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# Treatment of intracranial hypertension and aspects on lumbar dural puncture in severe bacterial meningitis

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**Background:** Brain stem herniation due to raised intracranial pressure (ICP) is a common cause of mortality in severe bacterial meningitis, but continuous measurements of ICP and the effects of ICP-reducing therapy in these patients have, to our knowledge, not been described.
**Methods:** During a four-year period, an ICP-monitoring device was implanted in patients admitted to our hospital with severe bacterial meningitis and suspected intracranial hypertension. ICP above 20 mmHg was treated using the Lund Concept, which includes antihypertensive therapy ($\beta_1$-antagonist,$\alpha_2$-agonist), normalization of the plasma colloid osmotic pressure and the blood volume, and antistress therapy.
**Results:** ICP above 20 mmHg was found in all 12 patients studied. It was effectively reduced in all but two patients, who died. Both patients had a low cerebral perfusion pressure (<10 mmHg), dilated pupils at start of therapy and were beyond recovery. Radiological signs of brain swelling were present in only five patients. Seven patients recovered fully, while mild audiological impairment was observed in two and minor neurological sequelae in one patient. Eight patients showed signs suggesting imminent brain stem herniation before start of ICP-reducing treatment, seven of whom had been subjected to diagnostic lumbar dural puncture shortly before development of the brain stem symptoms. These symptoms gradually regressed after initiation of therapy, and in one patient reversal of brain stem herniation was documented by MRI.
**Conclusions:** Severe bacterial meningitis can be associated with increased ICP, which can be reduced using the Lund Concept. The high survival rate, the low frequency of sequelae and the reversal of signs of imminent brain stem herniation in these high-risk patients indicated beneficial effects of the intervention. The study confirms earlier observations that lumbar dural puncture is potentially hazardous in patients with intracranial hypertension, because it may trigger brain stem herniation. A normal CT brain scan does not rule out intracranial hypertension.

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**Key words:** bacterial meningitis; brain stem herniation; CT-scan; intracranial pressure; lumbar dural puncture.



DESPITE effective antibiotic treatment and improved general intensive care, bacterial meningitis continues to be associated with a high mortality rate (1–5). In a recent US survey of unselected adult patients with bacterial meningitis, the hospital mortality rate was 27% and the rate of neurological deficit persisted at discharge was 9% (2). The mortality rate and the frequency of neurological sequelae were much higher in patients with more severe illness.

Causes of death in bacterial meningitis include cerebral vasculitis with infarction, herniation of brain tissue, sepsis with circulatory failure, and coagulation disturbances (6). Compression of the brain stem with complete cessation of cerebral circulation, however, is the most important cause of death and sequelae in these patients, and is due to increased intracranial pressure (ICP) (6–9). Brain edema is the main factor leading to increased ICP during bacterial meningitis, but increased intracranial blood volume and disturbances in cerebrospinal fluid circulation can also be of importance (3).

Intracranial hypertension, especially when combined with signs of imminent brain stem compression, indicates a more severe disease and much higher mortality than in patients with uncomplicated bacterial meningitis (3, 7, 10). Improvements in outcome can not be expected to come from new antimicrobial agents, but from novel treatment modalities based on a more complete understanding of the pathogenesis, including mechanisms responsible for the development of brain edema.

The standard diagnostic procedure in bacterial meningitis is examination of cerebrospinal fluid obtained by lumbar dural puncture. The benefit contra the risk of performing lumbar dural puncture in severe cases of bacterial meningitis with suspicion of intracranial

hypertension has been debated, because it may induce brain stem herniation and thus precipitate a life-threatening situation (11, 12).

To the best of our knowledge, there are no published human data on serial measurement of ICP during severe bacterial meningitis, nor on the effect of ICP-reducing therapy on ICP and on outcome. A CT-scan of the brain is often used to assess the existence of intracranial hypertension. Reliable measurement of ICP requires, however, placement of an intracranial monitoring device. Standard management of severe bacterial meningitis rarely includes invasive measurement of ICP and a therapeutic programme for institution of ICP-reducing treatment.

The management of patients with severe bacterial meningitis admitted to our hospital was revised some years ago, following a number of cases of fatal cerebral herniation after admission in otherwise healthy individuals. An ICP-monitoring device is implanted when clinical signs indicate intracranial hypertension, and the patient is treated with a strict ICP–reducing protocol similar to that used in our hospital for post traumatic brain edema (13, 14). This protocol, the Lund Concept for brain edema therapy, has been shown effective in reducing a raised ICP and in improving outcome of brain trauma (15, 16). In the present paper we describe serial invasive ICP measurements in the patients admitted to our hospital with severe life-threatening bacterial meningitis, the relationship between ICP and therapeutic intervention, as well as the functional outcome. The risk of lumbar dural puncture in patients with severe bacterial meningitis and raised ICP is discussed on the basis of the patients included in this report.

## *Patient material and methods*

The present report comprises all patients below the age of 65 treated at the University Hospital of Lund between January 1994 and December 1997, admitted with a diagnosis of bacterial meningitis and in whom a raised ICP exceeding 20 mmHg was documented. An intracranial pressure monitoring device was inserted in patients with a clinical picture considered indicative of increased ICP. This picture was a combination of the following signs: progressive loss of consciousness, agitation, focal neurological signs, ocular motility abnormalities (uni- or bilateral pupillary dilation, impairment or loss of the reaction to light), cranial nerve palsy (*N. occulomotorius*, *N. abducens*), increase in blood pressure and bradycardia. Of these signs, loss of consciousness, agitation, increase in blood pressure and pupil dilation were considered highly indicative of a life-threatening increase in ICP (17). The decision to insert the ICP measuring device was taken individually, based on assessment of each patient. Diagnostic lumbar puncture had invariably been performed in the emergency room before evaluation for ICP monitoring and transfer to the ICU.

The ICP monitoring device was implanted by standard surgical procedure, and ICP was measured continuously via an extracranial pressure transducer (Bentley, Inc., CA) connected to the intraventricular fluid space. Full intensive care was provided with ventilatory support and sedation. Initial antibiotic treatment was adjusted according to the sensitivity of isolated organisms.

Patients with an ICP exceeding 20 mmHg were treated with ICP-reducing therapy. The breakpoint of 20 mmHg used was arbitrarily based on earlier studies, where the mortality rate following head trauma was significantly higher with an ICP exceeding 20 mmHg (18). We used the Lund Concept for brain edema treatment to reduce the ICP. This concept includes (i) antihypertensive treatment through $\beta_1$-blockade (metoprolol 0.05–0.08 mg/kg × 6–8 iv, alternatively 50–100 mg × 2 per enteral sond) and $\alpha_2$-agonist stimulation (clonidine 0.3–0.8 µg/kg × 4–6 iv), (ii) infusion of thiopental to reduce brain metabolism and sympathetic stress (bolus doses of 2–4 mg/kg followed by continuous infusion of 0.5–3 mg/kg/h) (iii) volume substitution with plasma/albumin infusion and blood transfusion to a serum-albumin level of 35–40 g/l and Hb above 125 g/l to maintain normovolaemia and a normal plasma colloid osmotic pressure, and (iv) volume-controlled mechanical ventilation ($PaCO_2$ level of 4.6–5.0 kPa). It has been shown that intracranial infections are associated with depressed cerebral autoregulation (19, 20). In this state a reduction in arterial pressure will lower hydrostatic capillary pressure and thereby induce transcapillary absorption. If these measures, as applied in our study, did not reduce ICP to a level below 25–30 mmHg within 24 h, dihydroergotamin was added intravenously for a maximum of 2 days (3µg/kg × 4–6). The antihypertensive therapy used was tailored to the ICP value, if necessary, allowing a fall in the cerebral perfusion pressure (arterial pressure-ICP) to a lowest value of 50 mmHg for adults and 40 mmHg for young children. Vasopressor support with the intention to increase the cerebral perfusion pressure was not used. Thiopental and clonidine in combination with fentanyl (3–5 µg/kg/h) were given primarily as analgesia, but provided also adequate antistress and sedative effects. After 2–3 days, thiopental was replaced by midazolam to prevent barbiturate-induced pulmon-

ary side-effects (21). The same zero baseline level was used for measurements of arterial pressure and ICP.

Acute episodes of incipient brain stem symptoms before the patient was admitted to the ICU were managed in a few cases, using either short-term hyperventilation, a bolus infusion of thiopental (3–4 mg/kg), or temporary drainage of cerebrospinal fluid or a combination of these interventions. Osmotherapy was not used, due to the risk of an adverse rebound increase in ICP (22).

## Results

During the four-year study period, 53 patients were admitted to our hospital with the primary diagnosis of bacterial meningitis. Fifteen patients had a clinical picture compatible with intracranial hypertension. Three patients were excluded due to moribund clinical condition on arrival at the hospital (one patient) or cardiovascular failure combined with coagulation disturbances (two patients). An ICP measuring device was inserted into 12 patients without complications in terms of intracranial haemorrhage or infection. Demographic, clinical and outcome data of these 12 patients are summarised in Table 1. Seven patients were 16 years or younger; the oldest was 59 years. None of the patients had underlying chronic diseases. Streptococcus pneumoniae was the most common aetiology documented by culture in six patients. Spinal fluid cultures were negative in four patients who had received antibiotics prior to specimen collection. Corticosteroid therapy was given to six of the 12 patients (Table 1), a therapy recommended at the time of the study if it could be given before initiation of the antibiotic therapy (23, 24). Four patients were given dihydroergotamine (patients 1, 4, 5 and 10).

Intracranial hypertension with an initial ICP exceeding 20 mmHg was found in all 12 patients. ICP values before and after initiation of the ICP-reducing therapy are shown in Fig. 1. No further increase in ICP was noted after 2–3 h of treatment. In cases 5, 7 and 8 a clear trend of increasing ICP was broken shortly after the start of therapy. In general, ICP fell gradually but at various rates following commencement of the ICP-reducing treatment.

Ten patients survived, seven of whom recovered completely. Two patients were left with mild hearing impairment (patients 1 and 12) and one with permanent but mild ataxia combined with moderate urinary bladder dysfunction (patient 4). The follow-up time was at least 2 years after hospital discharge. Two patients died. Both showed insufficient cerebral perfusion pressure (<10 mmHg) from the initiation of therapies due to a significantly increased ICP, circumstances suggesting virtually no cerebral blood flow (patients 9 and 10). They had bilaterally dilated pupils nonresponsive to light stimulation. ICP continued to be close to the mean arterial pressure, their neurological status did not improve, and they were both beyond recovery.

Before implantation of the monitoring device, computerised tomography (CT scan) of the brain was performed in 10 patients and MRI was performed in one of these patients (patient 4, Fig. 2). Radiological signs indicating brain swelling were seen on CT scan in only five patients.

Diagnostic lumbar dural puncture was carried out in 11 of the 12 patients. Within 30 min to 2 h after the

*Table 1*

Demographic, clinical and outcome data.

| Case no. | Age (years) | Level of consciousness before sedation (RLS) | Etiologic agent | Lumbar dural puncture | Brain stem symptoms | Functional outcome |
|---|---|---|---|---|---|---|
| 1 | 2 | 4 | *S. pneumoniae* | Yes | Yes | Mild hearing impairment |
| 2 | 5 | 3–4 | Unknown* | Yes | Yes | Full recovery |
| 3 | 12 | 7 | *S. pneumoniae* | Yes | Yes | Full recovery |
| 4 | 14 | 7 | *S. pneumoniae* | Yes | Yes | Permanent mild ataxia and urinary bladder dysfunction |
| 5 | 15 | 4 | Unknown* | Yes | No | Full recovery |
| 6 | 16 | 3–4 | Unknown* | Yes | No | Full recovery |
| 7 | 16 | 3–4 | *S. pneumoniae* | Yes | No | Full recovery |
| 8 | 21 | 5 | Unknown* | Yes | Yes | Full recovery |
| 9 | 24 | 7 | *S. pneumoniae* | No | Yes | Died |
| 10 | 35 | 7 | *S. pneumoniae* | Yes | Yes | Died |
| 11 | 47 | 3–4 | *N. meningitidis* | Yes | No | Full recovery |
| 12 | 59 | 4 | *S. pneumoniae* | Yes | Yes | Mild hearing impairment |

*Cerebrospinal fluid culture negative.

procedure seven of these patients developed clinical signs compatible with mesencephalic brain stem symptoms (Table 1) (17). Signs noted were uni- or bilateral dilation of the pupils, marked increase in blood pressure, and in one case, opisthotonos (patient 1). Tentorial herniation was visualised by MRI in one patient (patient 4) (Fig. 2). After initiation of the pharmacological interventions, these signs regressed gradually with reduction in ICP. A second radiographical MRI examination of case 4 carried out 5 weeks later showed normalization of the MRI scan (Fig. 2).

## Discussion

Despite effective antimicrobial agents and high quality intensive care, bacterial meningitis continues to be a serious condition associated with significant hospital mortality and morbidity. A mortality rate of 20–25% is normally reported in patients with bacterial meningitis (1, 4, 5), and in a recent cohort of adult

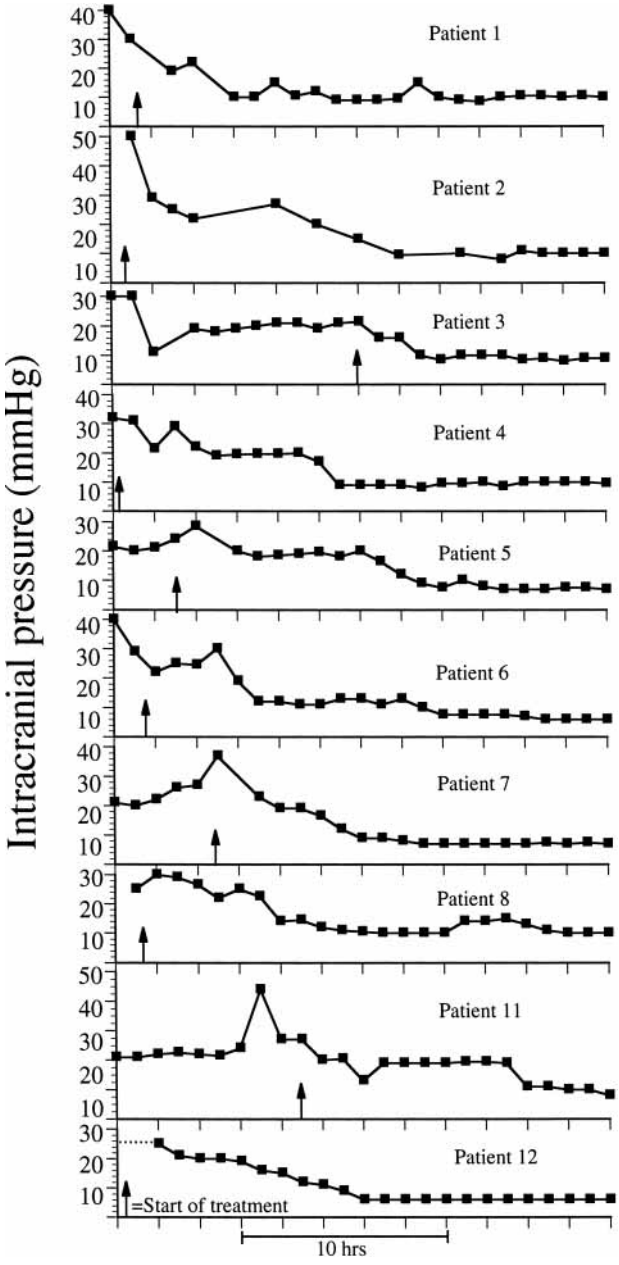


*Fig. 1. Intracranial pressure curves of surviving patients (patients 1–8 and 11,12). In patient 12 the ICP-reducing therapy had started just before installation of the ICP measurement device. The cases are presented in age order.*

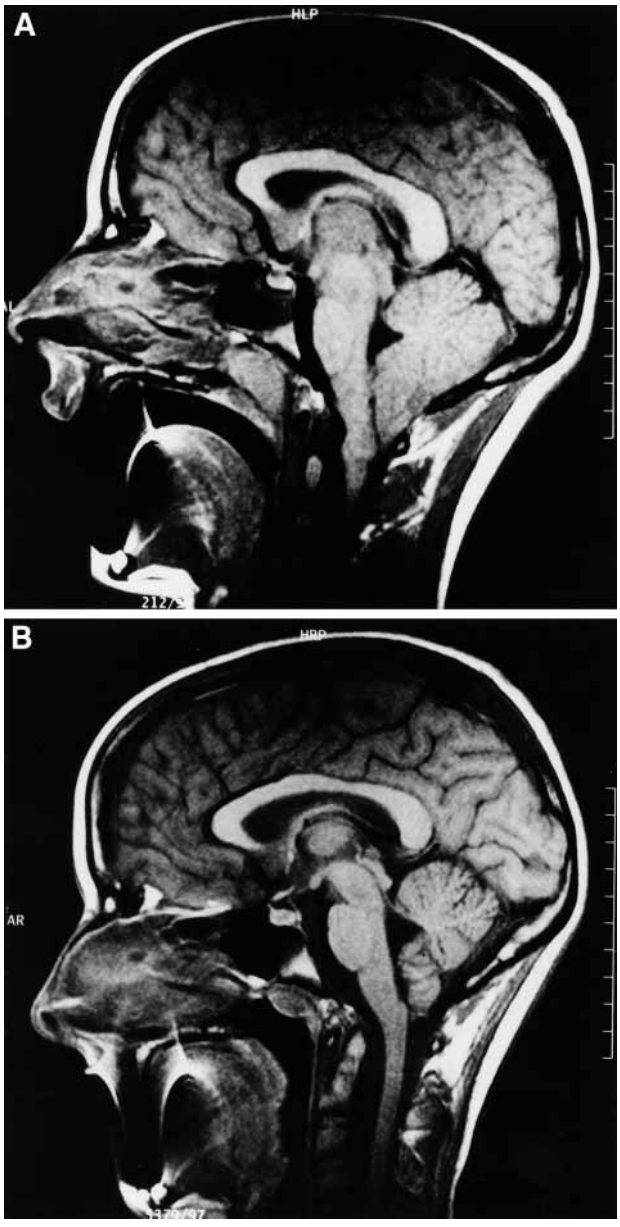


*Fig. 2. MRI brain scan of patient 4 (A) before start of the ICP-reducing therapy, showing a transtentorial herniation with protrusion of the cerebellum tonsils below the foramen magnum, and (B) 5 weeks later, showing a normal MRI scan.*

patients with community-acquired meningitis the hospital mortality was 27% (2–4). In more severe cases, such as the present subset of patients with significant intracranial hypertension and risk of brain stem herniation, a much higher mortality must be expected (3, 7, 10). The dangerously high ICP levels seen in some of our patients and the neurological signs compatible with imminent herniation clearly indicate that our patients were a true high-risk population.

The present investigation was not a randomised comparative study and the expected mortality without intervention is not known. A limited number of patients were included in our investigation, partly because of strict inclusion criteria and partly because the incidence of bacterial meningitis is low. A larger trial is required to assess the true benefit of our intervention. Nonetheless, our data are encouraging, with a mortality rate of only 17%. The clinical effect was clearly demonstrated in patients with neurological signs compatible with imminent tentorial herniation, including one patient in whom reversal of a pronounced herniation of the tonsils of the cerebellum was documented by MRI (Fig. 2).

It is worth noting that CT brain scanning failed to visualize brain swelling in half of our patients. The failure to detect brain swelling on a CT scan in patients with bacterial meningitis has been reported by others (9, 25). Neither can ophthalmoscopy be used to detect acute increases in ICP as papilledema requires several hours to days to develop and is rarely seen in patients with an acute increase in ICP. In the present investigation, clinical criteria were used presumptively to identify patients with critically raised ICP, and intracranial hypertension was confirmed in all patients identified on this basis.

The pathophysiological basis of brain edema is the inflammatory reaction initiated by the bacterial infection, and the subsequent disruption of the blood–brain barrier causing disturbances of normal haemostasis mechanisms of brain volume regulation (26–29). The brain edema can be explained by increased permeability for small solutes, which physiologically can be described as a reduced reflection coefficient for mainly sodium and chloride (27)

Our study is, to the best of our knowledge, the first to record continuously ICP during bacterial meningitis in humans. The ICP fell gradually from high to normal levels within 48–72 h after initiation of therapy. Some of the decline may be the natural recovery following effective antibiotic treatment. The pharmacological intervention, however, is the most likely explanation behind most of the fall in ICP, especially during the first 24-h period, when the inflammatory reaction was still at its height. Thus it is reasonable to assume that the Lund Concept, previously found to be effective in head trauma patients (13–16), effectively and safely can reduce a raised ICP caused by bacterial meningitis. The Lund Concept comprises several drugs, as well as optimised intensive care. It is therefore not possible to evaluate the effectiveness of each component. Besides controlled reduction of ICP, other factors might have contributed to the favourable outcome – for example, correction of hypovolaemia and reduction in cathecolamine release (30), measures known to improve microcirculation and oxygenation of the brain.

The present patient material therefore supports the view that the strategy of using invasive ICP monitoring and controlled reduction of a raised ICP improved the outcome. Continuous monitoring of ICP makes early intervention possible and can prevent fatal brain stem compression. Besides the reduced ICP, the effectiveness of the interventions may be illustrated by the fact that after initiation of treatment, the neurological status gradually improved in all surviving patients and no signs of brain stem symptoms occurred during therapy.

The pathophysiological mechanisms involved in the decline in ICP in our patients (Fig. 1) most probably include both reduction of the cerebral blood volume, due to arterial and venous vasoconstriction, and a more slow reduction in brain edema caused by transcapillary absorption (13, 14). The initial decrease in ICP was presumably caused by the vasoconstrictor effect of barbiturate. The dihydroergotamine bolus infusions may also have caused an intracranial blood volume reduction. Transcapillary absorption is presumed to be a direct effect of the antihypertensive therapy and of the preservation of the colloid osmotic pressure, as well as indirectly through improved microcirculation (14).

Diagnostic dural lumbar puncture is a routine procedure for the diagnosis of bacterial meningitis. However, there is ample clinical experience that this procedure is potentially hazardous in patients with intracranial hypertension, because it may precipitate brain stem herniation (11, 31, 32). Still, most of our patients had been subjected to diagnostic lumbar punctures at the various emergency departments before evaluation by our team. A substantial portion of the patients in our study developed life-threatening neurological signs of emerging brain stem herniation within min to h after lumbar puncture. Because of the temporal relationship and the documented ICP level in these patients, it is difficult to discard a possible causal relationship between the

dural puncture and the brain stem symptoms as reported by many other investigators (11, 31, 32). Thus, there are strong indications suggesting that lumbar puncture in patients with intracranial hypertension is associated with a significant risk of life-threatening complications and should be avoided. The problem facing the physician is to determine whether a dangerous intracranial hypertension is present or not. Other diagnostic methods such as CT brain scan or opthalmoscopy are of little assistance, because findings do not correlate well with the ICP level and may fail to identify patients at risk. Our study shows that patients with bacterial meningitis presenting clinical signs of intracranial hypertension invariably had dangerously high ICP levels and were at risk of herniation, especially when subjected to lumbar puncture. A safe approach in such circumstances is to abstain from lumbar dural puncture and, if possible, insert an intraventricular ICP-monitoring device as used in our patients. Spinal fluid for culture and for clinical chemistry can safely be obtained through the intraventricular catheter.

The mechanisms behind brain stem herniation, as well as spinal headache, following lumbar dural puncture is not understood, one fact which may explain why lumbar dural puncture is still used rather uncritically. It is classically explained as an effect of loss of cerebrospinal fluid volume by leakage through the needle perforation of the dural sac (33). This, however, can not be the only explanation, because the continuous production of cerebrospinal fluid should easily compensate for such an effect. We recently formulated the alternative explanation (34), that opening of the dural sac also results in reduction in the intradural and interstitial brain pressure, causing transvascular filtration across the disrupted blood–brain barrier and dilation of collapsed intracranial veins. Reduction in cerebrospinal counter-pressure around the brain stem also allows brain tissue to move sagitally, with loss of volume buffering capacity in this region (Fig. 2A).

We conclude that a significantly raised ICP level is a life-threatening condition during bacterial meningitis, and may precipitate brain stem compression, especially after lumbar dural puncture. This situation can be brought under control by pharmacological treatment of the brain edema using the Lund Concept, most probably reducing the imminent risk of herniation. Continuous ICP measurement and aggressive management of a raised ICP is warranted in severe cases with suspected intracranial hypertension, and should be considered in institutions capable of providing this level of care.

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