

**Uncomplicated & Severe Malaria  
Definitions and Treatment**

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**Background**

- Frequent cause of fever in travelers to developing countries (25 to 42%)
- Huge difference in malaria risk
- First cause of mortality among travellers with fever after return

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**Background**

**Falciparum malaria: data from ITM Fever Study 2000-2005**

- 22 % of fever cases
- 98 % imported from Subsaharan Africa
- 91 % occurring within one month after return
- 46 % hospitalization rate
- 19 % with severe malaria
- 1% overall mortality rate

Bottieau E, Clerinx J, et al. Etiology and outcome of fever after a stay in the tropics. Arch Intern Med. 2006 Aug 14-28;166(15):1642-6.

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### Fever study: conclusions

Malaria is by far the most important causative pathogen, and is associated with major morbidity

It is also the only tropical cause of mortality.

Revised criteria of severe malaria (WHO 2000): are these appropriate for disease management decision making?

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### Severe Malaria: revised WHO criteria

- Parasitaemia (>5% of RBC or >200 000/ $\mu$ l)
- Cerebral malaria or coma,
- Convulsions
- Acute renal failure (urine output <400/24h or creatinine >2,5 mg/dl)
- Respiratory failure and/or ARDS
- Circulatory collapse (RR < 80/50mmHg)
- Spontaneous bleeding and/or PLT < 20000/ $\mu$ l
- Hypoglycaemia (<40 mg/dl)
- Acidosis (pH <7.25)
- Jaundice (bilirubin >3 mg/dl or >50 $\mu$ mol/l)
- ALAT/ASAT >3 x UNL
- Anaemia (Hb <8 mg/dl)

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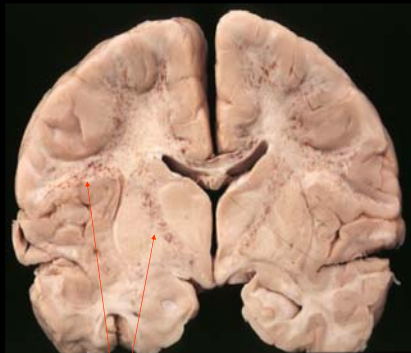
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Macroscopic changes in Cerebral Malaria



Perivascular hemorrhages in white matter

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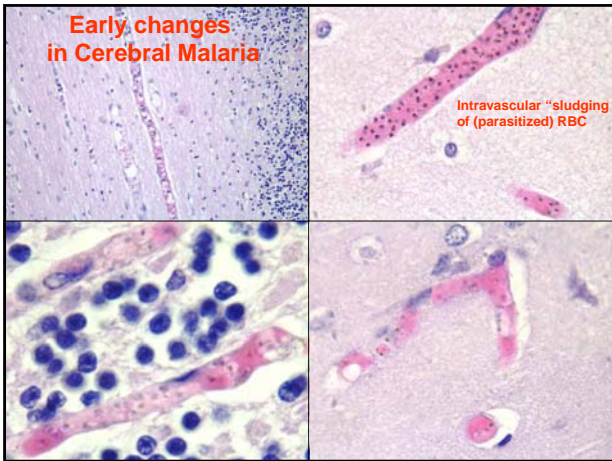
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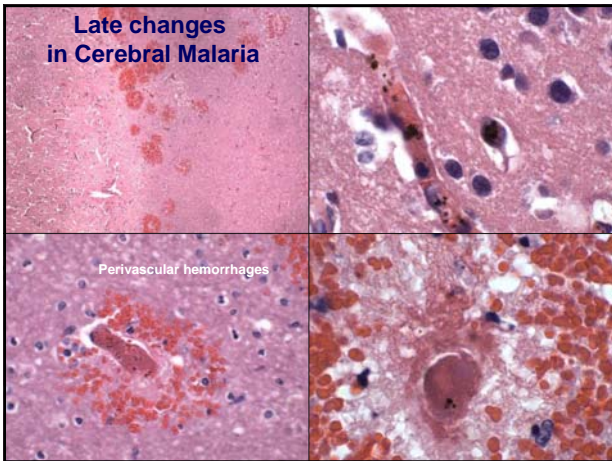
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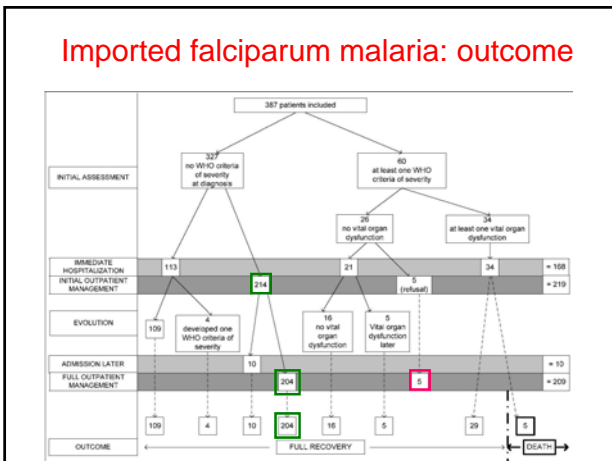
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**Imported falciparum malaria**  
**Revising criteria for clinical management**

**Issues:**

Is uncomplicated malaria as presently defined really uncomplicated in a timeframe?

Can patients with uncomplicated malaria be safely treated as outpatients?

And, if not, what are the best criteria of truly uncomplicated malaria?




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**Towards a new definition of malaria severity**  
**applicable to imported malaria**

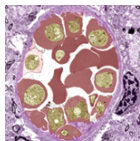
**Concerns for the clinician:**

Risk for further complications after initiating treatment

Mortality risk

Patient management

- Ambulatory treatment or hospitalization?
- Medium care or intensive care?
- Oral or parenteral treatment?
- Follow up?




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**Imported falciparum malaria**

Independent predictors of uncomplicated malaria  
in a multivariate model (n = 323)

	Odds ratio	95 % CI	P value
Total bilirubinemia < 1.3 mg/dL	50.4	9.9-257.4	< .001
Parasitemia < 1%	13.3	4.6-38.2	< .001
Fever < 72 h before diagnosis	4.57	1.61 -12.96	.004
Foreign visitor/migrant	1.21	1.01-1.46	.035
VFR traveler	1.13	1.01-1.27	.038

Bottieau E, Clerinx J, Van Gompel A. Hospitalization criteria in imported falciparum malaria. J Travel Med. 2008 Jan-Feb;15(1):60;

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### Imported falciparum malaria

Outcome of patients with uncomplicated malaria (n=321)

Criteria	uncomplicated		severe*	
	N	(%)	N	(%)
<i>All patients</i>				
Pf < 40000/μL or 1% & bilirubin <1.3mg/dl	170	(53)	1*	(0.3)
<i>Nonvomiting patients only</i>				
Pf < 40000/μL or 1% & bilirubin <1.3mg/dl	124	(39)	0	(0)

\*WHO expanded definition

\*patient already on ambulatory treatment with Malarone (pretreatment parasitemia of 9%) subsequently hospitalized because of vomiting, but with low residual parasitemia

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### Imported falciparum malaria

Outcome of patients with uncomplicated malaria (n=321)

Criteria	subsequent hospitalization rate	
	N/n	%
<i>All patients</i>		
Pf<40000/μL or <1% & bilirubin<1.3mg/dl	6/171	4
<i>Nonvomiting patients</i>		
Pf<40000/μL or <1% & bilirubin<1.3mg/dl	4*/124	3

\* one patient because of subsequent vomiting, one patient treated with Avc/Pg with persistent fever on D4, one patient with relapse 3 weeks after R/halofantrin, one patient hospitalized with nausea for confort

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### Fatal malaria:

Signs and symptoms at hospitalisation (n=5)

Patients Nr	1	2	3	4	5
<b>parasitemia (%)</b>	<b>32</b>	<b>35</b>	<b>15</b>	<b>40</b>	<b>18</b>
PLT <30,000/μL	x	x	-	-	x
anemia < 7g/dl	-	-	-	-	-
neurologic signs	x	x	x	x	-
jaundice	-	x	x	x	x
oliguria/ren.insuff.	x	-	?	x	x
dyspnea/ARDS	-	x	-	x	x
hypotension/shock	x	-	-	-	-
DIC	x	-	-	-	-
metabolic acidosis	x	-	-	-	-
<b>complication score</b>	<b>7</b>	<b>5</b>	<b>3</b>	<b>5</b>	<b>5</b>

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**Towards a new definition of malaria severity  
applicable to imported malaria**

*Our proposal: categorize patients with falciparum malaria according to practical management!*

**Green flag:** criteria for safe ambulatory treatment

**Orange flag:** uncomplicated so far, but...

**Red flag:** criteria for severe malaria

**Danger zone:** criteria for high mortality risk

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**Towards a new definition of uncomplicated malaria  
applicable to imported malaria**

**Green flag criteria:** Minimal morbidity



**Definition:** all criteria below have to be met!

- Parasitemia upto 1% or 40.000 trophozoites/ $\mu$ L
- and bilirubin < 1.3mg/dl
- and no vomiting

**Management:** safe ambulatory treatment

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**Imported falciparum malaria**



**Green flag:** saving at least one third of the hospitalization costs...

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Towards a new definition of severe malaria applicable to imported malaria

**Danger zone: High mortality risk**

**Definition:**

- Parasitemia >10% (400.000 trophozoites/μL)
- And/or at least 3 criteria of severe malaria, including at least one criterium of severe organ dysfunction.

**Management:**

*Hospitalization in ICU*  
*Close monitoring of above parameters, plus serum lactate levels, CPK, coagulation parameters. Circulating volume monitoring*  
**Artesunate IV**

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Towards a new definition of severe malaria applicable to imported malaria

**Red flag criteria: High morbidity risk**

**Definition:**

- Parasitemia > 5% < 10%
- At least one classical criterium of complicated malaria (except criteria from “danger zone”)

**Management:** *Hospitalization for IV (PO) treatment, close supervision of parasitemia and critical organ function*  
*R/ Quinine IV or Artesunate IV???*

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Towards a new definition of severe malaria applicable to imported malaria

**Orange flag criteria: Potential complications**

**Definition:**

- At least one of the following criteria:
  - Parasitemia 1 to 5% ( 40.000 to 200.000 troph/mm3)
  - Age > 60 years, pregnancy, comorbidity
  - Vomiting
  - Total bilirubin 1.3 to 3 mg/dl

and no other criteria of severe malaria.

**Management:**

*hospitalization preferred, but ambulatory treatment to be allowed under certain conditions*  
*PO treatment or IV treatment with Quinine. No indication for IV artesunate so far*

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**Severe falciparum malaria**

**Treatment recommendations: past and present**

**Past:**

- IV Quinine (dihydrochloride): 10mg/kg tid, with loading dose 20mg/kg over 4h
- Exsanguinotransfusion if parasitemia > 10%

**Present** (since 2006, WHO recommendations):

- IV Quinine: 10mg/kg tid, with loading dose 20mg/kg
- IV Artesunate: if parasitemia > 10% and/or > 3 criteria of severe malaria

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**Severe falciparum malaria**

**IV Artesunate vs IV Quinine  
Evidence for recommendation**

**SEAQUAMAT study in south east asian adults**

- Substantial reduction of mortality (38%)
- Subanalysis: mortality reduction almost entirely in the high parasitemia group (> 10% parasitemia)
- Shorter parasite clearance time and fever clearance time

**AQUAMAT study in african children**

- Substantial reduction of mortality (23%)

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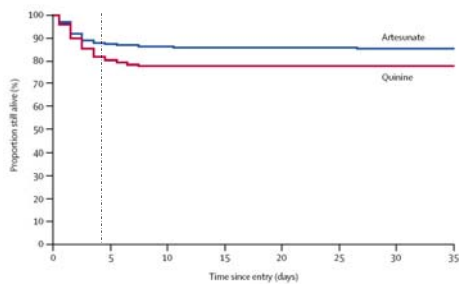
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**Severe falciparum malaria**

**SEAQUAMAT Study: Survival curve of in-hospital mortality in SE-Asean adults with severe falciparum malaria treated with either parenteral artesunate or quinine**



=> Substantial reduction of mortality (38%)

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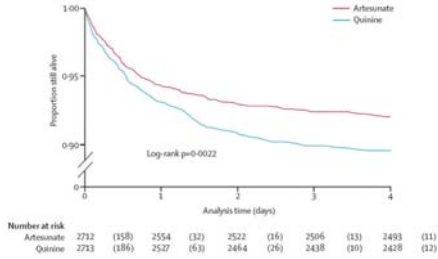
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### Severe falciparum malaria

AQUAMAT Study: Kaplan-Meier curves comparing survival in African children with severe falciparum malaria treated with either parenteral artesunate or quinine



=> Substantial reduction of mortality (23%)

### IV Artesunate vs IV Quinine in severe malaria Meta-analysis from various studies

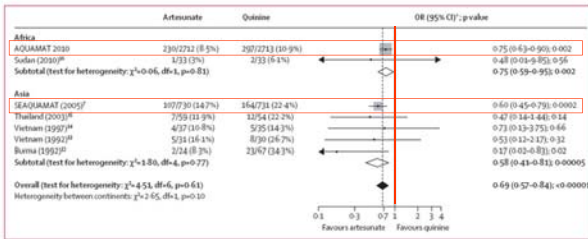


Figure 5: Meta-analysis of all randomised controlled trials that have compared parenteral artesunate and parenteral quinine in severe malaria<sup>14,15</sup>. The solid vertical line represents equality of the two groups, the dashed line is the overall treatment difference. The horizontal lines and the width of the diamonds show the CIs for the odds ratios. The size of the squares is proportional to the size, and therefore weight, of the trial. OR=odds ratio. \*95% CIs for total.

### SEAQUAMAT Study: mortality in subgroups of patients treated with parenteral artesunate compared to quinine

	Number of patients	Artesunate mortality	Quinine mortality	OR (95% CI)	p	Ratio of OR (95% CI)	p for ratio of OR
Blood smear positive	1202	105 of 519 (20%)	147 of 683 (22%)	0.62 (0.41-0.92)	0.007	2.64 (0.30-22.3)	0.36
Blood smear negative	79	2 of 43 (5%)	7 of 36 (19%)	0.22 (0.03-1.48)	0.11		
All <sup>#</sup>	1259	107 of 531 (20%)	154 of 719 (21%)	0.64 (0.46-0.87)	0.0005	1.42 (0.41-4.95)	0.71
Child	900	8 of 47 (2%)	21 of 105 (20%)	0.43 (0.13-1.42)	0.15		
Non-hyperparasitemia <sup>**</sup>	118	18 of 127 (14%)	29 of 143 (20%)	0.49 (0.34-0.67)	0.02	0.36 (0.18-0.70)	0.001
Hyperparasitemia <sup>**</sup>	1041	89 of 404 (22%)	125 of 576 (22%)	0.63 (0.46-0.86)	0.004		
Unspecified <sup>#</sup>	53	1 of 34 (3%)	5 of 26 (19%)	0.80 (0.26-2.36)	0.73		
Artesunate <sup>#</sup>	443	27 of 194 (14%)	121 of 189 (64%)	0.59 (0.41-0.82)	0.002	0.89 (0.37-1.84)	0.32
No artesunate <sup>#</sup>	442	14 of 137 (10%)	33 of 530 (6%)	0.77 (0.34-1.43)	0.32		
Unspecified <sup>#</sup>	127	14 of 57 (25%)	38 of 70 (54%)	1.05 (0.42-2.43)	0.91		
Sho <sup>#</sup>	105	12 of 75 (16%)	27 of 91 (30%)	0.55 (0.32-0.92)	0.02	0.54 (0.21-1.37)	0.1
Non-artesunate <sup>#</sup>	127	13 of 54 (24%)	13 of 63 (21%)	0.66 (0.34-1.27)	0.006		
Hyperparasitemia <sup>**</sup>	129	18 of 121 (15%)	27 of 148 (18%)	0.78 (0.54-1.12)	0.001	0.34 (0.17-0.69)	0.001
No hyperparasitemia <sup>**</sup>	1053	87 of 410 (21%)	127 of 571 (22%)	0.77 (0.55-1.07)	0.11		

"Patients with hyperparasitemia (admission parasitemia >10%) had a significantly greater treatment effect with artesunate than nonhyperparasitemic patients" (OR 0.34; 95%CI 0.17-0.69; p=0.001).

All analyses stratified by study site, and done by intention to treat unless otherwise indicated. \*\*Done on confirmed malaria (same positive blood).

Table 4. Results of prespecified subgroup analyses

**Intravenous artesunate for severe malaria  
Pharmacokinetics**

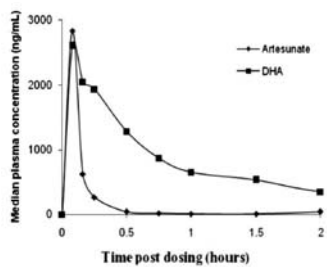


Figure 2 Mean artesunate and dihydroartemisinin plasma concentration versus time. Vertical bars represent standard error.

Byakika-Kibwika et al. Malaria Journal 2012, 11:132

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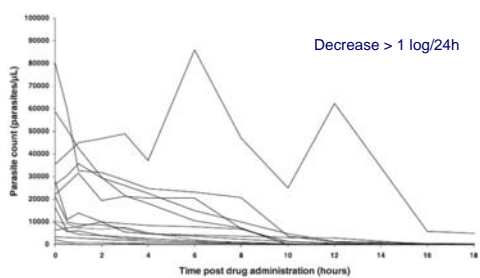
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**Intravenous artesunate for severe malaria  
Parasite decay**



Evolution of parasitaemia in 14 patients treated with IV artesunate

Byakika-Kibwika et al. Malaria Journal 2012, 11:132

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**Severe falciparum malaria  
IV Artesunate in imported malaria  
Experience in Europe**

Zoller T, Junghanss T, Kapaun A, Gjørup I, Richter J, Hugo-Persson M, Mørch K, Foroutan B, Suttrop N, Yürek S, Flick H.

**Intravenous artesunate for severe malaria in travelers, Europe.**

Emerg Infect Dis. 2011 May;17(5):771-7. doi: 10.3201/eid1705.101229.

Kreeftmeijer-Vegter AR, van Genderen PJ, Visser LG, Bierman WF, Clerinx J, van Veldhuizen CK, de Vries PJ

**Treatment outcome of intravenous artesunate in patients with severe malaria in the Netherlands and Belgium.**

Malar J. 2012 Mar 31;11:102.

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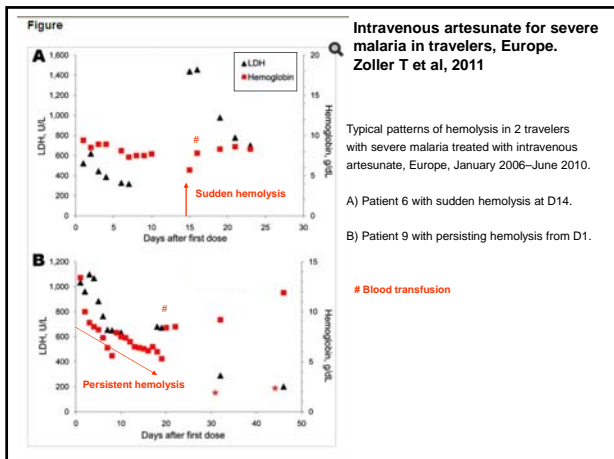
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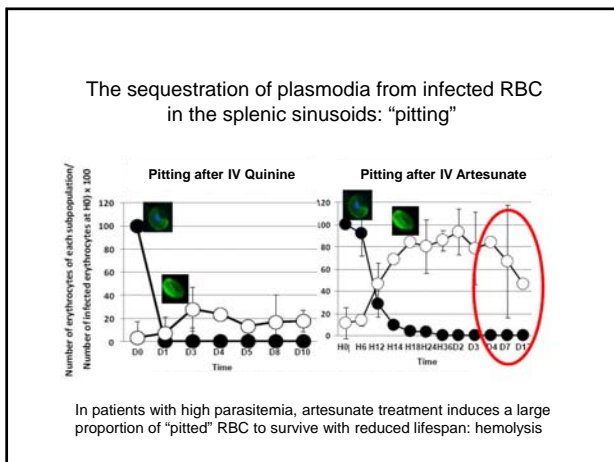
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**Severe falciparum malaria**

Procedures in preparation to assure reimbursement of IV Artesunate in imported malaria in Belgium

This procedure will be implemented from early 2014

**Rationale for the procedures:**

- IV artesunate is (relatively) expensive
- It is superior to IV Quinine in patients with high parasitemia
- There are concerns about severe posttreatment anemia

**Procedure outline:**

- Criteria for severe malaria (see next)
- Follow-up of patients
- Reporting treated cases after complete follow-up

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**Severe falciparum malaria**

Accepted criteria of severe malaria  
to be treated with IV Artesunate in Belgium

Parasitemia >10% (400.000 trophozoites/ $\mu$ L)  
and/or at least 3 criteria of severe malaria, including  
at least one criterium of severe organ dysfunction.

Cerebral malaria (even with < 3 criteria of severe  
malaria)

Contra-indication for IV Quinine

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**Severe falciparum malaria**

IV Artesunate in imported malaria : follow-up & reporting

Risk of (sudden) severe anemia is highest from D10 to  
D20 after start of IV Artesunate

Follow-up of patients, with full blood count is done at D7,  
D14, D21, and D28 (or D42) after start of IV Artesunate

A specific reporting form will be made available at the  
itg.be website in due course.

This case reporting form will be sent after completion of  
the patient follow-up to the ITMA for compilation, as a  
post-marketing surveillance

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