DRUG NAME: Alemtuzumab

SYNONYM(S): Campath, Ldp 103, Mabcambath, MabCampath-1H

COMMON TRADE NAME(S): MABCAMPATH®

CLASSIFICATION: molecular targeted therapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Alemtuzumab is a recombinant human IgG-derived monoclonal antibody that binds to antigen CD52 which is found on the surface of B and T lymphocytes, most monocytes, macrophages and NK cells, and certain granulocytes, but not hematopoietic stem cells.[1] Lysis of CD52-positive cells occurs via complement activation, antibody-dependent cytotoxicity, and apoptosis.[2]

PHARMACOKINETICS:

Table refers to intravenous (IV) dosing. Subcutaneous (SC) administration of alemtuzumab achieves concentrations similar to those with intravenous alemtuzumab, although with a slightly higher cumulative dose.[3,4]

Distribution	cross blood brain barrier?	no information found
	volume of distribution	mean 0.18 L/kg (range 0.1-0.4 L/kg)
	plasma protein binding	no information found
Metabolism	no information found	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	no information found	
	terminal half life	mean 11 h (range 2-32 h) after the first dose; 6 d (range 1-14 d) after 12 weeks
	clearance	wide variability, affected by tumour burden[5]; clearance decreases with repeated administration due to decreased receptor mediated clearance (loss of CD52 receptors in the periphery)
Elderly	comparable AUC in patients older than 65 years of age	

Adapted from standard reference[1] unless specified otherwise.

USES:

Primary uses:
*B-cell chronic lymphocytic leukemia[1,6]
T-cell prolymphocytic leukemia[6-8]

Other uses:
Cutaneous T-cell lymphoma[7]
Peripheral T-cell lymphoma[7]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindicated in patients who have a history of hypersensitivity reaction to alemtuzumab, active infections, underlying immunodeficiency (e.g., seropositive for HIV), or other active malignancies.[1]
Caution:

- in patients with previous hypersensitivity or anaphylactic reactions to other monoclonal antibodies[9]
- gradual dose escalation and appropriate pre-medication is required; for more information, see paragraph following the **Side Effects** table[1]
- single doses of alemtuzumab greater than 30 mg or cumulative doses greater than 90 mg per week should not be administered as they are associated with a higher incidence of pancytopenia[1]
- transfusion-related graft-versus-host-disease can occur in patients with severe lymphopenia and can be life threatening; patients receiving alemtuzumab should receive irradiated blood products, effectively eliminating this risk[1]
- *Pneumocystis* pneumonia (PCP) and herpes virus prophylaxis are recommended upon initiation of therapy[1,6,10,11]
- use alemtuzumab with caution in patients with recent exposure to the chicken pox virus[9]

Hepatitis B (HBV) reactivation: All lymphoma patients should be tested for both HBsAg and HBcAb. If either test is positive, such patients should be treated with lamivudine 100 mg/day orally, for the entire duration of chemotherapy and for six months afterwards.[6,10] Such patients should also be monitored with frequent liver function tests and HBV DNA at least every two months. If the HBV DNA level rises during this monitoring, management should be reviewed with a hepatologist and consideration given to halting chemotherapy.[6]

Cytomegalovirus reactivation: for more information, see paragraph following the **Side Effects** table

Carcinogenicity: no information found[1]

Mutagenicity: no information found[1]

Fertility: Alemtuzumab has been shown to bind to mature sperm.[1] No long term studies have been performed on men or women to determine the effect on infertility. Patients of reproductive potential should use effective contraceptive methods during treatment and for a minimum of 6 months following alemtuzumab therapy.[1]

Pregnancy: FDA Pregnancy Category C.[7] Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other), and there are no controlled studies in women, or studies in women and animals are not available. Alemtuzumab should be given only if the potential benefit justifies the potential risk to the fetus. Human IgG is known to cross the placental barrier, therefore alemtuzumab may also cross the placenta and cause fetal B and T lymphocyte depletion.[1]

Breastfeeding should be discontinued during treatment and for at least 3 months following the last dose of alemtuzumab as human IgG is excreted in breast milk.[1]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[12] When placebo-controlled trials are available, adverse events are included if the incidence is $\geq$ 5% higher in the treatment group.

Table refers to IV data unless specified. SC hematological and infectious complications are similar to IV.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	anaphylactic reaction (<1%)[13] first dose reactions, infusion-related reactions with SC use, injection site reactions and fever
	angioedema (<1%)[13]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	antibody development (2%)
	autoimmune diseases; Graves' disease, Guillain-Barre syndrome, hypothyroidism, Goodpasture's syndrome, autoimmune thyroiditis[14]
	mouth edema (1%, severe 1%)
blood/bone marrow/ febrile neutropenia	anemia (77-80%, severe 38%)[13]; autoimmune hemolytic anemia (1%)[13]
	atypical lymphocytes (1%, severe 1%)
	immunosuppression,[1,15] lymphopenia (100%)[15]; onset in 2-4 weeks, may persist for over one year[10]
	neutropenia (85%, severe 64%)[13]; during the first weeks of therapy,[15] nadir 4-6 weeks,[15] median duration 21 days[13]; febrile neutropenia (5-10%, severe 1%)[13]
	pancytopenia (5%, severe 3%),
	thrombocytopenia (72%, severe 50%) nadir 2-4 weeks,[15] median duration 21 d (range 2-165 d); autoimmune idiopathic thrombocytopenia (2%)
cardiovascular (arrhythmia)	arrhythmias (<1%)[13]
	tachycardia (5-11%, severe 1%)[13]
cardiovascular (general)	cardiac ischemia, infarction (<1%)[13,16,17]
	hypotension (30-32%, severe 3%)[13]; with SC use (0%)[3]
	hypertension (9-11%, severe 1%)[13]
coagulation	disseminated intravascular coagulation (<1%)[13,18]
	deep vein thrombosis, pulmonary embolism (<1%)[13]
	thrombocytopenic purpura (2%, severe 0%)
constitutional symptoms	asthenia (9%, severe 0%), malaise (5%, severe 0%), fatigue (27-34%, severe 4%)[13]; with SC use (5%, severe 2%)[3]
	fever (82-85%, severe 14%)[13]; usually occurs 5-6 hours after the start of the infusion[19] with SC use (70%, severe 2%)[3]
	insomnia (1-10%, severe 0%)[13]
	rigors (85%, severe 15%); with SC use (17%, severe 2%)[3]
	sweating (15%, severe 1%)
	temperature change sensation (5%, severe 0%)
	weight loss (5%, severe 0%)
dermatology/skin	*extravasation hazard: none[20]*
	bullous eruptions (1%, severe 1%)
	erythematous rash (4%, severe 1%)
	flushing (4%, severe 0%)
	injection site reaction (1%, severe 0%) with SC use (90%, severe 2%)[3]; onset approximately 24 h after the first dose, often persists until the fourth administration[21]
	pruritus/urticaria (21-30%, severe 1-5%)[13]; with SC use (0%)[3]
	rash (29-40%, severe 3%)[13]; with SC use (0%)[3]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
endocrine	ADH secretion abnormality (<1%)[22]
	hyperthyroidism (<1%)[1]
gastrointestinal	*emetogenic potential: rare*[23]
	anorexia (13-20%, severe 1%)[13]
	ascites (<1%)[13]
	colitis, enteritis (<1%)
	constipation (2%, severe 0%)
	dehydration (2%, severe 2%)
	diarrhea (13-22%, severe 1%)[13]; with SC use (0%)[3]
	dyspepsia (4%, severe 0%); ulcer (<1%)[13]
	mucositis (2%, severe 0%)
	nausea (49-54%, severe 2%)[13]; late nausea is rare[15] with SC use (0%)[3]
	stomatitis (5%, severe 1%); ulcerative stomatitis (3%, severe 0%)
	taste loss (2%, severe 1%)
	vomiting (37-41%, severe 4%)[13]; with SC use (0%)[3]
hemorrhage	GI hemorrhage (<1%)[13]
	hemoptysis (1%, severe 0%)
	CNS hemorrhage (<1%)[13]
	purpura (8%)[13]
hepatobiliary/pancreas	liver dysfunction (1%, severe 0%)
	pancreatitis (<1%)[13]
infection	***bacterial*** (34-40%)[10]; usually occurs within 8 weeks, mycobacterial and tuberculosis have occurred months later[10] bacteremia without sepsis (4%)[24] *Listeria monocytogenes* meningitis (1%, severe 1%) *Pneumocystis* pneumonia (PCP)
	fungal (18-21%)[10]; majority occur within 3 months of treatment, late infection have occured[10] *Aspergillosis* (2%, severe 1%) candidiasis (8-10%, severe 1%)[13] *Cryptococcal* pneumonia (1%, severe 1%) mucormycosis (2%, severe 2%) *Torulopsis* pneumonia (1%, severe 1%)
	not otherwise specified (7%, severe 1%)
	pneumonia (7-18%, severe 13%)[24]
	protozoan[7,24]
	sepsis (15-18%, severe 13%)[13]
	upper respiratory tract infection (6%, severe 0%)
	urinary tract infection (<3%, severe 0%)[24]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	viral (43-45%)[10] adenovirus[25] Cytomegalovirus (CMV) reactivation (4-66%)[3,10,14,15,24,26-28]; usually occurs between weeks 3-8 when T-cell numbers are low,[15] symptomatic CMV reactivations and infections (1-6%, severe 3%)[1,24,26,28] herpes simplex (10-13%, severe 1%)[13,24] herpes zoster (5%, severe 1%) Parvovirus B19 induced red cell aplasia (<1%)[29,30]
lymphatics	edema (1-13%, severe 0%)[13]
metabolic/laboratory	acidosis (<1%)[13]
	hypocalcemia (2%, severe 0%)
	hyponatremia (1%, severe 1%)
	increased alkaline phosphatase (<1%)[13]
	positive Coombs test without hemolysis (2%)
musculoskeletal	arthralgia (1%, severe 0%)
	myalgia (9-11%, severe 0%)[13]
neurology	anxiety (3%, severe 0%)
	confusion (2%, severe 1%)
	depression (2-7%, severe 0%)[13]
	dizziness (5-12%, severe 0%)[13]; vertigo (3%, severe 0%)
	leukoencephalopathy (<1%)[13]
	neurological symptoms associated with previous multiple sclerosis lesions; reversible, do not occur if pre-medicated with high dose steroids
	seizure (<1%)[13]
	sensory neuropathy; dysthesia (15%),[13] paresthesia (6%, severe 0%), hypoesthesia (3%, severe 0%)
	somnolence (3-5%, severe 0%)[13]
	tremor (6%, severe 0%)
ocular/visual	conjunctivitis (2%, severe 0%)
	endophthalmitis (1%, severe 1%)
	optic neuropathy (<1%)
pain	abdominal pain (6-11%, severe 2%)[13]
	back pain (5%, severe 2%)
	chest pain (6-10%, severe 1%)[13]
	headache (18-24%, severe 1%)[13]; with SC use (0%)[3]
	SC injection site pain (61%, severe 2%)[3]
	not otherwise specified (7%, severe 1%)
	skeletal pain (3-24%, severe 1%)[13]
pulmonary	bronchitis (9%, severe 1%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	bronchospasm (6%, severe 2%)
	cough (4-25%, severe 1%)[13]
	dyspnea (18-26%, severe 6%)[13]; with SC use (0%)[3]
	hypoxia (2%, severe 1%)
	pharyngitis (4-12%, severe 0%)[13]
	pneumonitis (3%, severe 3%)
	pulmonary infiltration (1%, severe 1%)
	respiratory depression (<1%)
	rhinitis (1-7%, severe 0%)[13]
	sinusitis (6%, severe 1%)
renal/genitourinary	hematuria (1%, severe 1%)
	decreased renal function/renal failure (<1%)[13,18]
sexual/reproductive function	binds to mature sperm
syndromes	influenza-like symptoms (5%, severe 0%)
	tumour lysis syndrome (<1%)[13]
vascular	phlebitis (<1%)
	vasospasm (1%, severe 0%)

Adapted from standard reference[1] unless specified otherwise.

Infusion reactions: Intravenous administration of alemtuzumab is usually accompanied by transient infusion-related side effects that manifest as flu-like symptoms. These acute cytokine-mediated reactions are generally mild to moderate. The reactions includes nausea and vomiting, hypotension, dizziness, rigors, fever, diarrhea, sudden sweating, shortness of breath, chills, and/or rash.[1,15] Serious and potentially fatal complications including myocardial infarction, cardiomyopathy, cardiac arrest, arrhythmias, bronchospasm, and acute respiratory distress have also been reported.[1,13] Symptoms are most common during the first week of therapy and decrease with each subsequent administration.[2,2,9,31] To prevent infusion related reactions:

- give diphenhydramine 50 mg PO and acetaminophen 650 mg PO 30 minutes prior to alemtuzumab[1,6]
- pre-medicate with prednisone 10 mg PO 15-30 minutes prior to alemtuzumab for the first 1-2 weeks[6,15]; since corticosteroids cause immunosuppression, prophylaxis should be discontinued after 1-2 weeks[15]
- start with low doses of alemtuzumab (3 mg) and escalate as tolerated[1] (for more information, see **Dosage Guidelines**); it is not known if the infusion reactions are strictly dose-related[5]
- meperidine 25 mg IV may lessen rigors,[6,9] patients experiencing meperidine-induced nausea should receive antiemetics[19]
- for patients experiencing severe rash, premedication with H_2 receptor antagonists (e.g., ranitidine) is recommended[19]
- fever commonly begins 5-6 hours after the infusion starts; a second dose of acetaminophen may be required[19]

During the infusion, the patient's pulse, respiratory rate and blood pressure should be monitored every 15 minutes during the first hour, then every 30 minutes.[6] Patients should be observed for 1 hour after the infusion.[6] To treat severe infusion-related symptoms, stop the alemtuzumab infusion and give hydrocortisone 200 mg IV.[1] Beta-2 agonists for wheezing and volume support for hypotension may be given.[32] If acute infusion reactions persist, the infusion time may be extended to up to 8 hours from the time of dose preparation.[31] Mild first-dose side effects tend to not preclude patients from completing therapy.[32]

Subcutaneous administration of alemtuzumab reduces infusion-related symptoms, while maintaining the same efficacy and improving convenience.[33] The incidence of nausea and vomiting, rigors, rash, hypotension, and dyspnea are significantly reduced with SC dosing, though fever may not be reduced appreciably (see Side Effects Table).[3] Almost all patients receiving SC alemtuzumab will develop a transient grade 1 or 2 local skin reaction.[3] IV corticosteroids do not affect the intensity or duration of these skin reactions.[3] Ice packs applied to the injection site 15 minutes prior to and 15 minutes post injection may decrease the severity of local skin reactions. Cold compresses applied to the injection site for 15-20 minutes, several times a day after treatment may also help alleviate symptoms. Most SC first-dose reactions disappear after 1-2 weeks.[3] Patients should be observed for 1 hour after the dose has been administered until at least three 30 mg doses have been given.[6] After that, monitoring may be discontinued.[6] Data from an ongoing study suggests that dose escalation may not be necessary with SC administration.[15]

Immunosuppression / opportunistic infections: Patients are at risk for opportunistic infections due to the profound lymphopenia induced by alemtuzumab.[1] Alemtuzumab-induced lymphopenia is non-dose dependant; single doses may reduce CD4+ and CD8+ T-cells for months.[15] Serious and sometimes fatal bacterial, fungal, viral and protozoal infections have occurred with infection rates ranging from 23-79% in pre-treated patients.[1,10] Although the majority of infections occur within 3 months of starting treatment, infections have been reported up to 6 months later.[10] If an infection occurs, alemtuzumab therapy should be interrupted but may be reinitiated following the resolution of the infection.[1] Upon initiation of alemtuzumab patients should receive prophylaxis against PCP and herpes virus infections with:

- trimethoprim/sulfamethoxazole (TMP/SMX) DS PO twice daily three times weekly (TMP/SMX is the preferred prophylaxis; dapsone, pentamidine and atovaquone have also be used[10]
- acyclovir 400 mg PO BID (alternatively, valacyclovir 500 mg PO twice daily)[3]

Prophylaxis should be continued for a minimum of 2 months following the last dose of alemtuzumab or until CD4+ counts are ≥200 cells/μL, whichever occurs later.[1] Full recovery of CD4+ and CD8+ counts may take more than 12 months[1]; optimal length of post-treatment prophylaxis has yet to be determined.[10,15,19] Prophylaxis against PCP and herpes may decrease, but not eliminate, the occurrence of these infections.[1] Routine antifungal prophylaxis is not currently recommended but may be considered for high risk patients.[10,26]

Cytomegalovirus reactivation is the most common infection associated with alemtuzumab. T-cell depletion increases the risk of reactivation of CMV.[15,19] Reactivation usually occurs 3-8 weeks after initiation of therapy and coincides with T-cell nadir. Patients receiving alemtuzumab should have weekly testing for CMV replication by PCR or CMV antigenemia (pp65ag) assays.[6,11,19] Patients should also be monitored for symptoms of CMV infection.[6,19,34] If a positive screening test occurs, alemtuzumab treatment should be interrupted until testing becomes negative. Patients who are symptomatic should be treated immediately with ganciclovir.[10,14,15,19] Alemtuzumab has been restarted after clinical symptoms resolve and PCR testing is negative without further reactivation.[3,14,15,19]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
diagnostic serum tests that utilize antibodies[1,13]	inaccurate test results[1] and potential for increased risk of allergic reactions[13]	monoclonal antibodies may result in the formation of human antichimeric antibodies (HACA); the presence of HACA may increase the risk of hypersensitivity reactions when other monoclonal antibodies are administered[13]	interpret with caution

AGENT	EFFECT	MECHANISM	MANAGEMENT
monoclonal antibodies[1,35]	increased risk of allergic or hypersensitivity reactions to monoclonal antibodies; especially in patients that experienced previous hypersensitivity reactions to monoclonal antibodies[1]	monoclonal antibodies may result in the formation of human antichimeric antibodies (HACA); the presence of HACA may increase the risk of hypersensitivity reactions, thrombocytopenia, or diminished therapeutic response when other monoclonal antibodies are administered; monoclonal antibodies that also form HACA may be of particular concern	monitor for toxicity/response, patients who developed hypersensitivity to alemtuzumab may develop hypersensitivity reactions to other monoclonal antibodies
killed virus vaccines[1]	ability to respond to vaccines following therapy is unknown; duration of decrease response unknown; estimates vary from 3 months - 1 year[9]	alemtuzumab may decrease the ability to generate a humoral response to vaccines	immunize prior to therapy if possible, potential for decreased benefit of vaccine if administered during or within 1 year after therapy
live virus vaccines[1]	ability to respond to vaccines following therapy is unknown, risk of infection by the live vaccine virus; duration of risk unknown; estimates vary from 3 months - 1 year[9]	alemtuzumab may potentiate replication of the vaccine virus, decrease the ability to generate a humoral response to the vaccine and enhance the adverse effects of live vaccines[9]	avoid during and within 1 year after therapy

SUPPLY AND STORAGE:

***Injection*:** Genzyme Canada Inc. supplies alemtuzumab as a 30 mg/mL preservative-free solution. Refrigerate. Do not freeze. Protect from direct sunlight.[36]

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information: *Diluted solution for infusion*: compatible with PVC bags and administration sets[1]
Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in ***bold***, ***italics***

Subcutaneous	***rotate sites on thighs or abdomen****
Intramuscular	no information found

BCCA administration guideline noted in ***bold***, ***italics***

Direct intravenous	contraindicated
Intermittent infusion	***over 2 hours***
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

*Subcutaneous administration of alemtuzumab significantly reduces flu-like symptoms making it the preferred route of administration.[12]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BCCA usual dose noted in ***bold, italics***

	Cycle Length:	
Intravenous:	***titration 1 week[1,6]:***	***3 mg IV for one dose on day 1, then 10 mg IV for one dose on day 3, and 30 mg IV for one dose on day 5*** • **titration may be handled more slowly if required (e.g., infusion-related toxicities > NCI Grade 2)** • gradual dose escalation is required at the initiation of therapy and after treatment interruptions of 7 days or more; dose escalation to the recommended maintenance dose of 30 mg is required and can be accomplished in 3-7 days in most patients • doses greater than 30 mg per day or greater than 90 mg per week are not recommended
	maintenance 1 week[1,6]:	***30 mg (range 3-30 mg) IV for one dose on days 1, 3 and 5 (total dose per cycle) 90 mg [range 9-90 mg])*** • consecutive daily dosing may also be used[1] • gradual dose escalation is required after treatment interruptions of 7 days or more
Subcutaneous:	***titration 1 week[3,6]:***	***3 mg SC for one dose on day 1, then 10 mg SC for one dose on day 3, and 30 mg SC for one dose on day 5*** • **titration may be handled more slowly if required (e.g., infusion-related toxicities > NCI Grade 2)** • gradual dose escalation is required at the initiation of therapy; dose escalation to the recommended maintenance dose of 30 mg is required and can be accomplished in 3-7 days in most patients • doses greater than 30 mg per day or greater than 90 mg per week are not recommended

BCCA usual dose noted in ***bold, italics***

Cycle Length:	
maintenance 1 week[3,6]:	***30 mg (range 3-30 mg) SC for one dose on days 1, 3 and 5 (total dose per cycle 90 mg [range 9-90 mg])*** • consecutive daily dosing may also be used[1]

Concurrent radiation: additive bone marrow suppression may occur; dose reduction may be required when used concurrently or consecutively[9]

Dosage in myelosuppression:[1] modify according to protocol by which patient is being treated; if no guidelines available, refer to the table below

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
< 0.25	or	≤ 25	**first occurrence:** hold treatment and resume at the same dose when ANC ≥ 0.5 and platelets ≥ 50 (restart at 3 mg if delay between doses ≥ 7 days and escalate to 30 mg as tolerated) **second occurrence:** hold treatment and resume at 10 mg when ANC ≥ 0.5 and platelets ≥ 50 (restart at 3 mg if delay between doses ≥ 7 days and escalate to a maximum dose of 10 mg) **third occurrence:** discontinue treatment permanently
For baseline ANC ≤ 0.5 and/or platelets ≤ 25: if ANC or platelets decrease to ≤ 50% of baseline value, hold therapy and resume when ANC and platelet count return to baseline values (restart at 3 mg if delay between doses ≥ 7 days and escalate to 30 mg as tolerated)			
There is no information on the safety of resumption of alemtuzumab in patients with autoimmune cytopenias or marrow aplasia. [1]			

Dosage in renal failure: no information found

Dosage in hepatic failure: no information found

Dosage in dialysis: no information found

Children: has been used[37]

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