fungoides/Sézary syndrome?	B
CQ6: Is radiation therapy recommended for mycosis fungoides/Sézary syndrome?	B
CQ7: Are oral retinoids recommended for mycosis fungoides/Sézary syndrome?	B-C1
CQ8: Is interferon therapy recommended for mycosis fungoides/Sézary syndrome?	B-C1
CQ9: Is extracorporeal photochemotherapy recommended for mycosis fungoides/Sézary syndrome?	B (erythroderma) C1 (non-erythroderma)
CQ10: Are molecular-targeted therapies recommended for mycosis fungoides/Sézary syndrome?	B-C1
CQ11: Is chemotherapy recommended for mycosis fungoides/Sézary syndrome?	B (refractory, extracutaneous lesions) D (early stage)
CQ12: Is hematopoietic stem cell transplantation recommended for mycosis fungoides/Sézary syndrome?	C1 (allogeneic) C2 (autologous)

Table 5. (MF/SS-1) Topical therapy of first choice recommended for stages I and IIA*

Treatment	Degree of recommendation	CQ
Monitoring the clinical course without treatment	C1 (stage IA only)/C2	CQ1
Topical steroid therapy†	B	CQ2
ACNU topical therapy‡	C1	CQ3
BB-UVB†	B	CQ4
NB-UVB	B	CQ4
PUVA	B	CQ4
Localized radiation therapy§	B	CQ6

*If the patient does not respond to the topical therapy selected for initial treatment, before proceeding to a second-line therapy recommended for stage I through IIA (Table 6 MFSS-2), consider the use of other first-line topical therapies. †Stage IA/IB. ‡Small area, short-term use. §Radical radiation therapy for "minimal" stage IA unilesional mycosis fungoides, or where multiple lesions are localized within the same radiation field or multiple field in close proximity, and palliative radiation for infiltrated plaques resistant to topical therapy other than radiation. ACNU, nimustine hydrochloride; BB, broad-band; NB, narrowband; PUVA, psoralen plus ultraviolet A therapy; UVB, ultraviolet B.

Recommendation: Oral etretinate can be useful in the treatment of MF/SS (Data S1).

CQ8: Is IFN therapy recommended for MF/SS?
Degree of recommendation: B-C1.

Recommendation: IFN-α therapy is recommended in early-stage MF/SS (stage IA–IIA) if systemic therapy is required, and in advanced disease (stage IIB–IVA1). This treatment option has not yet been approved in Japan. IFN-γ, which has been used for the treatment of MF in Japan, is considered as effective as IFN-α, and may prove useful (Data S1).

Table 6. (MF/SS-2) Second-line therapy recommended for stages I and IIA

Treatment	Degree of recommendation	CQ
TSEB*	B	CQ6
Etretinate†,‡	B-C1	CQ7
IFN-α†,§	B-C1	CQ8
IFN-γ†	B-C1	CQ8
RePUVA†	B	CQ5
IFN-α + PUVA †,§	B	CQ5
IFN-γ + PUVA †	B	CQ5
Chemotherapy¶	D/B¶	CQ11

*TSEB can be used as first-line therapy for stage IB/IIA (T2) with intense subjective symptoms accompanied by extensive highly infiltrated plaques and histopathological confirmation of folliculotropic mycosis fungoides or large cell transformation. †Can be a first-line treatment if systemic therapy is required (B1 or histopathological confirmation of folliculotropic mycosis fungoides or large cell transformation). BRM therapy (etretinate, IFN-α, IFN-γ) can be used as monotherapy or in concomitant administration with PUVA, and its concomitant use can also be investigated with topical therapies other than PUVA. ‡Duration of response to oral etretinate is usually short; consider for use as concomitant therapy. §IFN-α therapy has been used in only a few cases in Japan. ¶Third-line therapy for stage IB/IIA disease resistant to skin-targeted therapy and BRM therapy. BRM, biological response modifiers; IFN, interferon; PUVA, psoralen plus ultraviolet A therapy; TSEB, total skin electron beam.

CQ9: Is extracorporeal photochemotherapy (ECP) recommended for MF/SS?
Degree of recommendation: B (erythrodermic MF/SS), C1 (non-erythrodermic disease).

Recommendation: ECP/photopheresis is recommended for stage T4 erythrodermic MF and SS. It may also be considered in cases of refractory non-erythrodermic MF. ECP is

Table 7. (MF/SS-3) First-line therapy recommended for stage IIB*

Treatment	Degree of recommendation	CQ
Concomitant use of the following forms of BRM therapy and topical therapy		
BRM therapy		
Etretinate	B-C1	CQ5,7
IFN-α†,‡	B-C1	CQ5,8
IFN-γ‡	B-C1	CQ5,8
Topical therapy		
PUVA ± localized radiation therapy§	B	CQ4,5,6
Localized radiation therapy§	B	CQ6
TSEB¶	B	CQ6

*If the patient does not respond to initial treatment, before proceeding to a second-line therapy recommended for refractory stage IIB (Table 8 MFSS-4), consider other first-line topical therapies. †Concomitant therapy with IFN-α and PUVA: degree of recommendation = B. IFN-α therapy has been used in only a few cases in Japan. ‡IFN-α monotherapy or IFN-γ monotherapy can be used as first-line therapy. §Palliative radiation for localized tumors. ¶If lesions extend over <10% of body surface area, TSEB monotherapy can be used as first-line therapy. BRM, biological response modifiers; IFN, interferon; PUVA, psoralen plus ultraviolet A therapy; TSEB, total skin electron beam.

Table 8. (MF/SS-4) Treatment methods recommended for refractory stage IIB/III or stage IV mycosis fungoides

Treatment	Degree of recommendation	CQ
Chemotherapy*	B	CQ11

*Consider concomitant use of topical therapy appropriate for T classification.

Table 9. (MF/SS-5) First-line therapy recommended for stage III *

Treatment	Degree of recommendation	CQ
ECP ± IFN-α†	B	CQ9
TSEB + ECP†,‡	B	CQ6
Concomitant use of the following forms of BRM therapy and topical therapy		
BRM therapy		
Etretinate	B-C1	CQ5,7
IFN-α†,§	B-C1	CQ5,8
IFN-γ§	B-C1	CQ5,8
Topical therapy		
PUVA	B	CQ4,5
TSEB§	B	CQ6

*If the patient does not respond to initial therapy, before proceeding to a therapy recommended for refractory stage III (Table 8 MFSS-4), consider other first-line therapies. †ECP and IFN-α therapy have been used in only a few cases in Japan. ‡TSEB monotherapy can be used as first-line therapy for stage IIIA disease. §IFN-α monotherapy or IFN-γ monotherapy can be used as first-line therapy. BRM, biological response modifiers; ECP, Extracorporeal photochemotherapy; IFN, interferon; PUVA, psoralen plus ultraviolet A therapy; TSEB, total skin electron beam.

Table 10. (MF/SS-6) Recommended therapy for Sézary syndrome (stage T4, IVA1-IVB)*

Treatment	Degree of recommendation	CQ
ECP ± IFN-α†	B	CQ9
TSEB + ECP†	B	CQ6
Chemotherapy ± IFN-α†	B	CQ11

*For stage IVA1 Sézary syndrome with a low Sézary cell count, initial therapy selection may be the same as for stage IIIB (Table 9 MF/SS-5). †ECP and IFN-α therapy have been used in only a few cases in Japan. ECP, extracorporeal photochemotherapy; IFN, interferon; TSEB, total skin electron beam.

Table 11. (MF/SS-7) Treatment to be considered for refractory stage IV disease

Treatment	Degree of recommendation	CQ
Allogeneic hematopoietic stem cell transplantation	C1	CQ12
Autologous hematopoietic stem cell transplantation	C2	CQ12

not yet approved by the Japanese National Health Insurance system, and currently almost no Japanese medical institutions perform the procedure (Data S1).

CQ10: Are *molecular-targeted therapies recommended for* MF/SS?
Degree of recommendation: B-C1.
Recommendation: Treatment with denileukin diftitox, vorinostat or romidepsin may be useful in recurrent or refractory MF/SS. Vorinostat is the only drug in this category that is approved for coverage by Japanese health insurance (Data S1).

CQ11: Is chemotherapy recommended for MF/SS?
Degree of recommendation: B (if disease is refractory or accompanied by extracutaneous lesions), D (early-stage MF).
Recommendation: Chemotherapy is not recommended as a first line of treatment in early-stage MF (stage IA–IIA). Chemotherapy is *recommended for* MF/SS stage IB–IIIB that is resistant to topical therapy or biological response modifier therapy, and for MF/SS stage IVA1–IVB accompanied by extracutaneous lesions (Data S1).

CQ12: Is hematopoietic stem cell transplantation recommended for MF/SS?
Degree of recommendation: C1 (allogeneic hematopoietic stem cell transplantation), C2 (autologous hematopoietic stem cell transplantation).
Recommendation: Autologous hematopoietic stem cell transplantation with concomitant high-dose chemotherapy is not generally recommended for MF/SS. In young patients with advanced disease, allogeneic hematopoietic stem cell transplantation may be considered in the context of a clinical study (Data S1).

Cutaneous T/NK-cell lymphoma other than MF/SS (non-MF/SS)

Cutaneous T/NK cell lymphomas other than MF/SS are classified by WHO–EORTC into two broad categories: relatively aggressive lymphomas with poor prognosis (aggressive group), and indolent lymphomas with favorable prognosis (indolent group) (Table 12).[1,34–39] In patients with aggressive lymphomas including primary cutaneous $CD8^+$ aggressive epidermotropic cytotoxic T-cell lymphoma, primary cutaneous γδ T-cell lymphoma, and peripheral T-cell lymphoma, not otherwise specified, the 5-year survival rates are less than 20%. However, the clinical course is not uniform, and patients whose symptoms are limited to cutaneous lesions may live for much longer.

For patients who present with cutaneous lesions only, without general symptoms or notable laboratory test findings, skin-directed therapies used for MF/SS might be chosen as a first-line treatment. Systemic chemotherapy may be considered for patients with tumor infiltration into the lymph nodes or visceral organs. However, the best treatment option must be explored for each individual patient, based on that patient's conditions. Clinical questions (CQ) are not defined in this category because uniform guidelines are difficult to develop. In contrast, CQ have been defined in each lymphoma in the indolent group (primary cutaneous anaplastic large cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, and primary cutaneous $CD4^+$ small/medium T-cell lymphoma).

The MF/SS staging classifications are not applicable to cutaneous T/NK cell lymphomas other than MF/SS because of differences in disease progression. In 2007, the ISCL and EORTC jointly advocated the TNM classification system for cutaneous lymphomas other than MF/SS.[4] Because the prognostic impact of this classification system has not yet been validated, it might be premature to establish guidelines based on it. However, no other applicable classification systems are available at the present time. In order to obtain clinical information based on common criteria, we have adopted the TNM classification in the present guidelines.

Primary cutaneous anaplastic large cell lymphoma.

CQ13: Are localized therapies such as radiation therapy or surgical resection recommended for primary cutaneous anaplastic large cell lymphoma?
Degree of recommendation: B.
Recommendation: Remission can be induced by radiation therapy or surgical resection in many patients, so these methods are recommended where feasible (Data S1).

CQ14: Is chemotherapy recommended for primary cutaneous anaplastic large cell lymphoma?
Degree of recommendation: B (for lymph node lesions and visceral organ infiltration), C1 (symptoms limited to cutaneous lesions only).
Recommendation: For patients with cutaneous lesions only, if those lesions are resistant to topical treatment such as radiotherapy and surgical excision, or if they have multiple lesions, chemotherapy may be considered. Chemotherapy is recommended for lymph node lesions and for infiltration in the visceral organs (Data S1).

Subcutaneous panniculitis-like T-cell lymphoma.

CQ15: Is radiation therapy recommended for subcutaneous panniculitis-like T-cell lymphoma?
Degree of recommendation: C1.
Recommendation: Radiation therapy can provide control of localized lesions within the irradiated area. Radiation can be considered as initial therapy for skin lesions within a localized area (T1, T2) without systemic symptoms (Data S1).

CQ16: Are oral steroids recommended for subcutaneous panniculitis-like T-cell lymphoma?
Degree of recommendation: B.
Recommendation: Steroid monotherapy has been reported to relieve systemic symptoms such as pyrexia and abnormal hepatic function and to induce remission in some cases; oral steroids are recommended for subcutaneous panniculitis-like T-cell lymphoma (Data S1).

Table 12. Summary of CQ and degree of recommendation for cutaneous T-/natural killer cell lymphoma (non-MF/SS)

Clinical question	Degree of recommendation
CQ13: Are localized therapies such as radiation therapy B or surgical resection recommended for primary cutaneous anaplastic large cell lymphoma?	B
CQ14: Is chemotherapy recommended for primary cutaneous anaplastic large cell lymphoma?	B (extracutaneous lesions) C1 (cutaneous lesions only)
CQ15: Is radiation therapy recommended for subcutaneous panniculitis-like T-cell lymphoma?	C1
CQ16: Are oral steroids recommended for subcutaneous panniculitis-like T-cell lymphoma?	B
CQ17: Is combination chemotherapy recommended for subcutaneous panniculitis-like T-cell lymphoma?	B-C1
CQ18: Is radiation therapy recommended for primary cutaneous $CD4^+$ small/medium T-cell lymphoma?	B
CQ19: Is chemotherapy recommended for primary cutaneous $CD4^+$ small/medium T-cell lymphoma?	C1

CQ17: Is combination chemotherapy recommended for subcutaneous panniculitis-like T-cell lymphoma?
Degree of recommendation: B-C1.
Recommendation: Combination chemotherapy may be considered if the condition is resistant to steroid therapy. Prognosis is poor for patients complicated by hemophagocytosis; combination chemotherapy is recommended in such cases (Data S1).

Primary cutaneous CD4$^+$ small/medium T-cell lymphoma.

CQ18: Is radiation therapy recommended for primary cutaneous CD4$^+$ small/medium T-cell lymphoma?
Degree of recommendation: B.
Recommendation: Radiation therapy can induce remission in many cases, and survival rates are relatively good. Radiation therapy is recommended for single and localized lesions (T1, T2) (Data S1).

CQ19: Is chemotherapy recommended for primary cutaneous CD4$^+$ small/medium T-cell lymphoma?
Degree of recommendation: C1.
Recommendation: Chemotherapy can also be considered for primary cutaneous CD4$^+$ small/medium T-cell lymphoma with multiple lesions (Data S1).

ATLL (disease type limited to cutaneous lesions)

Adult T-cell leukemia/lymphoma is a form of T-cell lymphoma caused by HTLV-1 which occurs in a variety of organs (Table 13). Three major findings required for diagnosis: (i) appearance of morphologically abnormal T lymphocytes (typically CD4$^+$ and CD25$^+$); (ii) seropositivity for anti-HTLV-1 antibody; and (iii) Southern blot confirmation for monoclonal integration of HTLV-1 provirus into tumor cells.[15,40] For cutaneous symptoms to be diagnosed as eruptions specific to ATLL, histological confirmation is required for (i) and (iii). In particular, (iii) is required for a differential diagnosis to exclude other cutaneous lymphomas such as MF. The overall treatment guidelines for ATLL must involve cooperation and coordination with other departments, including departments of hematology and oncology. Thus, we limit these guidelines to instances in which only cutaneous lesions are detected. However, no uniform diagnostic criteria exist for the conventionally advocated concept of "cutaneous" ATLL.[40–43] The present guidelines cover ATLL cases, where systemic treatments such as chemotherapy and transplantation are not indicated.

Table 13. Summary of CQ and degree of recommendation for adult T-cell leukemia/lymphoma (ATLL) with cutaneous lesions only

Clinical question	Degree of recommendation
CQ20: Is ultraviolet light therapy recommended for ATLL with cutaneous lesions only?	B-C1
CQ21: Is radiation therapy recommended for ATLL with cutaneous lesions only?	B
CQ22: Are oral retinoids recommended for ATLL with cutaneous lesions only?	C1
CQ23: Is interferon therapy recommended for ATLL with cutaneous lesions only?	C1
CQ24: Is single-agent chemotherapy recommended for ATLL with cutaneous lesions only?	B-C1

Eruptions specific to ATLL are defined as cutaneous symptoms in cases seropositive for anti-HTLV-1 antibody and where cutaneous histology shows monoclonal integration of HTLV-1. In the present guidelines, we have provisionally considered "ATLL with cutaneous lesions only" to be "cases in which ATLL cells account for <5% of all peripheral blood cells, excluding the acute, lymphoma, and chronic types".[19,40]

CQ20: Is UV light therapy recommended for ATLL with cutaneous lesions only?
Degree of recommendation: B-C1.
Recommendation: PUVA therapy can induce remission in ATLL with cutaneous lesions only, and may be useful. Regardless of whether extracutaneous lesions are present, PUVA can be expected to relieve cutaneous symptoms. However, beneficial effects of PUVA on extracutaneous lesions or the prognosis of patients have not been confirmed (Data S1).

CQ21: Is radiation therapy recommended for ATLL with cutaneous lesions only?
Degree of recommendation: B.
Recommendation: Radiation therapy can be expected to provide symptomatic relief in ATLL with cutaneous lesions only, and is recommended. However, beneficial effects on the prognosis of patients have not been confirmed (Data S1).

CQ22: Are oral retinoids recommended for ATLL with cutaneous lesions only?
Degree of recommendation: C1.
Recommendation: Retinoids can induce remission in ATLL with cutaneous lesions only, and may be considered for use (Data S1).

CQ23: Is IFN therapy recommended for ATLL with cutaneous lesions only?
Degree of recommendation: C1.
Recommendation: IFN-γ can relieve symptoms in ATLL with cutaneous lesions only, and may be considered for use. Beneficial effects on extracutaneous lesions or the prognosis of patients have not been confirmed (Data S1).

CQ24: Is single-agent chemotherapy recommended for ATLL with cutaneous lesions only?
Degree of recommendation: B-C1.
Recommendation: Single-agent chemotherapy can be useful for disease refractory to skin-direct therapy in cases where combination chemotherapy is not indicated. However, beneficial effects on the prognosis of patients have not been confirmed (Data S1).

Other T/NK-cell lymphomas

In addition to ENKL, the WHO classification for hematopoietic malignancies, revised in 2008, has listed hydroa

vacciniforme-like lymphoma as an independent disease (Table 14).[2] This condition has been reported in Asia, including Japan, in Mexico, and in Peru. Hydroa vacciniforme-like lymphoma is a form of T-cell lymphoma that is associated with EBV. It occurs most frequently in children and adolescents, and is often accompanied by photosensitivity and hypersensitivity to insect bites. Prognosis, although varied, is poor if complicated by systemic conditions such as hemophagocytosis. There have been no reports of treatment for this condition alone, but a few reports are available on treatment of chronic active EBV infection and on EBV^+ T/NK-cell lymphoproliferative diseases. Treatment has been attempted with antiviral therapy using the antiviral agents acyclovir and ganciclovir, immunotherapy using agents such as IFN-α and interleukin 2, and chemotherapy using corticosteroids and etoposide.[44] However, the reports involve a very small number of cases, insufficient even for descriptive research, so findings cannot be considered conclusive.

Blastic plasmacytoid dendritic cell neoplasm is a rare disease formerly designated as $CD4^+/CD56^+$ hematodermic neoplasm.[45] Most patients usually respond to initial polychemotherapy, but the relapse rate is high. The prognosis is dismal, with a median overall survival of 12–14 months.

ENKL, nasal type.

CQ25: Is CHOP (cyclophosphamide, adriamycin, vincristine, prednisone) chemotherapy recommended for ENKL, nasal type?
Degree of recommendation: C2.
Recommendation: ENKL, nasal type, generally responds poorly or only temporarily to CHOP therapy; this treatment is not recommended (Data S1).

CQ26: Is combination radiation therapy and chemotherapy recommended for ENKL, nasal type?
Degree of recommendation: B.
Recommendation: For localized lesions, radiation therapy with simultaneous or subsequent DeVIC (dexamethasone, VP16, ifosfamide, carboplatin) chemotherapy is recommended (Data S1).

Blastic plasmacytoid dendritic cell neoplasm.

CQ27: Is chemotherapy recommended for blastic plasmacytoid dendritic cell neoplasm?
Degree of recommendation: C1.
Recommendation: No standard treatment has been established for blastic plasmacytoid dendritic cell neoplasm. Multidrug chemotherapy may be considered. However, such treatment provides only temporary effectiveness, and almost all patients die within a few years (Data S1).

Hydroa vacciniforme-like lymphoma.

CQ28: Is allogenic hematopoietic stem cell transplantation recommended for hydroa vacciniforme-like lymphoma?
Degree of recommendation: B-C1.
Recommendation: Allogenic hematopoietic stem cell transplantation may be useful in the treatment of hydroa vacciniforme-like lymphoma (Data S1).

Cutaneous B-cell lymphoma

The WHO–EORTC classification of 2005 lists the following subtypes within the category of cutaneous B-cell lymphoma:[1] primary cutaneous marginal zone B-cell lymphoma (PCMZL); primary cutaneous follicle center cell lymphoma (PCFCL), primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL, leg type); PCLBCL, other; and intravascular large B-cell lymphoma (IVL) (Table 15). In the 2008 revision of the WHO classification of hematopoietic malignancies, the nomenclature, the PCMZL was replaced by "extranodular marginal zone B-cell lymphoma (MALT lymphoma)".[2] The term, PCDLBCL, leg type, was entered as a subcategory of "diffuse large B-cell lymphoma, not otherwise specified". The term "primary cutaneous diffuse large B-cell lymphoma, other" was removed from the list. Disease type is an important prognostic factor for cutaneous B-cell lymphoma. Both PCFCL and PCMZL are indolent-type lymphomas with a favorable prognosis, while prognosis is poor in PCDLBCL and IVL. In the following discussion, cutaneous B-cell lymphoma is divided into two groups: the indolent group and diffuse large cell group.

No randomized clinical trials have been conducted in these disease groups, and research has been limited primarily to descriptive studies. However, in 2008, the EORTC and ISCL published guidelines for the treatments of cutaneous B-cell lymphoma, based on previous reports.[46] Most of the reported treatment methods for topical therapy involved radiation and/or surgical resection. Most of the methods for systemic therapy involved chemotherapy and the administration of rituximab. However, a few reports were found on topical administration of IFN-α and on the use of photodynamic therapy.

Table 14. Summary of CQ and degree of recommendation for other natural killer (NK)/T-cell lymphomas and related diseases

Clinical question	Degree of recommendation
CQ25: Is CHOP (cyclophosphamide, adriamycin, vincristine, prednisone) chemotherapy recommended for extranodal NK/T-cell lymphoma, nasal type?	C2
CQ26: Is combination radiation therapy and chemotherapy recommended for extranodal NK/T-cell lymphoma, nasal type?	B
CQ27: Is chemotherapy recommended for blastic plasmacytoid dendritic cell neoplasm?	C1
CQ28: Is allogenic stem cell transplantation recommended for hydroa vacciniforme-like lymphoma?	B-C1

Table 15. Summary of CQ and degree of recommendation for primary cutaneous B-cell lymphoma (indolent type: primary cutaneous follicle center lymphoma and extranodal marginal zone lymphoma)

Clinical question	Degree of recommendation
CQ29: Is radiation therapy recommended for indolent-type primary cutaneous B-cell lymphoma?	B
CQ30: Is surgical resection recommended for indolent-type primary cutaneous B-cell lymphoma?	B
CQ31: Is rituximab monotherapy recommended for indolent-type primary cutaneous B-cell lymphoma?	B-C1
CQ32: Is combination chemotherapy recommended for indolent-type primary cutaneous B-cell lymphoma?	C1
CQ33: Is combination chemotherapy recommended for primary cutaneous diffuse large B-cell lymphoma?	B
CQ34: Is rituximab monotherapy recommended for primary cutaneous diffuse large B-cell lymphoma?	B
CQ35: Are surgical resection and radiation therapy recommended for diffuse large B-cell lymphoma?	C1

CQ29: Is radiation therapy recommended for indolent-type primary cutaneous B-cell lymphoma?
Degree of recommendation: B.
Recommendation: Radiotherapy is recommended for diseases in the indolent group (PCMZL and PCFCL) (Data S1).

CQ30: Is surgical resection recommended for indolent-type primary cutaneous B-cell lymphoma?
Degree of recommendation: B.
Recommendation: Surgical resection is recommended for resectable lesions of diseases in the indolent group (PCMZL and PCFCL) (Data S1).

CQ31: Is rituximab monotherapy recommended for indolent-type primary cutaneous B-cell lymphoma?
Degree of recommendation: B-C1.
Recommendation: Rituximab may be useful for the treatment of diseases in the indolent group (PCMZL and PCFCL), particularly in cases of multiple lesions (Data S1).

CQ32: Is combination chemotherapy recommended for indolent-type primary cutaneous B-cell lymphoma?
Degree of recommendation: C1.
Recommendation: Combination chemotherapy may be considered for diseases in the indolent group that are refractory to other treatment regimens, and for advanced extracutaneous disease (Data S1).

CQ33: Is combination chemotherapy recommended for PCDLBCL?
Degree of recommendation: B.
Recommendation: Combination chemotherapy, and particularly the concomitant use of rituximab, is recommended for PCDLBCL, leg type, and for IVL (Data S1).

CQ34: Is rituximab monotherapy recommended for PCDLBCL?
Degree of recommendation: B.
Recommendation: Rituximab monotherapy is recommended for the treatment of PCDLBCL in cases where combination therapy may be poorly tolerated, such as in the elderly and in patients with severe complications (Data S1).

CQ35 Are surgical resection and radiation therapy recommended for PCDLBCL?
Degree of recommendation: C1.
Recommendation: In patients who cannot tolerate rituximab combination chemotherapy, such as the elderly and patients with severe complications, surgical resection and radiation therapy may be considered (Data S1).

ACKNOWLEDGMENTS

This work has been made possible by a collaborative project of the Japanese Dermatological Association (JDA), Japanese Skin Cancer Society (JSCS) – Lymphoma Study Group, and Japanese Society of Clinical Oncology – Skin Cancer Guideline Committee, and supported by grants from the Ministry of Health, Labour and Welfare: H21-Clinical Cancer Research-023 (chief researcher, Koichi Hirata), H23-Clinical Cancer Research -021 (chief researcher, Toshiki Watanabe), and H23-Clinical Cancer Research-020 (chief researcher, Kaoru Uchimaru).

REFERENCES

1 Willemze R, Jaffe ES, Burg G *et al.* WHO-EORTC classification for cutaneous lymphomas. *Blood* 2005; **105**: 3768–3785.
2 Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon: IARC Press.
3 Olsen E, Vonderheid E, Pimpinelli N *et al.* Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood* 2007; **110**: 1713–1722.
4 Kim YH, Willemze R, Pimpinelli N *et al.* TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood* 2007; **110**: 479–484.
5 Whittaker SJ, Marsden JR, Spittle M, Russell Jones R. Joint British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T-cell lymphomas. *Br J Dermatol* 2003; **149**: 1095–1107.
6 Trautinger F, Knobler R, Willemze R *et al.* EORTC consensus recommendations for the treatment of mycosis fungoides/Sezary syndrome. *Eur J Cancer* 2006; **42**: 1014–1030.
7 Dummer R. Primary cutaneous lymphomas: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2007; **18**(Suppl 2): ii61–ii62.
8 Iwatsuki K, Kawai K, Ohtsuka M *et al.* Guidelines for the management of cutaneous malignant tumors II: cutaneous lymphomas. *Jpn J Dermatol* 2009; **119**: 1189–1211.

9 Kim EJ, Hess S, Richardson SK *et al.* Immunopathogenesis and therapy of cutaneous T cell lymphoma. *J Clin Invest* 2005; **115**: 789–812.
10 Bunn PA Jr, Huberman MS, Whang-Peng J *et al.* Prospective staging evaluation of patients with cutaneous T-cell lymphomas. Demonstration of a high frequency of extracutaneous dissemination. *Ann Intern Med* 1980; **93**: 223–230.
11 Sausville EA, Eddy JL, Makuch RW *et al.* Histopathologic staging at initial diagnosis of mycosis fungoides and the Sézary syndrome. Definition of three distinctive prognostic groups. *Ann Intern Med* 1988; **109**: 372–382.
12 Olsen EA, Whittaker S, Kim YH *et al.* Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. *J Clin Oncol* 2011; **29**: 2598–2607.
13 Vonderheid EC, Bernengo MG, Burg G *et al.* Update on erythrodermic cutaneous T-cell lymphoma: report of the International Society for Cutaneous Lymphomas. *J Am Acad Dermatol* 2002; **46**: 95–106.
14 Senff NJ, Willemze R. The applicability and prognostic value of the new TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: results and comparison with the system used by the Dutch Cutaneous Lymphoma Group. *Br J Dermatol* 2007; **157**: 1205–1211.
15 Shimoyama M. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the Lymphoma Study Group (1984–87). *Br J Haematol* 1991; **79**: 428–437.
16 Lister TA, Crowther D, Sutcliffe SB *et al.* Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: cotswolds meeting. *J Clin Oncol* 1989; **7**: 1630–1636.
17 Lymphoma Study Group of Japanese Pathologists. The World Health Organization classification of malignant lymphomas in Japan: incidence of recently recognized entities. *Pathol Int* 2000; **50**: 696–702.
18 Suzuki S, Ito K, Ito M, Kawai K. Prognosis of 100 Japanese patients with mycosis fungoides and Sézary syndrome. *J Dermatol Sci* 2010; **57**: 37–43.
19 Sawada Y, Hino R, Hama K *et al.* Type of skin eruption is an independent prognostic indicator for adult T-cell leukemia/lymphoma. *Blood* 2011; **117**: 3961–3967.
20 Suzuki R, Suzumiya J, Yamaguchi M *et al.* Prognostic factors for mature natural killer (NK) cell neoplasms: aggressive NK cell leukemia and extranodal NK cell lymphoma, nasal type. *Ann Oncol* 2010; **21**: 1032–1040.
21 Suzuki R, Nakamura S, Suzumiya J *et al.* Blastic natural killer cell lymphoma/leukemia (CD56-positive blastic tumor). Prognostication and categorization according to anatomic sites of involvement. *Cancer* 2005; **104**: 1022–1031.
22 Agar NS, Wedgeworth E, Crichton S *et al.* Survival outcomes and prognostic factors in mycosis fungoides/Sézary sundrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. *J Clin Oncol* 2010; **28**: 4730–4739.
23 Benner MF, Willemze R. Applicability and prognostic value of the new TNM classification system in 135 patients with primary cutaneous anaplastic large cell lymphoma. *Arch Dermatol* 2009; **145**: 1399–1404.
24 Willemze R, Jansen PM, Cerroni L *et al.* Subcutaneous panniculitis-like T-cell lymphoma: definition, classification, and prognostic factors: an EORTC Cutaneous Lymphoma Group Study of 83 cases. *Blood* 2008; **111**: 838–845.
25 Zinzani PL, Quaglino P, Pimpinelli N *et al.* Prognostic factors in primary cutaneous B-cell lymphoma:the Italian study group for cutaneous lymphoma. *J Clin Oncol* 2006; **24**: 1376–1382.
26 Sneff NJ, Hoefnagel JJ, Jansen PM *et al.* Reclassification of 300 primary cutaneous B-cell lymphoma according to the new WHO-EORTC classification for cutaneous lymphomas: comparison with previous classifications and identification of prognostic markers. *J Clin Oncol* 2007; **25**: 1581–1587.
27 Kim YH, Liu HL, Mraz-Gernhard S, Varghese A, Hoppe RT. Long-term outcome of 525 patients with mycosis fungoides and Sezary syndrome. *Arch Dermatol* 2003; **139**: 857–866.
28 Bekkenk MW, Jansen PM, Meijer CJ, Willemze R. CD56+ hematological neoplasms presenting in the skin: a retrospective analysis of 23 new cases and 130 cases from the literature. *Ann Oncol* 2004; **15**: 1097–1108.
29 Stadler R, Otte HG, Luger T *et al.* Prospective randomized multicenter clinical trial on the use of interferonα 2a plus acitretin versus interferonα-2a plus PUVA in patients with cutaneous T-cell lymphoma stages I and II. *Blood* 1998; **92**: 3578–3581.
30 Stadler R, Kremer A, Luger T, Sterry W. Prospective, randomized, multicentre clinical trial on the use of interferon a 2a plus PUVA versus PUVA monotehrapy in patients with cutaneous T-cell lymphoma, stage I and II. *J Clin Oncol*, 2006 ASCO Annual Meeting Proceedings, 2006; **24**: 7541.
31 Kaye FJ, Bunn PA Jr, Steinberg SM *et al.* A randomized trial comparing combination electron-beam radiation and chemotherapy with topical therapy in the initial treatment of mycosis fungoides. *N Engl J Med* 1989; **321**: 1784–1790.
32 Child FJ, Mitchell TJ, Whittaker SJ, Scarisbrick JJ, Seed PT, Russell-Jones R. A randomized cross-over study to compare PUVA and extracorporeal photopheresis in the treatment of plaque stage (T2) mycosis fungoides. *Clin Exp Dermatol* 2004; **29**: 231–236.
33 Prince HM, Duvic M, Martin A *et al.* Phase III placebo-controlled trial of denileukin diftitox for patients with cutaneous T-cell lymphoma. *J Clin Oncol* 2010; **28**: 1870–1877.
34 Toro JR, Beaty M, Sorbara L *et al.* Gamma delta T-cell lymphoma of the skin: a clinical, microscopic, and molecular study. *Arch Dermatol* 2000; **136**: 1024–1032.
35 Santucci M, Pimpinelli N, Massi D *et al.* Cytotoxic/natural killer cell cutaneous lymphomas. Report of EORTC Cutaneous Lymphoma Task Force Workshop. *Cancer* 2003; **97**: 610–627.
36 Lu D, Patel KA, Duvic M, Jones D. Clinical and pathological spectrum of CD8-positive cutaneous T-cell lymphomas. *J Cutan Pathol* 2002; **29**: 465–472.
37 Toro JR, Liewehr DJ, Pabby N *et al.* Gamma-delta T-cell phenotype is associated with significantly decreased survival in cutaneous T-cell lymphoma. *Blood* 2003; **101**: 3407–3412.
38 Bekkenk MW, Vermeer MH, Jansen PM *et al.* Peripheral T-cell lymphomas unspecified presenting in the skin: analysis of prognostic factors in a group of 82 patients. *Blood* 2003; **102**: 2213–2219.
39 Berti E, Tomasini D, Vermeer MH, Alessi E, Willemze R. Primary cutaneous CD8-positive epidermotropic cytotoxic T cell lymphomas. A distinct clinicopathological entity with an aggressive clinical behavior. *Am J Pathol* 1999; **155**: 483–492.
40 Setoyama M, Katahira Y, Kanzaki T. Clinicopathologic analysis of 124 cases of adult T-cell leukemia/lymphoma with cutaneous manifestations: the smouldering type with skin manifestations has a poorer prognosis than previously thought. *J Dermatol* 1999; **26**: 785–790.
41 Takahashi K, Tanaka T, Fujita M *et al.* Cutaneous-type adult T-cell leukemia/lymphoma. A unique clinical feature with monoclonal T-cell proliferation detected by Southern blot analysis. *Arch Dermatol* 1988; **124**: 399–404.
42 Johno M, Ohishi M, Kojo Y, Yamamoto S, Ono T. Cutaneous manifestations of adult T-cell leukemia/lymphoma. *Gann Monogr Cancer Res* 1992; **39**: 33–42.
43 Amano M, Kurokawa M, Ogata K *et al.* New entity, definition and diagnostic criteria of cutaneous adult T-cell leukemia/lymphoma: human T-lymphotropic virus type 1 proviral DNA load can distinguish between cutaneous and smoldering types. *J Dermatol* 2008; **35**: 270–275.
44 Cohen JI, Kimura H, Nakamura S, Ko YH, Jaffe ES. Epstein–Barr virus-associated lymphoproliferative disease in non-immunocompromised hosts: a status report and summary of an international meeting, 8–9 September 2008. *Ann Oncol* 2009; **20**: 1472–1482.

45 Herling M, Jones D. CD4+/CD56+ hematodermic tumor: the features of an evolving entity and its relationship to dendritic cells. *Am J Clin Pathol* 2007; **127**: 687–700.
46 Sneff NJ, Noordijk EM, Kim YH *et al.* European Organization for Research and Treatment of Cancer and International. Society for Cutaneous Lymphoma consensus recommendations for the management of cutaneous B-cell lymphomas. *Blood* 2008; **112**: 1600–1609.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Data S1. References used for treatment recommendations (CQ1–CQ35).

Table S1. *Terminology for clinical features of mycosis fungoides/Sézary syndrome.*

Table S2. Tumor, lymph nodes, metastasis, blood (TNMB) classification for mycosis fungoides/Sézary syndrome.

Table S3. TNMB staging for mycosis fungoides/Sézary syndrome (International Society for Cutaneous Lymphomas/European Organization for Research and Treatment of Cancer, Cutaneous Lymphomas Task Force).

Table S4. Tumor–node–metastasis classification for primary cutaneous lymphomas other than mycosis fungoides/Sézary syndrome.

Table S5. Ann Arbor/Cotswold staging.

Figure S1. Clinicopathological features of mycosis fungoides/Sézary syndrome.

Figure S2. Clinical features of anaplastic large cell lymphoma.

Figure S3. Clinical features of adult T-cell leukemia/lymphoma.

Figure S4. Clinicopathological features of subcutaneous panniculitis-like T-cell lymphoma.

Figure S5. Clinical features of extranodal natural killer/T-cell lymphoma, nasal type.

Figure S6. Clinicopathological features of hydroa vacciniforme-*like lymphoma.*

Figure S7. Clinical features of blastic plasmacytoid dendritic cell neoplasm.

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

特集　産科外来診療フローチャート―妊婦管理のすべて―

母児感染症の診断と管理

鮫島　梓*　齋藤　滋*

感染症を合併した妊娠を診察する場合，母体に対する影響と胎児への影響の両方を考慮して，その管理を行う必要がある。母子感染は経胎盤感染（胎内感染），産道感染，母乳を介した感染があるが，病原体により感染経路も児への影響も様々である。また，感染の時期によっても児への影響は異なる。本稿では種々の母子感染症について解説する。

はじめに

産科外来において感染症の診療を行うことは少なくない。妊娠中の感染症が問題となる理由としては，母体から胎児への垂直感染があること，児の先天異常の原因となること，母体自身が重症化することが挙げられる。母体，胎児への影響はそれぞれの病原体で異なり，また経胎盤，産道，母乳と児への感染経路も様々であるため，それに応じた対応が必要となる。

1．HTLV-1 (Human T-cell leukemia virus type 1)

これまでHTLV-1はキャリアの多い九州・沖縄地区だけが対策が必要な地域とされてきたが，2006年，2007年に行われた厚生労働省山口班の報告でHTLV-1キャリアが少なくとも100万人以上存在し，九州・沖縄地区だけでなく，全国に拡散していることがわかった。この結果を受けて，全国的な母子感染予防対策が必要と国の方針が変更され，平成21（2009）年に厚生労働特別研究事業「HTLV-1の母子感染予防に関する研究班」が発足し，平成23（2011）年から妊婦に対するHTLV-I抗体検査が公費補助されるようになった。

HTLV-1は成人T細胞白血病・リンパ腫（adult T-cell leukemia；ATL），HTLV-1関連脊髄症（HTLV-1 associated myelopathy；HAM），HTLV-1ぶどう膜炎（HTLV-1 uveitis；HU）などの疾患を引き起こす。ATLは40歳までは発症することはほとんどないが，40歳を過ぎると年間に1,000～1,500人に1人の割合で発症する。治療法としては多剤併用化学療法があるが，aggressive ATLの生存期間中央値は13カ月にとどまっており，満足できるものではない。HAMは年間に3万人に1人の割合で発症し，重症化すると，歩行障害や排尿障害，難治性の疼痛などの症状が残る。HUは飛蚊症，霧視，視力低下などの症状を呈し，治療反応性は良好だが再発も多い。

HTLV-1の感染経路は母子感染，性行為感

＊　Azusa Samejima, Shigeru Saito　富山大学医学部産科婦人科

染，輸血があるが，現在は母子感染ならびに性行為感染が主要な感染経路と考えられている。母子感染は主に母乳を介し，約 15～25％に生じ[1)～3)]，胎内感染や産道感染のため，人工栄養でも約 3％に母子感染が生じてしまう[2)3)]。母乳感染については，4 カ月以上母乳哺育を継続した場合の感染率が約 18％であるのに対して，3 カ月以内の場合は約 2％と低い。これは単純に曝露期間が長くなることと，胎児へ移行した中和抗体が 4 カ月後には大きく低下することが関係している。また，HTLV-1 の感染は凍結母乳により感染を低下させる可能性もある[2)3)]。これらの観点から産婦人科診療ガイドラインでは，キャリアの場合，① 人工栄養，② 凍結母乳栄養，③ 3 カ月以内の短期母乳栄養，の 3 つの方法から選択してもらうようにしている。凍結母乳や 3 カ月以内の短期母乳方法については，厚生労働科学研究板橋班のウェブサイトを参照していただきたい。

HTLV-1 キャリアからの発症予防については現時点では有効な治療法はなく，キャリアと診断された妊婦には，母子感染のリスクだけでなく，自身の ATL などの発症のリスクという大きな精神的ストレスを与えることになる。このため，適切な説明が必要であり，各都道府県で HTLV-1 母子感染対策協議会を設置し，対応することとなった。

HTLV-1 スクリーニング検査では偽陽性があるため，必ずウエスタンブロット法（保険収載）による確認試験を行う必要がある。ウエスタンブロット法で陰性であれば偽陽性と判定し，母乳哺育を勧めればよいが，問題は判定保留が 10～20％あることである。この場合には自費診療となるが，PCR 法を施行する方法もある。厚生労働科学研究板橋班では，無償で判定保留者に対する PCR 法を行っているので，相談していただきたい（HTLV-1 母子感染予防研究板橋班ウェブサイト http://htlv-1mc.org/）。

2．HIV（ヒト免疫不全ウイルス）

HIV は性感染，血液感染により感染する。約 10 年の無症候期の後，AIDS（後天性免疫不全症候群）を引き起こす。

HIV 感染妊婦からの母子感染率は 35～49％とされ，そのうち胎内感染は約 8％，分娩時の感染が約 15％，母乳による感染は 12～26％とされる[4)5)]が，現在は適切な治療により，1％以下にまで母子感染を抑制できるようになった。

HIV スクリーニング検査の陽性的中率は 3.8～7.7％と非常に低い。HIV スクリーニング検査で陽性の場合は，必ず保険収載でウエスタンブロット法と PCR 法を同時に行い，確認検査を行う。

母子感染予防のため，妊娠中の抗 HIV 療法（AZT もしくは多剤併用療法）は推奨される。各地区の HIV/AIDS 拠点病院に紹介することが望ましい。分娩方法に関しては選択的帝王切開により母子感染が減少するため，陣痛発来前の選択的帝王切開術が勧められる。母乳保育による感染率も低くないことから，出生直後からの人工乳での育児が望ましい。出生した児には，出生後 6 週間 AZT シロップを投与する。

3．B 型肝炎

B 型肝炎は血液を介して感染するが，感染後数カ月でウイルスが排除される一過性感染と，長期間ウイルスが残るキャリア状態とに分かれる。

初期検査で HBs 抗原が陽性であると判明した妊婦の多くは HBV キャリアである。HBs 抗原陽性の場合は，必ず HBe 抗原を検査する。HBe 抗原陽性の妊婦に感染予防措置を行わなかった場合，85～90％が持続感染状態に陥る。一方，HBe 抗体陽性妊婦から生まれた児では，約 10～15％に感染が起こるが，キャリア化することは稀である。胎内感染の頻度は 5％以下で母子感染の多くが分娩時に起こる。分娩直後に適切な予防措置を行えば，95％～97％にキャリア化を阻止することができる。

HBV の母子感染予防には，高力価 HBs ヒト免疫グロブリン（HBIG）（分娩直後，出生 2 カ月）と B 型肝炎ワクチン（出生 2 カ月，3 カ月，

5カ月）とを組み合わせて用いる。母親がHBe抗体陽性の場合，出生2カ月のHBIGは省略することができる。HBIGは出生後できるだけ早期に筋注することが必要である。

母子感染予防が適切に行われている限り，特に授乳を制限する必要はない。ただし，母親の乳首に傷や出血がある場合には，感染を防御できる量以上のHBVが児に入る可能性があるため授乳は控える。

4．C型肝炎

C型肝炎は血液を介して感染する。HCV抗体陽性の場合，キャリアと感染既往の鑑別のために，HCV-RNA定量検査を行う。定量検査で検出されない場合は母子感染のリスクはないが，検出された場合のリスクは約10%である[6]。HCV-RNA量高値例では予定帝王切開により母子感染率を低くする可能性がある。しかし，もし母子感染が起こっても，3割は3歳までに陰転化し，陽性児にはインターフェロン療法を行うことで半数はウイルスを排除できる。分娩方法に関しては十分な情報の提供を行った上で，患者家族の意見を尊重する。

5．トキソプラズマ

トキソプラズマ感染では倦怠感，発熱，筋肉痛，斑状丘疹状皮疹や頸部リンパ節腫脹などの症状を呈するが，無症状のことも多い。ネコ科動物を終宿主とし，ヒトなどの恒温動物を中間宿主とする人蓄共通寄生虫である。

約40%に胎内感染が起きるが，不顕性感染や軽症例が多い。妊娠14週までの感染では胎児感染率は10%以下と低いが，重症例が多く，流死産，脳内石灰化，水頭症などを合併する[7]。先天性トキソプラズマ症の新生児は水頭症，小頭症，脳内石灰化，脈絡網膜炎，失明，精神運動発達遅延，血小板減少，貧血などを合併する。

妊婦での抗体陽性率は約7%程度と低い。予防のために妊婦には，生肉は摂取しない，土を触るときには手袋をする，猫との接触は避けることなどを指導する。

トキソプラズマ感染の診断には特異的IgG，IgM抗体の検査を行う。IgM抗体が陰性の場合は4カ月以上前の感染となる。しかし，IgM抗体が陽性でも必ずしも4カ月以内の感染ではない。このような場合はIgG avidityの測定を行う。IgG抗体の抗原との親和性は時間経過とともに高くなるため，IgG avidityが高値の場合は4カ月以上経過していると推定できる。

初感染の妊婦にはアセチルスピラマイシンを投与する。胎児感染と診断された場合にはピリメタミンとスルファジアジンの投与が勧められている。ピリメタミンは催奇形性があり，また28週以降の投与では新生児に核黄疸を起こすことがあるため，妊娠16～27週での使用が推奨される。

本邦ではピリメタミン，スルファジアジンは入手できないので，代替としてファンシダールが投与されていたが，発売中止となった。治療が必要となった場合は東京大学医科学研究所感染免疫内科に連絡をとり，供給してもらうことができる。

6．水痘帯状疱疹ウイルス

水痘は発熱，発疹（紅斑，丘疹，水疱，膿皮，痂皮が混在）を主症状とし，空気感染と水疱内容物の接触感染を感染経路とする。病歴や臨床症状のみで診断可能であるが，血清VZV-IgM抗体の検出などからも診断できる。

約95%の妊婦は抗体を保有するが，罹患歴のない妊婦の感染は重症化しやすく，特に妊娠末期では死亡することもある。

妊娠20週以前の罹患では，2%に四肢低形成，脈絡網膜炎，白内障などの先天性水痘症候群が起こる。分娩3週前～6日前の罹患では児に水痘が発症しうるが，母体からの移行抗体により軽症となる。しかし，母体の発症が分娩5日前～2日後の場合では，母体からの移行抗体が不十分であり，30～40%の児が重症の新生児水痘を発症し[8]，死亡率は約30%という報告もある。このため母体への高力価の免疫グロブリン筋注が勧められる。

水痘患者との接触があった未罹患妊婦に対しては予防的ガンマグロブリンの静注を行う。アシクロビル投与は約3%に胎児奇形が認められると報告されているが，妊娠末期の場合は母児の予後を考慮し，治療を行う。また，妊娠末期の場合は子宮収縮抑制剤の投与により妊娠期間の延長を図る場合もある。

現在までの報告では水痘ワクチン接種による胎児異常の報告はないが，水痘ワクチンは生ワクチンであり，妊娠中の接種は禁忌である。

妊婦に帯状疱疹が出ることもあるが，帯状疱疹による垂直感染はないとされている。

7．風　疹

風疹は発疹，リンパ節腫脹，発熱を主症状とする。不顕性感染は約15%とされる。成人では小児に比べ重症となり，高熱や全身の関節痛を合併することがある。

妊娠初期に風疹に罹患すると，白内障や眼症状，先天性心疾患，難聴などの症状を呈する先天性風疹症候群（congenital rubella syndrome；CRS）を引き起こすことがある。CRS発症のリスクは妊娠週数が早いほど高く，妊娠4～6週では100%，7～12週では80%，13～16週では45～50%，17～20週では6%まで低下し，20週以降では0%である[9]。不顕性感染の場合でも2～4%にCRSが発症する。

風疹の診断には問診が重要であり，風疹患者との接触，症状の有無などを確認する。問診でいずれもない場合には胎児感染の可能性は極めて低いと思われる。

妊娠初期に風疹HI抗体価を測定し，抗体陰性または16倍以下の場合には，人ごみや子供の多いところは避けるなど予防に努める。また，産褥早期の風疹ワクチン接種を勧める。風疹ワクチンは弱毒生ワクチンであり，妊娠中には接種できないが，風疹ワクチン接種によるCRSの報告はない。

HI抗体価が256倍以上の場合には再度HI，IgMを測定する。HIの4倍以上の上昇，または，IgM陽性の場合は罹患の可能性を考え，追加検査を行う。しかし，HI抗体価が256倍以上となるのが妊婦の約17%という報告もあり[10]，必ずしも感染を意味するものではない。また，IgMが長期間，陽性が持続するpersistent IgMにも注意が必要である。

8．サイトメガロウイルス（CMV）

サイトメガロウイルス（CMV）は発熱，頸部リンパ節腫脹などを呈するが，無症状のこともある。輸血，尿・唾液や性行為により感染する。

わが国では先天性CMV感染が0.5～1%に起こると推定されている。約10%は出生時に症候性であるが，90%を占める無症候性の先天性サイトメガロウイルス感染症でも，後になり10～15%が精神遅滞，運動障害，難聴などを続発する[11]。症候性の場合には，胎児発育不全，肝脾腫，腹水，小頭症，脳室拡大，脳内石灰化，血小板減少，貧血，黄疸，網膜症，白内障などを認める。出生前より腹水や肝腫大が認められた場合は60%が死亡し，出生児の90%に神経学的障害を続発する[12]。

1990年ごろは日本での妊婦の抗体保有率は90%台だったが，現在は70%程度まで低下し，妊娠中初感染のリスクが高まっている。

血液検査にてIgM抗体が陽性の場合はサイトメガロウイルスの初感染を疑うが，persistent IgMがあるので注意する。超音波所見などから胎内感染が強く疑われる場合には羊水中のウイルス培養検査またはPCR法を行うこともある。

胎児治療については胎児腹腔内への免疫グロブリン投与や，母体への高力価免疫グロブリン投与，母体へのガンシクロビル投与で治療効果が期待できるとの報告もあるが，現時点では確立されたものはない。

乳幼児は不顕性感染が多く，感染後数年間ウイルスを排泄するため，乳幼児からの水平感染が起こりやすい。予防対策として，オムツや唾液に接触した場合には十分に手洗いを行う，子どもと食べ物や食器を共有しないなどの指導を行う。

9．単純ヘルペスウイルス

HSVは潰瘍または水疱性の病変を形成する。疼痛が強く，排尿困難となることもある。ウイルスは腰仙髄神経節などに潜伏感染し，ウイルスが再活性化されると，性器病変が再燃する。再発の場合は症状が軽いことが多い。

診断には病変からのHSV分離培養法がある。血清抗体は診断には有用でないが，IgG抗体，IgM抗体の測定から初感染か否か判断できる。

新生児ヘルペスの病型は皮膚，眼，口限局型，中枢神経型，全身感染に分類され，死亡率はそれぞれ，0%，15%，57%であり，中枢神経型，全身感染の場合には生存しても後遺症を残す可能性がある[13]。

妊娠中にHSV感染を認めた場合は，妊娠中期以降の感染ではアシクロビルの全身投与を行う。

初感染の場合には産道感染のリスクは30～60%と高い。再発型では母体ウイルス量が少なく，中和抗体も胎児に移行するため，産道感染のリスクは0～3%と低い[14]。分娩時にヘルペス病変が外陰部に残存している場合，初感染発症から1カ月以内に分娩となる可能性が高い場合，再発または非初感染初発から1週間以内の場合は帝王切開とし，産道感染を予防する。

10．パルボウイルス

パルボウイルス感染症では感冒症状の1～2週間後に特徴的な発疹（頬部の紅斑，レース状の発疹）を認めるが，成人の感染の場合には発疹が目立たないことが多い。また，不顕性感染も多く，症状のみではパルボウイルス感染の有無は判定できないことが多い。

パルボウイルスは赤血球系前駆細胞に感染し，アポトーシスもしくはオートファジー細胞死を誘導するため，結果として貧血となる。妊娠時に感染すると，催奇形性はないものの経胎盤感染により，約10%に胎児の貧血，胎児水腫，心不全が起こり，胎児死亡に至る場合もある[15]。特に妊娠20週未満の感染例で子宮内胎児死亡が多い。胎児水腫の9割は母体感染から8週間で発生し，約1/3に自然寛解が認められる[16]。生存例においては，長期予後は非感染妊婦から出生した児と差はない。

成人までに免疫を獲得していることが多いが，妊婦の同居者がパルボウイルス19感染した場合は約50%，感染が流行している学校に勤務している場合は約20%，流行地域の居住者では約6%に感染の可能性があるという報告があり[17]，同居者の感染などがあった場合にはパルボウイルス19感染症を疑う。

PB19-IgMの検出により診断をする。感染を確認した場合は定期的に超音波検査を行い，胎児水腫の有無，羊水過多をチェックし，胎児中大脳動脈収縮期最高血流速度を測定し，胎児貧血の評価を行う。

胎児治療としては胎児輸血が予後を改善する可能性が報告されている。ほかにも胎児腹腔内免疫グロブリン投与による奏効例が報告されているが，確立した診療法とはなっていない。

11．麻疹ウイルス

麻疹は発熱，咳，鼻汁，結膜炎などのカタル期があり，その3～4日後より高熱を伴って紅斑性丘疹が出現する。解熱後，しばらくの間，色素沈着を残す。カタル期のKoplik斑などから診断可能ではあるが，ウイルス学的にはHI抗体価の4倍以上の上昇やIgM抗体の上昇などで診断できる。

麻疹には催奇形性はないと考えられているが，流早産やIUGRの発生率は有意に高い。また，母体の麻疹発症前後に出生した児は，出生直後に感染した場合予後不良であり，注意を要する。

麻疹患者との接触後6日以内の免疫グロブリン投与は有効とされるが，発症後の効果は少ない。母体の感染から分娩までの時間によって，対応は異なる。分娩前6～15日に感染した場合は，分娩後母児を別々に隔離し，両者にグロブリンを投与する。分娩前0～6日の場合は分娩後，母のみを隔離し，両者にグロブリンを投与

する。分娩前後の麻疹発症の場合は児が発症していなければ，母のみ隔離し，児にグロブリン投与を行う。発疹出現後7日以降に分娩時期を延長できれば，先天性麻疹の発症を予防できるため，可能であれば子宮収縮抑制剤などで分娩時期を延長する。

また，麻疹ワクチンは生ワクチンであるが，前述の通り催奇形性はないため，妊娠に気がつかず接種しても妊娠継続は可能である。

12. 梅　毒

ペニシリンが開発された1940年代以降，梅毒の発生率は激減し，また妊婦の梅毒スクリーニング検査が行われ，早期治療が行われるようになり，先天梅毒児は減少した。しかし，近年，成人の梅毒患者は再度増加傾向にあり，日本でも2003年以降，増加に転じた。

T. pallidum が胎盤を通過する妊娠16週から20週までに十分に治療を行えば，胎児の感染は予防できると考えられ，妊娠初期のスクリーニングが重要である。スクリーニング検査はガラス板法などの非特異的検査と，TPHA 法などの特異的検査があり，この2つを組み合わせて行う。非特異的検査法で16倍以上陽性かつ特異的検査陽性の場合，梅毒感染とする。STS は生物学的偽陽性があり，注意が必要である。

ペニシリンなどの抗菌薬による効果は高いとされるが，妊娠中の治療に関するエビデンスは少なく，治療方法は各国で異なる。日本では経口合成ペニシリン剤を第1期梅毒では2〜4週間，第2期では4〜8週間，第3期以降では8〜12週間投与を行う。ペニシリンアレルギーではアセチルスピラマイシンの内服とする。STS 法検査で8倍以下を確認した時点で治癒と判定する。治療後6カ月以上経過しても16倍以上を示すときは再治療を推奨している。

妊娠中は超音波検査で胎児の肝腫大，腹水などを観察し，妊娠28週から32週と分娩時に血清抗体検査を行う。出生児には TPHA IgM 抗体検査，梅毒血清抗体価の測定を行い，先天梅毒の症状の有無を観察する。

13. クラミジア

クラミジアの主な感染経路は主に性行為によるものである。クラミジア子宮頸管炎による症状は帯下増量感，下腹部痛などあるが自覚症状は乏しいことが多い。

産道感染により，結膜炎，咽頭炎，肺炎などの新生児クラミジア感染症を発症するため，スクリーニング検査を妊娠30週頃までに行う。

妊娠中の治療にはアジスロマイシン，またはクラリスロマイシンを投与する。治療3〜4週間後に核酸増幅法，EIA 法により治療効果判定を行う。

14. B 群溶血性連鎖球菌（GBS）感染症

GBS は10〜30％の妊婦で膣から直腸で検出される[18)19)]。GBS 保菌母体から上行性子宮内感染，産道感染により新生児 GBS 感染症が発症する確率は0.005〜0.02％前後と高くない[19)]。発症は稀だが，敗血症や髄膜炎，肺炎，骨髄炎などの原因となり，児死亡や後遺症を有することもある。産婦人科ガイドラインでは妊娠33〜37週にスクリーニング検査を行うことを勧めている。採取方法は膣入口部，肛門内または肛門周囲から採取するのが望ましいとしている。

スクリーニング検査で陽性，前児が GBS 感染症，GBS 検査の結果が確認されていない場合は GBS として，経膣分娩中にペニシリン系抗生剤の静注により感染を予防する。

ペニシリン過敏がない場合はアンピシリンを初回量2 g 静注，以後4時間ごと1 g を分娩まで継続する。ペニシリン過敏症がある場合はクリンダマイシン，エリスロマイシンに変更する。

おわりに

母子感染は適切な対応によりその感染を防げることが少なくない。また，感染により，合併症を発症しても，新生児期から適切な管理を行うことで，日常生活が可能となることも少なくない。母子感染が疑われたときに，胎児感染の評価を十分に行わないまま，人工妊娠中絶とな

らないよう二次施設へ相談し，適切な対応を行うように注意する。

文　献

1) Hirata M et al : The effects of breastfeeding and presence of antibody to p40tax protein of human T cell lymphotropic virus type-1 on mother to child transmission. Int J Epidemiol 21 : 989-994, 1992
2) Ando Y et al : Long-term follow-up study of HTLV-1 infection in bottle-fed children born to seropositive mothers. J Infect 46 : 9-11, 2003
3) 研究代表者 齋藤　滋：齋藤班厚生労働省研究厚生労働科学研究費補助金厚生労働科学特別研究事業 HTLV-1の母子感染予防に関する研究班 平成21年度総括研究報告書，2010
4) Leroy V et al : International multicentre pooled analysis of late postnatal mother-to-child transmission of HIV-1 infection. Ghent International Working Group on Mother-to-Child Transmission of HIV. Lancet 352 : 597-600, 1998
5) Kourtis AP et al : Understanding the timing of HIV transmission from mother to infant. JAMA 285 : 709-712, 2001
6) NIH Consensus Conference Statement : Management of Hepatitis C : 2002
7) Hohlfeld P et al : Prenatal diagnosis of congenital toxoplasmosis with a polymerase-chain-reaction test on amniotic fluid. N Engl J Med 331 : 695-699, 1994
8) Centers for Disease Control and Prevention (CDC) : Prevention of varicella : recommendations of the Advisory Committee on Immunization Practices (ACIP). Mobidity and Mortality Weekly report 45 (RR-11) : 1-25, 1996
9) Ghidini A, Lynch L : Prenatal diagnosis and significance of fetal infections. West J Med 159 : 366-373, 1993
10) Okuda M et al : Positive rates for rubella antibody in pregnant women and benefit of post-partum vaccination in a Japanese perinatal center. J Obstet Gynaecol Res 34 : 168-173, 2008
11) Stagno S, Whitley RJ : Herpesvirus infections of pregnancy. Part Ⅰ : Cytomegalovirus and Epstein-Barr virus infections. N Eng J Med 313 : 1270-1274, 1985
12) Maruyama Y et al : Fetal manifestations and poor outcomes of congenital cytomegalovirus infections : possible candidates for intrauterine antiviral treatments. J Obstet Gynaecol Res 33 : 619-623, 2007
13) Whitley R et al : Predictors of morbidity and mortality in neonates with herpes simplex virus infections. The National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. N Engl J Med 324 : 450-454, 1991
14) Management of herpes in pregnancy : ACOG practice bulletin, Clinical Management Guidelines for Obstetrician-Gynecologists 82 : 1489-1498, 2007
15) Valeur-Jensen AK et al : Risk factors for parvovirus B19 infection in pregnancy. JAMA 281 : 1099-1105, 1999
16) Rodis JF et al : Management of parvovirus infection in pregnancy and outcomes of hydrops : a survey of members of the Society of Perinatal Obstetricians. Am J Obstet Gynecol 179 : 985-988, 1998
17) Adler SP, Koch WC : Human parvovirus infections, Infectious Disease od the Fetus and Newborn Infant, 6th ed (ed : Remington JS et al), p867-870, Elsevier Saunders, 2006
18) Reiff-Eldridge R et al : Monitoring pregnancy outcomes after prenatal drug exposure through prospective pregnancy registries : a pharmaceutical company commitment. Am J Obstet Gynecol 182 : 159-163, 2000
19) 保科　清ほか：最近6年間のB群レンサ球菌(GBS) 感染症についてのアンケート調査結果．日周産期・新生児医誌 42 : 7-11，2006