clinical practice guidelines

Extranodal diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]

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aim of the guidelines

The aim of these guidelines is to provide practical clinical guidance and recommendations to clinicians to manage diffuse large B-cell lymphomas (DLBCLs) that arise in extranodal sites. DLBCL may arise in virtually any extranodal sites, but the majority of these are treated as the nodal counterpart, i.e. gastric DLBCL. For the recommended treatment, the reader can refer to the 2015 ESMO DLBCL guidelines [1]. The choice of the entities included in these guidelines is based on the clinical need to give recommendations for those entities which require a specific therapeutic approach. Recommendations for primary cutaneous DLBCL have been already reported by ESMO.

incidence and epidemiology

DLBCL is one of the most common lymphoid neoplasms, representing 30%–58% of non-Hodgkin's lymphoma (NHL) and with a crude incidence in Europe of 3.8/100 000/year. Despite a common morphology characterised by the diffuse proliferation of mature large B cells, these tumours are clinically and biologically very heterogeneous. Most DLBCLs originate in lymph nodes, but ≤40% initially present in extranodal sites [2]. Differences in molecular pathogenesis, clinical presentation and natural history indicate that extranodal DLBCLs are distinct entities [2]. The most common site of origin is the gastrointestinal tract, but many other organs and tissues may be involved such as the mediastinum, testis, central nervous system (CNS), breast and bone. Here, we provide guidelines for the clinical management of DLBCLs arising as primary tumours of the mediastinum, testis, CNS, breast and bone, whereas nodal DLBCLs have been considered separately [1]. These subtypes of extranodal DLBCLs represent ~1%–5% of all NHLs, and this low frequency makes the analysis of disease-specific epidemiological factors difficult [3].

diagnosis and pathology/molecular biology

The diagnosis of DLBCL should be carried out in a reference haematopathology laboratory with expertise in morphological interpretation and the facilities to carry out the full range of phenotypic and molecular investigations. Details on methods for pathological diagnosis, immunohistochemistry and molecular biology have been fully reported in ESMO guidelines for nodal DLBCLs [1].

primary mediastinal large B-cell lymphoma

Primary mediastinal large B-cell lymphoma (PMBCL) represents ~10% of all DLBCLs and it is more commonly seen in women in their third to fourth decades of life [3]. These tumours derive from a medullary thymic B cell and are composed of large cells expressing pan B-cell markers, but are negative for surface Ig. The tumour cells are usually positive for CD23, weakly positive for CD30 and negative for CD15. BCL6, CD10 and IRF4 are expressed in a variable number of cases. Some tumours have morphological, phenotypic and molecular features close to nodular sclerosing Hodgkin's lymphoma (HL). These tumours have been included in the World Health Organization (WHO) category of B-cell lymphoma as unclassifiable and with features intermediate between DLBCL and classical HL [3]. The molecular alterations detected in PMBCL target three major mechanisms: *NFkB* activation (REL

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amplification, inactivating mutations of TNFAIP3), *JAK-STAT* pathway activation (inactivating mutations of SOCS1, JAK2 amplification and IL13 overexpression) and modulation of tumour cell interactions with the microenvironment and immune system (down-regulation of HLA class II, PDL-1 and 2 amplifications or translocations) [4].

primary testicular lymphomas

Primary testicular lymphomas (PTLs) are mainly DLBCLs (80%–90%) and a minority of other histological subtypes such as plasmablastic, Burkitt's or mantle cell lymphoma and, rarely, low-grade follicular lymphomas (FLs) or T-cell lymphomas [5]. Some features of DLBCL (e.g. plasmacytoid differentiation, somatic hypermutation of immunoglobulin heavy-chain genes and higher frequency of the loss of HLA-DR and DQ expression) suggest the possibility of antigen-driven stimulation. In addition, an altered expression of cell surface adhesion molecules may explain the propensity to disseminate to extranodal sites. Cell of origin (COO) studies show an activated B-cell (ABC) pattern in 60%–96% of cases. Mutations of *MYD88* were found in ∼70% of PTLs, compared with <20% in patients with nodal DLBCLs. Interestingly, 19% of these *MYD88*-mutated cases also carry CD79a mutations [6]. Inactivating mutations of *B2M* and rearrangements of *PDL*, *CIITA* and *FOXP1* have also been found in 2%–10% of the cases, emphasising the role of tumour microenvironment interactions in the pathogenesis of these tumours.

primary central nervous system lymphomas

Primary CNS lymphomas (PCNSLs) in immunocompetent patients represent 2%–3% of all brain tumours. Most of these cases are DLBCLs and 10%–20% develop intraocular lesions. Extraneural dissemination is rare, but clonally related cells have been detected in the blood of some of these patients [7]. Different studies to determine the COO have yielded inconclusive results with many tumours expressing both germinal centre (GC) markers and the ABC marker IRF4 [7]. Molecular studies have shown activation of *NFkB* and *BCR/MYD88* pathways and deletions of the HLA gene locus at 6p21.32, suggesting that, similarly to PTLs and PMBCLs, interactions with the microenvironment are important pathogenic mechanisms [7]. *MYD88* mutations have been detected in 30%–75% of cases and CD79A/B mutations in up to 45%, with substantial overlap in the positive cases, so that many carry both mutations [8].

primary diffuse large B-cell lymphoma of the breast

Primary breast lymphoma (PBL) is an uncommon tumour representing <1% of NHLs and <0.5% of all breast tumours. Histologically, these lymphomas are heterogeneous and include DLBCLs, which are the most common form, mucosa-associated lymphoid tissue (MALT) lymphomas, FL, Burkitt's lymphomas (mainly occurring during pregnancy or lactation) and anaplastic lymphoma kinase-negative T-cell lymphomas, which are associated with breast implants. Molecularly, primary breast DLBCLs are mainly of ABC-subtype and cytogenetic studies have observed trisomy 3 and 18 and chromosome 18 translocations involving *IGH/MALT1* as in low-grade MALT lymphomas [9].

primary diffuse large B-cell lymphoma of the bone

Primary bone lymphoma (PBoL) is a rare category accounting for <1% of NHLs and ∼5% of either all primary extranodal NHLs or all bone tumours. It is defined as a lymphoma confined to bones and is usually radiologically evident. These tumours may be clinically distinct from *primary bone marrow* lymphomas, in which the tumour cells are restricted to the marrow cavity without radiological or histological evidence of cortical bone destruction [10]. However, this distinction is challenged in the present positron emission tomography (PET) era by the increasing recognition of asymptomatic lesions with focal bone marrow uptake, sometimes but not necessarily accompanied by alterations of the bone tissue. They are more common in mid-elderly men and the vast majority are DLBCLs, although other subtypes may also rarely occur. Non-GC phenotype is slightly more common than GC. *BCL2, BCL6* and *MYC* rearrangements may be found in 19%, 14% and 9% of the cases, respectively. There is insufficient literature and too few reported patient outcomes to enable firm conclusions regarding the prognostic impact of the COO.

staging and risk assessment

Baseline assessments and procedures do not generally differ from those required for patients presenting with nodal DLBCLs and include: physical exam, determination of performance status (PS), B symptom assessment, complete blood count, routine blood chemistry with lactate dehydrogenase (LDH) and screening tests for human immunodeficiency virus and hepatitis B and C (Table 1).

Based on the new consensus recommendations for staging and restaging of lymphoma developed by the clinical and imaging working groups of the International Conference on Malignant Lymphomas, fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) scan is now recommended as standard practice both for staging patients with DLBCL and for response assessment based on the visual Deauville criteria (five-point scale, Table 2) [11].

Additional and specific staging procedures are reported in each section for different extranodal sites and are summarised in Table 1.

The disease staging is established as nodal DLBCL according to the Ann Arbor classification system (Table 3). In extranodal DLBCL, the discriminating utility of the International Prognostic Index (IPI) and age-adapted IPI (aaIPI) is not fully evaluated; however, these tools should be calculated for prognostic purposes at least to differentiate between localised versus advanced stage disease [II, A] (Table 4). Specific risk score models have been developed by the International Extranodal Study Group (IELSG) for PCNSL and PBoL; they are described in each related paragraph below and are summarised in Table 5 [12] and Table 6 [13].

treatment

The treatment and recommendations for each entity are detailed separately in each section. The International Lymphoma Radiation Oncology Group have recently published comprehensive guidelines on the use of radiotherapy (RT) in extranodal lymphomas,

Table 1. Summary of diagnostic work-up

Diagnostic work-up for all entities				
Physical examination	Peripheral lymph nodes, liver, spleen			
Laboratory	Blood cell and differential count, renal and liver function, LDH, uric acid			
Serology	Hepatitis B (including HBsAg, anti-HBs and anti-HBc antibodies) and C, HIV serology			
Imaging	CT neck, chest, abdomen and pelvis, PET/CT			
Bone marrow	Histology			
Additional diagnostic work-up for specific entity	PTL	PCNSL	PBL	PBoL
Brain MRI	Yes	Yes	Yes	No[a]
Cytology and flow cytometry of cerebral spinal fluid	Yes	Yes	Yes	No[a]
Testicular ultrasound	Yes	Elderly males yes	No	No
Ocular slit-lamp examination	No	Yes	No	No
Involved MRI of bone lesion	No	No	No	Yes

LDH, lactate dehydrogenase; HIV, human immunodeficiency virus; CT, computed tomography; PET/CT, positron emission tomography/computed tomography; PTL, primary testicular lymphoma; PCNSL, primary central nervous system lymphoma; PBL, primary breast lymphoma; PBoL, primary bone lymphoma; MRI, magnetic resonance imaging.
[a]Only if involvement of skull and/or spine.

Table 2. Positron emission tomography (PET) five-point scale (Deauville criteria)

1	No uptake
2	Uptake ≤mediastinum
3	Uptake >mediastinum but ≤liver
4	Moderately increased uptake compared with liver
5	Markedly increased uptake to liver and/or new lesions

Table 3. Ann Arbor staging classification

Stage	
I	Involvement of a single lymphatic region (I) or localised involvement of single extralymphatic organ or site (IE)
II	Involvement of two or more lymphatic regions on the same side of the diaphragm (II) or localised involvement of a single extralymphatic organ or site and of one or more lymphatic regions on the same side of the diaphragm (IIE)
III	Involvement of lymphatic regions on both sides of the diaphragm
IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without lymphatic involvement

Table 4. International prognostic index (IPI)

International prognostic index—IPI		
Risk factors	Age >60 years	
	Serum LDH > normal	
	Stage III–IV	
	PS 2–4	
	Extranodal sites >1	
Risk categories	Low	0–1
	Low intermediate	2
	High intermediate	3
	High	4–5
Age-adjusted international prognostic index—aaIPI—in patients ≤60 years		
Risk factors	Serum LDH > normal	
	Stage III–IV	
	PS 2–4	
Risk categories	Low	0
	Low intermediate	1
	High intermediate	2
	High	3

LDH, lactate dehydrogenase; PS, performance status.

and these guidelines should be referenced in every section regarding the detailed techniques and dose requirements [14].

primary mediastinal large B-cell lymphomas

PMBCLs usually present with a bulky tumour in the anterior mediastinum, with local compressive symptoms including dyspnoea, cough, dysphagia and a superior vena cava syndrome in ~50% of cases. Pleural or pericardial effusions are often present. Particular extranodal sites such as kidneys, adrenal glands, liver and ovaries may be involved, particularly in the setting of disease recurrence. For prognostic characterisation, the IPI remains the standard score, but its discriminatory utility in

PMBCL is limited by the age distribution of the disease and its usual confinement to the mediastinum.

FDG-PET/CT scan is mandatory to assess disease extent and to obtain better definition of the residual mediastinal masses at the completion of treatment, because PMBCL shows universal avidity for [18F]-2-fluoro-2-deoxyglucose.

treatment. The combination of rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) or with VACOP-B (etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone and bleomycin)/MACOP-B (methotrexate,

Table 5. The International Extranodal Lymphoma Study Group (IELSG) prognostic score for PCNSL

Variable	Favourable feature (value '0')	Unfavourable feature (value '1')
Age (years)	<60	>60
ECOG PS score	0–1	>1
Lactate dehydrogenase serum level	Normal	Elevated
Cerebrospinal fluid protein level	Normal	Elevated
Involvement of deep regions of the CNS[a]	No	Yes

IELSG score 0–1, low risk; 2–3, intermediate risk; 4–5, high risk.
PCNSL, primary central nervous system lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; CNS, central nervous system.
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[a]Deep regions include the corpus callosum, basal ganglia, brain stem and cerebellum.

Table 6. The International Extranodal Lymphoma Study Group (IELSG) staging system for DLBCL of the bone

Lymphoma extension	IELSG Stage
Single bony lesion	IE
Single bony lesion with involvement of regional lymph nodes	IIE
Multifocal disease in a single bone or lesions in multiple bones in a disease exclusively limited to the skeleton (without lymph nodal or visceral disease)[a]	IVE
Disseminated lymphoma with at least one bony lesion	IV

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[a]Also called *multifocal osteolymphoma* or *polyostotic lymphoma*.

doxorubicin, cyclophosphamide, vincristine, prednisolone and bleomycin) (R-V/MACOP-B), dose-dense CHOP (R-CHOP14) or more intensive chemotherapy regimens such as DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine cyclophosphamide, doxorubicin and rituximab) are the current standard treatments for PMBCLs and any of them can be used according to the centre's experience [III, A] [15, 16].

Consolidative mediastinal RT is recommended in responding patients treated with standard-dose chemoimmunotherapy (R-CHOP/R-V/MACOP-B) [II, A] [16].

Based on the results of a small phase II study, consolidative mediastinal RT could be omitted in patients with a complete metabolic response (CMR) only after DA-EPOCH-R [III, C] [15]. However, these results need to be validated in a larger, multicentre series.

Where used, consolidative mediastinal RT should be administered with doses in the range 30–36 Gy, in 1.5–2.0 Gy fractions [II, A].

The role of consolidative mediastinal RT in the 50% of patients with CMR (PET/CT negative) post-chemoimmunotherapy is currently being investigated. The results of the ongoing comparative randomised trial (IELSG-37) (NCT01599559) will determine whether consolidative RT could be omitted in patients with a CMR at the post-chemoimmunotherapy PET/CT scan following R-CHOP-like regimens. Outside of a clinical trial, there are insufficient data to support omission, especially as relapses are difficult to salvage with poor outcomes.

Based on the good results achieved with rituximab chemotherapy combination regimens ± RT, high-dose chemotherapy followed by autologous stem cell transplantation (HDCT/ASCT) is not recommended in patients who achieved complete remission (CR), even in initially poor-risk patients who attain an adequate response to initial therapy [III, A].

In young patients who do not obtain an adequate response (i.e. less than partial response) with an elevated FDG uptake at the post-chemoimmunotherapy PET/CT scan, if residual disease is confirmed by biopsy when feasible, an intensification therapy with HDCT/ASCT is recommended [III, B].

post-treatment evaluation. A PET/CT scan in PMBCL has an excellent negative predictive value, but it also has a low positive predictive value due to the high frequency of false-positive scans. Thus, positive PET scans require further investigation before modifying planned therapy. Several patients with persistent metabolically active masses underwent biopsies, which showed necrosis but no lymphoma. False increased FDG uptake may be due to an inflammatory response produced by the addition of rituximab to chemotherapy or a thymic rebound, which is particularly relevant, given the location of the disease [17]. Thus, positive PET scans require further investigation before modifying planned therapy. A post-treatment PET/CT response evaluation should not be carried out until at least 5–6 weeks from the last infusion of chemotherapy to minimise the incidence of these false-positive scans. Serial scanning may be required to fully evaluate areas of residual post-treatment PET tracer uptake, with many patients manifesting gradual resolution.

treatment of relapsed/refractory PMBCL. The probability of recurrence after successful initial therapy for PMBCL appears to be lower than for other DLBCLs, and those patients who achieve a response lasting longer than 18 months are likely to be cured.

Salvage treatment strategies of relapsed/resistant patients are similar to nodal DLBCLs, and include attempting reinduction with non-cross-resistant agents followed by consolidation with HDCT/ASCT in patients with chemosensitive disease [II, A].

If radiation has not been a component of initial therapy, RT should be incorporated into the salvage treatment programme for patients with relapsed disease, ideally post-transplant if significant mediastinal or lung volumes are involved.

primary testicular lymphomas

PTLs usually present as a limited stage disease with most patients having a unilateral testicular mass, although bilateral testicular involvement occurs in ~10%. There is a propensity for an aggressive clinical behaviour with dissemination to multiple extranodal sites, such as lung, pleura, skin (up to 35%), soft tissues and

Waldeyer's ring (5%). CNS relapses are frequent and occur in up to 30% of PTL patients within 1–2 years of diagnosis, but can also be delayed in presentation [18]. For staging, in addition to the standard tests, ultrasound of the contralateral testis, brain nuclear magnetic resonance imaging (MRI) and diagnostic lumbar puncture with cytological and flow cytometric analysis on cerebrospinal fluid (CSF) are mandatory. Orchiectomy remains a mandatory step in the management of PTL, both for diagnostic and for therapeutic aims [III, A] [19].

treatment. In the IELSG retrospective series, chemotherapy with anthracycline-containing regimens significantly improved the outcome in all patients [19]. Despite the lack of randomised studies, some retrospective studies and a prospective one (IELSG10) provided evidence of the benefit of the addition of rituximab to chemotherapy [20]. Six to eight cycles of R-CHOP given every 21 days is the current standard [II, A].

If orchiectomy is not carried out, RT is given to the involved testis. The addition of RT to the contralateral testis significantly reduces or abrogates testicular relapses in retrospective and prospective studies [19–21]. Hence, prophylactic RT to the contralateral testis and scrotum is strongly recommended [III, A]. The dose to the testis should be 25–30 Gy in 1.5–2 Gy fractions. Such treatment to the remaining testis is associated with a substantial risk of hypogonadism; therefore, sequential monitoring of testosterone levels and replacement therapy are clinically important and should be included in the follow-up programme for these patients. RT was given in the past to involved abdomino-pelvic nodes in stage IIE disease; however, the lack of well-conducted trials makes it difficult to assess the role of nodal RT in this setting. Indeed, also in nodal DLBCL, with the introduction of PET reassessment after R-CHOP, consolidation RT is less frequently used in patients who achieved a PET-negative CR. Based on these indirect data and considering the increased toxicity, RT to involved nodes could be safely omitted if PET negative after R-CHOP chemotherapy [III, C], as in the ongoing IELSG30 phase II study (NCT00945724).

Although some conflicting data exist, a prophylactic therapy to reduce the risk of CNS relapse should be added to the treatment [III, B]. Two options can be considered: intrathecal chemotherapy with methotrexate (MTX) is the most common one; alternatively, intravenous systemic MTX can be employed as part of overall treatment [III, B] [5]. The best strategy to further reduce CNS recurrence remains an open issue. The ongoing IELSG30 phase II study that includes both intrathecal chemotherapy with liposomal cytarabine and systemic prophylaxis with a lower dose of MTX (1.5 g/m^2) to spare toxicity in elderly PTL patients aims at addressing this issue.

In summary, the recommended treatment for stage I–II PTL consists of R-CHOP21 × 6–8 courses, with the addition of CNS prophylaxis and prophylactic RT to the contralateral testis.

The therapy of advanced-stage PTLs is not different from the standard treatment of advanced-stage nodal DLBCLs. Unlike nodal DLBCLs, two treatment issues should be incorporated in the therapeutic strategy: prophylactic testicular RT and CNS prophylaxis [18].

post-treatment evaluation. As in nodal DLBCLs, FDG-PET/CT can be considered the recommended standard for post-treatment assessment in PTL.

treatment of relapsed/refractory PTL. Standard therapeutic option for these patients has not yet been defined in prospective trials. HDCT/ASCT, if feasible, should be the preferred treatment strategy in chemosensitive relapse as in nodal DLBCL [I, A] [22]. However, many PTL patients are elderly, with poor PS and multi-organ dysfunction; the inclusion of these patients in clinical trials testing novel drugs is advisable.

primary CNS lymphomas

PCNSLs are rare diseases defined by involvement of the cerebral parenchyma, leptomeninges, eyes or spinal cord without evidence of systemic disease.

Patients with PCNSL usually present with focal neurological deficits and/or neuropsychiatric symptoms. Symptoms of increased intracranial pressure and seizures are less frequent [12]. Approximately 10%–20% of patients have ocular involvement, with floaters, blurred vision, diminished visual acuity and painful red eyes. About one-third of patients present with multifocal neurological disease, with highly diverse deficits.

Stereotactic biopsy is recommended as a minimal invasive technique to obtain histopathological diagnosis [III, A]; therefore, resection of PCNSL cannot be recommended, because of the associated morbidity and lack of evidence for benefit [23]. Glucocorticoid therapy can interfere with an accurate histopathological diagnosis; therefore, it should be avoided before biopsy if possible without clinically compromising the patient [24].

At diagnosis, patients should undergo contrast-enhanced brain MRI as the standard for baseline and response assessment, as well as cytological evaluation and flow cytometry of the CSF. In addition, slit-lamp examination should be carried out to investigate possible ocular involvement. CT scans of the chest, abdomen and pelvis or a PET/CT scan is carried out to exclude systemic disease. Additionally, testicular ultrasound examination in elderly male patients is recommended [V, B] [23]. In PCNSL, the value of a bone marrow examination is controversial; however, it is still part of baseline investigations in current PCNSL trials.

The IELSG has proposed a prognostic system for PCNSL based on the following independent prognostic factors: age >60 years, Eastern Cooperative Oncology Group (ECOG) PS >1, elevated serum LDH, elevated CSF protein concentration and tumour localisation within the deep regions of the brain. Three risk classes are defined for patients with 0–1 (good-risk), 2–3 (intermediate-risk) or 4–5 (poor-risk) prognostic factors (Table 5) [12]. Another validated risk score developed by Abrey et al. [25] only requires age and clinical PS to build three different risk groups good risk (patients <50 years), intermediate risk (patients ≥50 years and Karnofsky performance score [KPS] ≥70) and high risk (patients ≥50; KPS <70).

first-line treatment. Historically, whole-brain radiotherapy (WBRT) has been the standard treatment for PCNSL. Despite the high CR rate, the disease relapses in almost all patients after a few months, with a median survival of 12 months and few long-term survivors. The addition of chemotherapy to WBRT has been recommended to improve survival of PCNSL patients.

High-dose MTX (HD-MTX; at least 3 g/m^2 over 2–4 hours rapid infusion time) is considered the most effective single agent for treating PCNSL [25]; however, based on prospective studies,

CR rates are usually <30% with single-agent, high-dose MTX. The addition of high-dose cytarabine (HD-ara-C) has been shown to significantly improve response rate (RR) and failure-free survival, compared with high-dose MTX alone in a phase II randomised trial [26]. Other CHOP-like protocols were associated with unsatisfactory results in PCNSL [26]. Several single-arm studies have investigated other drugs in combination with HD-MTX without clear additional benefit, including ifosfamide, thiotepa, procarbazine, vincristine and temozolomide [27].

The role of prophylactic intrathecal chemotherapy is unclear. Retrospective studies do not suggest a benefit from adding intrathecal chemotherapy combined to systemic high-dose MTX. On the other hand, other non-randomised studies suggested that intraventricular treatment combined with an MTX-based chemotherapy was effective in reducing relapse rate [28]. Thus, the effectiveness of intrathecal therapy is contradictory and may different according to the route of administration. In summary, intrathecal chemotherapy cannot be routinely recommended if appropriate systemic chemotherapy is applied, but could be considered in the case of severe meningeal involvement [IV, C] [24, 29].

RT with doses between 40 and 45 Gy in 20–25 fractions is primarily used as consolidative therapy following HD-MTX-based chemotherapy. Higher RT doses following chemotherapy are associated with an increased risk of neurotoxicity, which is particularly pronounced in the older age group (30% of all patients and 40%–50% of those >60 years of age). This neurotoxicity led to testing lower RT doses, as low as 30–36 Gy for WBRT or 23.4 Gy after chemotherapy-induced CR [27]. These regimens appeared to be effective and without prohibitive RT-related toxicity, even in elderly patients [27, 29–31].

HDCT/ASCT represents an alternative strategy for consolidation treatment aimed at sparing neurotoxicity, avoiding RT and improving outcome. HDCT/ASCT has been used as part of front-line treatment in PCNSL patients with encouraging results, mostly using thiotepa-based conditioning regimens with overall remission rates of up to 91% and a 5-year overall survival (OS) of 87% for those who completed HDCT [32]. Another approach to avoid WBRT is consolidation with dose-intensive conventional chemotherapy, such as etoposide and ara-C after HD-MTX-based induction [24].

Recently, the preliminary results of IELSG32 randomised study (NCT01011920, Eudra CT number 2009-014722-42) suggested a benefit of the addition of rituximab and thiotepa in newly diagnosed PCNSL with regard to RR, progression-free survival (PFS) and OS [33]. This is also supported by retrospective series investigating combination of rituximab with HD-MTX.

elderly patients (age >70 years or patients with comorbidities).
Selected elderly patients are often able to tolerate HD-MTX-based treatment, with dosage guided by renal function [24]. Based on a recent systematic review and individual patient data meta-analysis, HD-MTX-based treatment was associated with an improved survival outcome [34]. Further combinations with oral alkylating agents such as lomustine (CCNU) and procarbazine ± vincristine are feasible, active and are warranted to be compared with HD MTX alone [31, 35]. Overall, HD MTX-based treatment should be considered whenever possible in elderly patients with PCNSL [II, A]. WBRT should not be a routine component of front-line therapy in elderly patients able to tolerate other therapies, due to its high rate of neurotoxicity, and is reserved for frail patients or patients with refractory disease [14].

In summary, HD-MTX-based regimens, in combination with HD-ara-C, are recommended for induction treatment if possible based on patient age, PS and organ function [I, A]. HD-MTX-based treatment should be considered whenever possible in elderly patients with PCNSL [II, A].

The use of WBRT as consolidation after HD-MTX-based chemotherapy is still commonly applied in young patients and generally avoided in those >60 years, as the risk of neurotoxicity (including cognitive deterioration) is particularly high in elderly patients [III, B].

Thus, we recommend that consolidation RT should be avoided in elderly patients who achieved CR [III, B], while in those not reaching CR, it is preferable to use lower doses of WBRT (36 or 23.4 Gy) based on response [III, B].

Whether RT can safely be omitted without compromising long-term outcome also in younger patients in CR remains controversial [III, C]. HDCT/ASCT as consolidation treatment could be considered as an alternative to WBRT in eligible patients [III, B].

post-treatment evaluation. Brain MRI is the standard for response evaluation. For patients with previous CSF involvement, CSF analysis (cytology and flow cytometry) should be added, as well as spinal imaging as clinically indicated. In the follow-up, brain MRI monitoring may be helpful to rule out progression, but the overall clinical utility of such a surveillance strategy is unproven. For patients with prior CSF or ocular involvement, specific assessments (i.e. CSF evaluation or ophthalmologic evaluation) are needed as clinically indicated. Based on the rarity of systemic progressions, additional systemic evaluation (i.e. CT or CT/PET scans) are indicated only in the case of clinical signs or symptoms of systemic progression.

treatment of relapsed/refractory PCNSL. HDCT/ASCT has been prospectively investigated in patients with disease relapse after HD-MTX with a median survival of 18.3 months (58.6 months for those who received HDCT/ASCT) [36]. Only a few agents have been investigated prospectively in the relapse/refractory setting, namely temozolomide [36], temozolomide plus rituximab [37], topotecan and pemetrexed. However, none of these showed convincing activity sufficient to be established as standard in this situation. Re-exposure to the same HD-MTX-based protocol can be considered; however, there are no data on the relationship between efficacy and the duration of prior response. When RT is used as a single modality therapy, i.e. WBRT as primary treatment for non-candidates for chemotherapy, higher doses (40–50 Gy, 1.5–1.8 Gy/fraction) are required. Doses of 36 Gy have been shown to be beneficial in a salvage setting, but the optimal dose and the role of boost doses remain uncertain [38].

In summary, choice of salvage treatments depends on the clinical status, toxicities from previous treatments and duration of remission. Based on the limited evidence available so far, no standard protocol can be recommended. Fit patients should be considered for HDCT/ASCT [III, B]. WBRT remains an important palliative treatment in PCNSL lymphoma for those

unable to tolerate or relapsing after high-dose, CNS-penetrating chemotherapy and not fit for further chemotherapy [III, B].

primary breast lymphoma

PBL is typically a disease of older women (median age 62–64 years), but with lower median ages in specific geographic areas (i.e. in East Asian countries) [39, 40]. PBL almost exclusively affects women, with very rare male cases reported, but with apparently similar outcomes [41]. The typical presentation is a painless breast mass (median 4 cm diameter), slightly more frequently on the right side and with systemic symptoms present in <5% of patients, almost always those with disseminated disease [42].

Currently, up to 20% of patients are diagnosed incidentally [42, 43], but there are no definitive radiologic features of PBL; therefore, a diagnostic biopsy is mandatory [IV, A].

The specific additional staging procedures recommended for PBL include contralateral breast examination for potential bilateral involvement, which would usually be dealt with adequately by whole-body PET/CT. CNS imaging with MRI of the brain and CSF analysis by cytology and flow cytometry should also be carried out even in the absence of CNS symptoms [IV, B]. Approximately 70% of patients have stage IE disease, with the other 30% having regional nodal involvement (stage IIE) [41]. From 4% to 13% of patients have bilateral breast involvement at presentation [41].

The standard IPI is predictive of outcome, but this has low discriminatory ability, while the stage-modified IPI has a better prognostic discrimination, mainly through the adverse impact of stage IIE disease [41, 44]. Other reproducible adverse prognostic factors among patients with localised disease include tumour size >4–5 cm [44, 45] and bilateral involvement that was found to be a significant adverse predictor of both PFS and OS, with a high risk of CNS relapse [41, 43].

Reminiscent of PTL, PBL displays extranodal tropism at relapse [46]. The ipsilateral and contralateral breasts were involved at relapse in 12%–44% of series with available data [40], with ipsilateral breast relapse occurring in the first few years following treatment, while in contrast, contralateral breast relapse occurred up to 13.3 years later [41]. Other extranodal sites including the bone marrow, lung or pleura, skin, gastrointestinal tract and CNS have all been reported to occur more commonly in PBL than among nodal DLBCLs [39, 44].

From larger series, CNS relapse developed in 5%–16% of patients, with a weighted average of ~12%. Other than potentially bilateral disease, there are no reproducible predictors of CNS relapse risk.

treatment. Surgical resection as a sole modality results in inadequate local control, and the application of mastectomy is associated with inferior outcomes [41, 44]. In the rare instance of patients who have undergone surgical excision, they should still be managed identically as recommended below [V, B].

The retrospective IELSG-15 study reinforced the importance of an anthracycline-containing chemotherapy regimen with a strongly favourable impact on both PFS and OS. Most recent contemporary series have used CHOP ± rituximab and RT with 5-year PFS and OS of 50%–70% [41, 42, 47]. In cohorts without

stratification by risk, abbreviating the number of chemotherapy cycles to fewer than 4 has resulted in inferior outcomes [39, 41]. Although there are no randomised studies addressing the question, most historical comparisons suggest some favourable impact from the incorporation of rituximab, and given its established role in DLBCL treatment, it should be routinely included in front-line chemoimmunotherapy as part of R-CHOP q 21d [III, B]. There are no data supporting the use of more aggressive or dose-escalated regimens as part of primary therapy [III, B].

Whole-breast RT is generally recommended after chemotherapy based on the benefit in OS observed in the large IESLG study [41], but some experts consider partial breast RT in cases where the resulting morbidity reduction is likely to offset the potential increase in marginal relapse rate, especially where PET scanning has been used in initial staging to allow accurate delineation of the involved area and nodal status [14]. The uninvolved lymph nodes need not be included in the RT volume, provided initial staging has used PET [14].

treatment recommendations. The recommended treatment for PBL is as follows: 6 cycles of R-CHOP, if therapy is well tolerated [III, A], followed by consolidative whole ipsilateral breast RT (30–36 Gy) [III, B]. CNS-directed prophylaxis should be considered for individual patients [III, B], and is recommended in high-risk patients, i.e. bilateral involvement [III, A]. No specific CNS prophylaxis treatment can be recommended due to the lack of data; in nodal DLBCL, either intrathecal or i.v. MTX could be appropriate [48]. Patients with bilateral breast involvement represent a particularly high-risk group, and investigation of more intensive chemotherapy regimens in the context of clinical trials is justified in such cases [IV, C].

post-treatment evaluation. As in nodal DLBCL, FDG PET/CT can be considered the recommended standard for post-treatment assessment in PBL (Table 2). The Lugano 2014 criteria are also applied to PBL.

treatment of relapsed/refractory PBL. The outcome of patients after relapse is poor; in the IELSG-15 series, the median survival after relapse was 1.0 year, with a 5-year OS of 20% [41]. The management strategy should be as per other instances of relapsed DLBCL, with reinduction chemoimmunotherapy aiming to proceed to HDCT/ASCT, where feasible, in patients with responsive disease [IV, B].

primary bone lymphoma

PBoL may present as a single bone lesion with or without an associated soft tissue mass arising from local extension and with or without regional lymphadenopathy or as a multifocal polyostotic disease exclusively involving the skeleton [13].

The median age at diagnosis varies from 45 to 60 years. Patients with PBoL typically present with bone pain (80%–95%), a tumour mass in 30%–40% of the cases and pathological fracture, most frequently of the humerus, in 10%–15% of patients. Approximately 15% of patients show spinal cord compression and 10% have hypercalcaemia, usually in the presence of rapidly progressive disease. The femur, the pelvic bones and the spine are the most common sites of involvement [13, 49].

Most patients have early-stage disease at diagnosis [13], and PET/CT has increased the detection of asymptomatic bone lesions as part of the initial presentation of disseminated DLBCL [49]. In comparison with CT scan, MRI better defines the local extent of the disease and cortical changes. An adapted staging system for PBoL has been proposed by the IELSG (Table 6) [13, 50].

The prognosis of primary bone DLBCLs mainly depends on the disease extent: 5-year OS rates vary from >80% for stage IE to <40% for disseminated DLBCL with bone localisation [51]. The role of the IPI in predicting prognosis of primary DLBCL of the bone seems limited [13, 49, 51].

treatment. Primary bone DLBCL should be treated with anthracycline-containing chemotherapy regimens together with rituximab, although the benefit of the addition of rituximab has not formally studied specifically in the subset of patients with PBoL. The role of consolidation RT is not well defined because the available data are very controversial and mainly come from retrospective analyses that suggest benefit [51, 52]. Indeed, R-CHOP ± consolidation RT remains the standard approach for the patients with any stage of DLBCL with bone involvement [III, B]. Whether RT to sites of bone involvement is truly needed or can be spared (at least in cases with a negative PET scan after chemoimmunotherapy) should be addressed in appropriately designed prospective randomised trials [51]. When consolidation RT is given to localised lesions, there is limited additional benefit from the use of extensive radiation volumes and RT and dose range is 30–40 Gy, depending on the certainty that a CR has been obtained with chemotherapy [13].

The risk of CNS recurrence associated with skeletal involvement is also a matter of debate [13]. In the IELSG-14 study, conducted in the pre-rituximab era, CNS involvement (mainly meningeal) occurred in 2.5% of patients with localised primary bone DLBCL [51]. Hence, CNS prophylaxis is not routinely required in these patients [III, B]. However, an accurate assessment (CSF flow cytometry and brain MRI) and prophylaxis can be recommended in patients with involvement of anatomic areas in close apposition to the CNS (skull and/or spine) [III, B]. CNS recurrence occurs in 7% of these patients, particularly those with disseminated DLBCL and other high-risk features, and decisions regarding CNS prophylaxis should be made on the basis of established risk profiling [48].

The presence of pathological fracture at presentation is associated with an inferior outcome in PBoL in the IELSG14 study [49]. The initial surgical stabilisation of the pathological fracture should be directed at achieving a better quality of life (e.g. control pain, prevent bone displacement, allow weight-bearing); however, there is no evidence that initial surgical stabilisation improves the lymphoma outcome, with a 5-year OS of 45% and 54%, respectively, for patients who either did or did not receive surgery. These data suggest that initial surgery should be considered only if chemotherapy delays can be avoided [IV, C] [49].

Patients with a pathological fracture should be initially managed similarly to standard PBoL. Consolidation RT (30–40 Gy) to the fractured bone may be given [IV, C]. Indeed, the initial RT of a fractured bone before chemotherapy does not seem to improve disease control or OS when compared with the chemoradiotherapy sequence but may improve pain and potentially hasten healing [13].

response assessment and post-treatment evaluation. Post-treatment evaluation is difficult because bone lesions remain detectable upon CT scan. PET scan is mandatory in response assessment as in nodal DLBCL; however, residual PET uptake can persist and may resolve slowly, representing bone healing rather than active disease. New treatments such as HDCT/ASCT or alternative chemoimmunotherapy are only recommended in the case of biopsy-proven persisting disease or clear clinical or radiological progression [III, A].

Finally, long-term bone health preventive measures should also be taken into account in patients with PBoL, including evaluation and treatment of any underlying osteoporosis, and/or vitamin D deficiency.

follow-up

Follow-up monitoring is not different from that of nodal DLBCL [1].

personalised medicine

There are still many open issues in the treatment of extranodal DLBCL. New agents targeting distinct molecular pathways involved in disease pathogenesis are in progress and are being tested in ongoing trials. So far, none of these agents is appropriate for standard clinical practice.

For instance, in PMBCLs based on some molecular alterations detected such as *JAK-STAT* pathway activation and modulation of tumour cell interactions with the microenvironment and immune system, the role of biological drugs targeting selective pathways as JAK-STAT and PDL1, PDL2 should be evaluated.

PTLs are predominantly of ABC subtype, and lenalidomide and ibrutinib, which preferentially target this DLBCL subtype and have been proved to be effective in nodal ABC DLBCL, may be tested in PTL patients in an effort to improve their outcome [53, 54]. Moreover, both PTLs and PCNSL show a high frequency of MYD88 and CD79a mutations [6] and ibrutinib that targets this pathway may be active in these patients. Recently, ibrutinib was reported to cross the blood–brain barrier and have potential activity in PCNSL.

methodology

These clinical practice guidelines were developed in accordance with the ESMO standard operating procedures for clinical practice guidelines development, www.esmo.org/Guidelines/ESMO-Guidelines-Methodology. The relevant literature has been selected by the expert authors. A summary of common and specific diagnostic procedures for each extranodal DLBCL type is shown in Table 1. Table 7 summarises the recommendations for first-line treatment. A summary of recommendations is shown in Table 8. Levels of evidence and grades of recommendation have been applied using the system shown in Table 9. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty. This manuscript has been subjected to an anonymous peer review process.

Table 7. Recommended first-line treatment strategies in extranodal diffuse large B-cell lymphoma (DLBCL)

Primary sites	Treatment	Consolidation	CNS prophylaxis
Primary testicular lymphoma	R-CHOP21X6-8	RT to contralateral testis (25–30 Gy)	IT MTX or i.v. systemic MTX
Primary central nervous lymphoma	HD-MTX (MTX ≥ 3 g/m^2) plus HD-ara-C HD-MTX-based (adjusted dose on ECOG PS, renal function, etc.) in elderly patients	WBRT is not routinely recommended HDCT/ASCT suggested in young patients (clinical trial)	N/A
Primary mediastinal lymphoma	R-CHOP or R-V/MACOP-B or R-CHOP14 or DA-EPOCH-R	Mediastinal RT (30 Gy) in responding patients; RT could be omitted in CMR only after DA-EPOCH-R HDCT/ASCT is not recommended in CR1	Not recommended
Primary breast lymphoma	R-CHOP21X6	Whole ipsilateral breast RT (30–36 Gy). Partial breast RT in selected cases (see text)	To be considered in all patients Mandatory in high risk
Primary bone lymphoma	R-CHOP21X6-8 RT before chemotherapy is not recommended	RT (30–40 Gy) to involved bone	Only if involvement of the skull and/or spine

CNS, central nervous system; R-CHOP21, cyclophosphamide, doxorubicin, vincristine and prednisone treatment combined with rituximab given every 21 days; RT, radiotherapy; IT, intrathecal; MTX, methotrexate; i.v., intravenous; HD-MTX, high-dose methotrexate; HD-ara-C, high-dose cytarabine; ECOG PS, Eastern Cooperative Oncology Group performance status; WBRT, whole-brain radiotherapy; HDCT/ASCT, high-dose chemotherapy followed by autologous stem cell transplantation; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-V/MACOP-B, rituximab, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone, bleomycin)/rituximab, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisolone, bleomycin; R-CHOP14, cyclophosphamide, doxorubicin, vincristine and prednisone treatment combined with rituximab given every 14 days; DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine cyclophosphamide, doxorubicin and rituximab; CMR, complete metabolic response; CR1, first complete remission.

Table 8. Summary of recommendations

The disease staging is established as nodal DLBCL according to the Ann Arbor system. In extranodal DLBCL, the discriminating utility of the IPI and aaIPI is not fully evaluated; however, they should be calculated for prognostic purposes at least to differentiate between localised versus advanced stage disease [II, A]

PMBCLs

- R-CHOP, R-VACOP-B, V-MACOP-B, R-CHOP14 or more intensive chemotherapy regimens such as DA-EPOCH-R should be considered the current standard treatment for PMBCLs; any of them can be used according to the centre's experience [III, A]
- Consolidative mediastinal RT is recommended in responding patients treated with standard dose chemoimmunotherapy (R-CHOP/R-V/MACOP-B) [II, A]
- Consolidative mediastinal RT could be omitted in patients with a CMR only after DA-EPOCH-R [III, C]
- Where used, consolidative mediastinal RT should be administered with doses in the range 30–36 Gy, in 1.5–2.0 Gy fractions [II, A]
- HDCT/ASCT is not recommended in patients who achieved CR, even in initially poor-risk patients who attain an adequate response to initial therapy [III, A]
- In young patients who do not obtain an adequate response (i.e. less than partial response) with an elevated FDG uptake at the post-chemoimmunotherapy PET/CT scan, if residual disease is confirmed by biopsy when feasible, an intensification therapy with HDCT/ASCT is recommended [III, B]
- Salvage treatment strategies of relapsed/resistant patients include attempting reinduction with non-cross-resistant agents followed by consolidation with HDCT/ASCT in patients with chemosensitive disease [II, A]

PTLs

- Orchiectomy remains a mandatory step for diagnostic and therapeutic aims [III, A]
- Six to eight cycles of R-CHOP given every 21 days is the current standard [II, A]
- Prophylactic RT to the contralateral testis and scrotum is strongly recommended [III, A]
- RT to involved nodes could be safely omitted if PET is negative after R-CHOP chemotherapy [III, C]
- A prophylactic therapy to reduce the risk of CNS relapse such as intrathecal chemotherapy with (MTX or intravenous systemic MTX should be added to the treatment) [III, B]
- HDCT/ASCT, if feasible, should be the preferred treatment strategy in chemosensitive relapse [I, A]

Continued

Table 8. *Continued*

PCNSLs

- Stereotactic biopsy is recommended as a minimal invasive technique to obtain a histopathological diagnosis [III, A]; therefore, resection of PCNSL cannot be recommended
- Additionally, testicular ultrasound examination in elderly male patients is recommended [V, B]
- HD-MTX-based regimens, in combination with HD-ara-C, are recommended for induction treatment if possible based on patient age, PS and organ function [I, A]
- HD-MTX-based treatment should be considered whenever possible in elderly patients [II, A]
- Intrathecal chemotherapy cannot be routinely recommended if appropriate systemic chemotherapy is applied and could be considered in the case of severe meningeal involvement [IV, C]
- WBRT as consolidation after HD-MTX-based chemotherapy is still commonly applied in young patients and generally avoided in those >60 years, as the risk of neurotoxicity (including cognitive deterioration) is particularly high in elderly patients [III, B]
- Consolidation RT should be avoided in elderly patients who achieved CR [III, B], while in those not reaching a CR, it is preferable to use lower doses of WBRT (36 or 23.4 Gy) based on response [III, B]
- Whether RT can safely be omitted without compromising long-term outcome also in younger patients in CR remains controversial [III, C]
- HDCT/ASCT as consolidation treatment could be considered as an alternative in eligible patients [III, B]
- For salvage treatments, no standard protocol can be recommended. Fit patients should be considered for HDCT/ASCT [III, B]
- WBRT remains an important palliative treatment in PCNSL lymphoma for those unable to tolerate or relapsing after high-dose, CNS-penetrating chemotherapy and not fit for further chemotherapy [III, B]

PBL

- Diagnostic biopsy is mandatory [IV, A]
- In the rare instance of patients who have undergone surgical excision, they should still be managed identically as recommended below [V, B]
- Incorporation of rituximab should be routinely included in front-line chemoimmunotherapy as part of R-CHOP q 21d [III, B]
- The recommended treatment is 6 cycles of R-CHOP [III, A], followed by consolidative whole ipsilateral breast RT (30–36 Gy) [III, B]
- More aggressive or dose-escalated regimens as part of primary therapy are not indicated [III, B]
- CNS-directed prophylaxis should be considered for individual patients [III, B], it is recommended in high-risk patients, i.e. bilateral involvement [III, A]
- Patients with bilateral breast involvement represent a particularly high-risk group, and investigation of more intensive chemotherapy regimens in the context of clinical trials is justified in such cases [IV, C]
- After relapse, the management strategy should be as for other instances of relapsed DLBCL, with reinduction chemoimmunotherapy aiming to proceed to HDCT/ASCT, where feasible, in patients with responsive disease [IV, B]

PBoL

- R-CHOP ± consolidation RT (30–40 Gy) remains the standard approach for the patients with any stage of DLBCL with bone involvement [III, B]
- CNS prophylaxis is not routinely required in these patients [III, B]; however, an accurate assessment (CSF flow cytometry and brain MRI) and prophylaxis can be recommended in patients with involvement of anatomic areas in close apposition to the CNS (skull and/or spine) [III, B]
- Patients with a pathological fracture should be initially managed similarly to standard PBoL. Consolidation RT (30–40 Gy) to the fractured bone may be given [IV, C]
- Initial surgery should be considered only if chemotherapy delays can be avoided [IV, C]

New treatments such as HDCT/ASCT or alternative chemoimmunotherapy are only recommended in the case of biopsy-proven persisting disease or clear clinical or radiological progression [III, A]

DLBCL, diffuse large B-cell lymphoma; IPI, international prognostic index; aaIPI, age-adapted IPI; PMBCLs, primary mediastinal large B-cell lymphomas; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; R-VACOP-B; rituximab, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone, bleomycin; R-MACOP-B, rituximab, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisolone, bleomycin; R-CHOP14, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone every 14 days; DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine cyclophosphamide, doxorubicin and rituximab; RT, radiotherapy; CMR, complete metabolic response; HDCT/ASCT, high-dose chemotherapy followed by autologous stem cell transplantation; CR, complete remission; FDG, fluorodeoxyglucose; PET/CT, positron emission tomography/computed tomography; PTLs, primary testicular lymphomas; CNS, central nervous system; MTX, methotrexate; PCNSLs; primary central nervous system lymphomas; HD-MTX, high-dose methotrexate; HD-ara-C, high-dose cytarabine; PS, performance status; WBRT, whole-brain radiotherapy; PBL, primary diffuse large B-cell breast lymphoma of the breast; PBoL, primary diffuse large B-cell bone lymphoma of the bone; CSF, cerebral spinal fluid; MRI, magnetic resonance imaging.

Table 9. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System)[a]

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, …), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [55].

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conflict of interest

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