SUMMARY

Background: Delirium is common, has multiple causes and causes distress to numerous patients and their relatives.

Method: Selective review of the literature in PubMed and PsycINFO, with reference to selected national and international guidelines.

Results: The hypoactive subtype of delirium is commoner than the hyperactive type, and often overlooked. Delirium in an elderly individual is associated with an additional burden, a possible loss of potential for rehabilitation, and a marked increase in mortality. The diagnosis of delirium is primarily clinical. All professionals involved in patient care must be able to recognize the features of delirium. Dementia, dehydration and polypharmacy are particularly strongly associated, in the elderly. A careful history and examination with appropriate investigation allows underlying causes to be detected and treated. Rehabilitation strategies should be initiated without delay. Neuroleptics and benzodiazepines have an established role in the pharmacological treatment even of the hyperactive subtype. Non-pharmacological treatments include the creation of a calm and patient centred environment, and the involvement of relatives.

Conclusion: In many cases, delirium can be diagnosed and treated in good time. Prevention is preferable to treatment.

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Definition

“Delirium” is loosely defined and has many synonyms.
Postoperative delirium can also be an expression of pain.

The following information and recommendations as to diagnostic assessment and drug therapy reflect the current German and American literature and the available treatment guidelines. At the moment, there is no S3 guideline covering the treatment of delirium with its many causes and mechanisms. This review therefore incorporates the recommendations of the current guideline of the German Society for Neurology (Deutsche Gesellschaft für Neurologie) and the German Society for Psychiatry (Deutsche Gesellschaft für Psychiatrie).

**Learning objectives**

This article is intended to enable readers to:
- gain an overview of the predisposing factors for delirium and the different clinical forms it can take;
- know the essential components of the diagnostic assessment of delirium;
- become acquainted with the options for treating delirium with drugs and other means.

**The cost of treatment for delirium**

Patients with delirium cause the health-care system considerable expense. Leslie et al. (8) calculated that hospitalized patients with delirium give rise to $295 in additional expenses per day compared to those without delirium. If one combines this figure with Inouye’s (9) rough estimate that 20% of hospitalized patients over age 65 suffer from delirium, then the annual additional expense for the United States alone turns out to lie in the range of $143 to $152 million dollars. Patients with delirium who are under specialized medical care occasion 39% higher costs in the intensive care unit and 31% higher illness costs overall than patients without delirium (10). Patients with delirium also give rise to markedly higher total costs over a three-year time span (11). A German study (12) identified delirium as a major cost factor in hospitals, largely because of the staff time required to deal with it. Manpower costs, the costs of medical supplies, and the longer hospital stay of patients with delirium were found to add up to an average additional expense of €947.55 per hospitalized patient (12).

**Pathophysiology and etiology**

There are fundamental pathophysiological differences between delirium due to the withdrawal of a substance, e.g., alcohol, benzodiazepines, nicotine, and delirium of other causes. In delirium due to alcohol withdrawal, there is an imbalance of inhibitory and excitatory mechanisms in the participating neurotransmitter systems (6). Regular alcohol consumption leads to inhibition of the NMDA receptors and activation of the GABA-A receptors. Cerebral disinhibition is associated with neurotransmitter changes that reinforce dopaminergic and noradrenergic transmission. These changes bring about the characteristic manifestations of delirium, including marked sympathetic activation and a tendency toward epileptic seizures (13). On the other hand, benzodiazepine withdrawal causes delirium by way of decreased GABA-ergic transmission. Here, too, epileptic seizures may occur.

Delirium that is not due to substance withdrawal comes about by a number of different mechanisms. The final common pathway of delirious states seems to consist of a cholinergic deficit combined with dopaminergic hyperactivity. The significance of other neurotransmitters, such as serotonin and noradrenaline, for delirium is less clear at present. Interactions between these neurotransmitters and the cholinergic and dopaminergic systems may play a role.

The altered neuronal transmission that is found in delirium arises through a variety of mechanisms. For simplification, it can be said that current explanations involve three main hypotheses:
- First hypothesis—direct effect: Some substances have direct effects on neurotransmitter systems, in particular, anticholinergic and dopaminergic agents. Moreover, metabolic disturbances such as hypoglycemia, hypoxia, or ischemia can also directly impair neuronal function and thus lessen the synthesis or release of neurotransmitters. In particular, hypercalcemia commonly causes delirium in women with breast cancer.
- Second hypothesis—inflammation: Delirium can also be caused by a primary disturbance that originates outside the brain, such as an inflammatory disease, trauma, or a surgical procedure. In such cases, a systemic inflammatory response leads to the increased production of cytokines, which can, in turn, activate microglia to produce an inflammatory reaction in the brain. Aside from this harmful effect on neurons, cytokines can also impair the synthesis and release of neurotransmitters. It
appears that inflammatory processes play a role in causing delirium in patients with primary diseases of the brain (particularly neurodegenerative diseases).

Third hypothesis—stress: Stress factors that induce the sympathetic nervous system to release more noradrenaline, and the hypothalamic-pituitary-adrenocortical axis to release more glucocorticoids, can also activate glia and thereby damage neurons (14).

Diagnostic evaluation

The cardinal manifestations of delirium are a cognitive disturbance with impaired orientation, temporal fluctuation, and onset over a few hours or days. Hyperactive, hypoactive, and mixed types of delirium have been described (13). Hyperactive delirium is characterized by increased psychomotor activity, with agitation, vegetative disturbances, impatience, and (sometimes) aggression; hypoactive delirium is characterized by generalized slowing, so that the patient seems calm or even apathetic (7). The manifestations vary greatly across and even within individuals. There can be marked swings across the spectrum of psychomotor disturbance, ranging from agitation (hyperactivity) at one end to low drive (hypoactivity) at the other; each of the two main forms of delirium can be replaced by the other without warning. In most cases, the manifestations of delirium tend to fluctuate both in type and in severity, with lucid intervals in between.

The diagnostic assessment of delirium begins with its differentiation from other syndromes and the identification of an etiology. First, the cardinal and accessory manifestations of delirium are characterized by history-taking and physical examination. Delirium is diagnosed on clinical grounds: The entity is characterized by its typical manifestations, acute onset, and fluctuating course. The etiology is then sought. The features of delirium in the individual patient, the past medical history, and the patient’s pre-existing cognitive deficits (if known) can point the way to whatever further diagnostic testing may be indicated (Box 1).

The immediate initiation of a time-consuming detailed workup can be dispensed with if, for example, delirium in a patient with advanced dementia is found to have been induced by a typical precipitating factor (drugs, dehydration, etc.). Once the offending substance has been discontinued, or the patient rehydrated, one generally waits for the patient to recover from delirium before doing any further tests (15).

Hypoactive delirium poses a special diagnostic problem, because the patient’s attention deficit may seem to reflect nothing more than impaired cognitive performance. Thus, the correct diagnosis of hypoactive delirium is often hard to make, and delayed diagnoses often result in delayed specific treatment (16). One cause of hypoactive delirium, for example, is non-convulsive status epilepticus; once this has been diagnosed by EEG, anti-epileptic drug treatment can be begun (16). Delirium is often accompanied by further clinical problems that weigh on the patient and the treating staff alike, including incontinence, falls, uncooperativeness, refusal of treatment and food, and a tendency to run away (poriomania).

Epidemiology

Delirium syndromes are very common among elderly, acutely hospitalized patients. About 20% of all 65-year-olds admitted to hospital are in delirium on admission (17); the prevalence of delirium among elderly hospitalized patients has ranged from 14% to 56% in different studies (14, 18); and a further study revealed a 58% prevalence of delirium among patients in nursing homes (19). Hypoactive delirium

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**BOX 1**

**Delirium: basic diagnostic evaluation**

- ECG
- echocardiography
- laboratory tests (complete blood count, creatinine, CRP, electrolytes, calcium, hepatic and renal function tests, glucose, TSH, urinalysis)
- CSF studies
- EEG
- chest x-ray
- CT of the head
is probably more common than the hyperactive kind but is frequently missed. Thus, 30% to 60% of all cases of delirium probably remain undiagnosed (20). It follows that medical staff should be particularly watchful for delirium in patients with impaired communicative abilities.

**Age-dependency of delirium**

Both epidemiological studies and studies of hospitalized patients have clearly shown that delirium is more common in old age (21). In most of these studies, however, it remains unclear to what extent age itself is an independent risk factor, aside from the influence of other age-related conditions such as poor general health and various kinds of sensory impairment. Biological aging is characterized by the progressive loss of adaptability, with decreasing functional reserves and diminution of the ability to recover from a physiological injury. At the same time, aging can lead to a multiplicity of diseases and to polypharmacy, along with changes in the patient’s physical and personal environment. The elderly are given anticholinergic drugs more often than persons in other age groups; such drugs are prescribed very frequently even to patients for whom they present a known risk, such as those with Alzheimer’s disease (22, 23). The use of anticholinergic substances is an independent, cumulative risk factor for delirium (24, 25, e2).

Among elderly patients in particular, the occurrence of delirium is considered a complication that worsens the overall prognosis (e3) and one that partially or totally blocks the ability of the patient to be rehabilitated (e4). The associated worsening of the quality of life has also been documented (e5). Patients with delirium suffer a markedly higher mortality (10% to 65%) than patients of the same age without delirium (e6, e7).

Men suffer from delirium more commonly than women because they more commonly drink alcohol to excess (e8).

**Risk factors and clinical comorbidities**

The risk factors for dementia can be divided into predisposing and precipitating factors. Predisposing factors (“vulnerability factors”) are those that make delirium more likely to occur, e.g., in hospitalized patients (e9). For elderly persons, such factors include impaired visual acuity (worse than 20/70 on the Jaeger chart), hardness of hearing (a score below 7/12 on the whisper test), immobility (the inability to transfer oneself or to walk unaided), sleep disturbances (e.g., due to nocturia), chronic pain, pre-existing cognitive deficits (a score below 24 on the MMSE), senile dementia of Alzheimer type (e10), infectious diseases, dehydration (blood urea nitrogen [BUN]/creatinine ratio above 25), malnutrition (albumin concentration under 3 g/dL), severe illness of any kind (Apache II score over 16 points) (e11), acute metabolic derangements, and more than three new medications (e12)

The precipitating factors for delirium include noxious substances and hospitalization-related factors (triggers). Common ones are acute illnesses (infections), operations, catheters, diagnostic procedures, sedatives, anticholinergic drugs, sensory deprivation, psychosocial stress, physical restraints, moves from one room to another, changes of the treating staff, surgical complications, iatrogenic complications of any kind (new pressure sores, catheter-related complications), acute metabolic derangements, and more than three new medications (e11).

**Dementia**

Among all diseases of old age, dementia is the one most commonly identified as a risk factor for delirium (e8, e13). The “severity of dementia” appears to be an independent predictor of delirium (e9). Moreover, dementia is the most important differential diagnosis of the delirium syndrome. The main criteria that speak for delirium and against dementia are acute onset, fluctuating course with impairment of the day-night rhythm, and reduced clarity of consciousness and level of attention. Among very old persons in particular, the combination of delirium and dementia is much more common than pure delirium (15). Often, delirium and dementia cannot be clearly distinguished from each other at any particular point in time. Their secure differentiation requires observation over the course of the patient’s illness.

**Patients with cancer**

Delirium is the third most common symptom among patients with advanced cancer, after pain and cachexia (e14, e15). The percentage of patients admitted to a palliative care unit who are in delirium on admission varies from 28% to 42% (e16). As many
as 90% of cancer patients suffer from agonal delirium just before death (e17). Delirious cancer patients have a much shorter life expectancy than others (e14). The common causes of delirium in cancer patients are metabolic disturbances such as hypercalcemia (due to bone metastases) and hypoglycemia, dehydration, and hepatic/renal failure (e18). Delirium can also be caused by drugs, e.g., opioid or benzodiazepine overdose or withdrawal or changes in drugs that the patient has already been taking over the long term, e.g., antidiabetic glycosides. Moreover, spread of the underlying disease into the central nervous system can play a role as well (brain metastases, carcinomatous meningitis). In addition, cancer patients are especially vulnerable to stresses such as anxiety, depression, emotional trauma, and spiritual crises.

It is particularly important that the goal of treating delirium should be discussed with cancer patients in advance. Agonal delirium should be treated symptomatically, rather than with the intent to cure.

**Drug-induced delirium**

Particularly in multimorbid patients, many different drug side effects and interactions can induce or worsen the manifestations of delirium. 11% to 30% of elderly persons with delirium have drug-induced delirium (mean, 20%) (e19). That anticholinergic drugs can cause delirium has already been mentioned; the amount of anticholinergic medication prescribed is well correlated with the severity of delirium (e20). Delirium is well known to arise after stroke, and, in many such cases, delirium seems to be due to anticholinergic drugs. Intracranial bleeding and anticholinergic drugs are among the more important independent predictors of delirium, while ischemic stroke seems to be less important (e22). Likewise, in other age-related neurological disorders, such as Parkinson’s disease, the elevated risk of delirium is at least partly due to drug effects (21). An overview of medications that favor the development of delirium is provided in Box 3.

**Delirium in cancer patients**

The common causes of delirium in cancer patients are metabolic disturbances such as hypercalcemia (due to bone metastases) and hypoglycemia, dehydration, and hepatic/renal failure.
Disturbances of fluid & electrolyte balance

Disturbances of fluid and electrolyte balance are a main cause of confusion among elderly hospitalized patients, alongside infections and drug effects (e23). Delirium is closely linked to dehydration, which is a multifactorial problem due, among others, to multiple physiological changes of old age, among others (e24). Such changes can also cause hyponatremic dehydration, which is not at all rare in the elderly. In the literature, hyponatremia is cited among the more common causes of delirium in the elderly (e25).

The most common scenario is diuretic-induced hyponatremia in a patient taking multiple drugs. Hyponatremia can also be induced organically by the release of active vasopressin (antidiuretic hormone). Further causes of deranged fluid balance include the syndrome of inappropriate antidiuretic hormone release (SIADH), glucocorticoid deficiency, hypothyroidism, and chronic renal failure. The clinical features of such cases range from a nongoal specific loss of appetite to acute delirium and overt neurological deficits (e26, e27).

Dehydration often goes unrecognized in elderly persons who are at home. Its classic signs—poor skin turgor, dryness of the skin and mucous membranes, and intraocular hypotension—are often unreliable in the elderly. Relatively mild and easily diagnosable problems like dehydration frequently escape diagnosis and are thus treated too late, or not at all; all too often, this can lead to delirium in an elderly patient being misdiagnosed as untreatable dementia (e28).

The treatment of delirium

It is best to recognize incipient delirium early, so that preventive measures can be taken (Box 4). Patients at risk should be identified, adequate hydration ensured, and drug treatment optimized. The nursing staff has the closest contact with such patients and therefore plays a decisive role in the early phase of delirium.

The treatment of delirium can be directed at the causes of delirium, its manifestations, or both; symptomatic treatment can be either with drugs or with non-pharmacological means. The level of evidence for each particular intervention is low, as prospective studies are lacking. In what follows, we will briefly mention the available evidence for each therapeutic measure.

Because the manifestations of delirium typically fluctuate, delirious patients need continuous observation so that the course of the disturbance and the effect of treatment can be assessed. There must be an opportunity to modify the treatment rapidly in case the patient’s condition worsens, or in case his or her behavior starts to endanger himself/herself or others.

As mentioned, delirium elevates both morbidity and mortality. Thus, delirious patients require not only clinical psychiatric monitoring, but medical monitoring as well.

The cause of delirium in the individual patient should be treated, if possible. For example, fluid and electrolyte imbalances should be corrected, infections cured with antibiotics, anticholinergic drugs...

Dehydration

Dehydration often goes unrecognized in elderly persons who are at home. Its classic signs—poor skin turgor, dryness of the skin and mucous membranes, and intraocular hypotension—are often unreliable in the elderly.

The prevention of delirium

Take preventive measures early! Identify patients at risk, ensure adequate hydration, and optimize drug treatment.
The pharmacotherapy of delirium is based on its cause (Box 5). The preferred treatment of delirium due to alcohol withdrawal is with drugs that increase the activity of the GABA-ergic system, with clomethiazole as the drug of first choice. The dosage should be based on the symptomatic response; no more than 24 capsules should be given per day. The additional administration of benzodiazepines is also justified in patients suffering from delirium due to alcohol withdrawal. Diazepam, lorazepam, or even midazolam can be given. Severely agitated patients with delirium due to alcohol withdrawal can be treated with up to 60 mg of midazolam SC over 24 hours. Likewise, delirium due to benzodiazepine withdrawal can be treated with continuously administered midazolam in a tapering dose.

Patients with other (hyperactive) types of delirium are usually treated with antipsychotic drugs, despite the sparsity of scientific evidence for this practice (e29). The data support the use of haloperidol more than the use of other drugs, although, even for haloperidol, no standardized dose recommendations can be given. It is usually administered in 1-mg doses every two to four hours, with a maximum daily dose of 25 mg. Patients in severe delirium may need much higher doses, particularly if they are very aggressive. In the elderly, treatment with haloperidol should start at lower doses in the range of 0.25 to 0.5 mg every four hours. Physicians ordering haloperidol should always be watchful for cardiac arrhythmias with prolongation of the QT interval, especially in elderly patients and whenever higher doses are used.

There is also some evidence pointing to the efficacy of newer antipsychotic drugs, such as quetiapine, olanzapine, and risperidone, against delirium (e30, e31). Nonetheless, the scant data from clinical studies do not allow any general recommendation.

The treatment of delirium with benzodiazepines is controversial (e32), as these drugs have often been reported to cause paradoxical reactions, respiratory depression, and oversedation. Nonetheless, for patients with severe psychomotor agitation, the administration of benzodiazepines in addition to antipsychotic medication is an important component of the treatment of delirium. In fact, delirium in the setting of palliative care is often treated with a benzodiazepine as the initial and sole medication.

Delirium due to anticholinergic substances can be treated with cholinesterase inhibitors, but here, too, adequate scientific evidence is lacking.

The treatment of delirium
Treatment can be directed at the causes of delirium, at its manifestations, or both; symptomatic treatment can be either with drugs or with nonpharmacological means.

Drug treatment
Delirium due to alcohol withdrawal is usually treated with GABA-ergic drugs. Hyperactive types of delirium are treated with antipsychotic drugs, although there is little scientific evidence to support this.
Delirium due to anticholinergic substances

Delirium due to anticholinergic substances can be treated with cholinesterase inhibitors, but here, too, adequate scientific evidence is lacking.

Non-pharmacological treatments of delirium

Non-pharmacological measures also play a major role in the treatment of delirium (Box 6).

It should be made clear to the patient’s family and, if possible, to the patient himself or herself that delirium, though it often arises in connection with physical illness, is usually reversible. The patient’s family and friends can be mobilized to help with cognitive reorientation by repeatedly reminding the patient of the situation, time, and place.

<table>
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<th>BOX 6</th>
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<td><strong>The non-pharmacological treatment of delirium</strong></td>
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<tr>
<td>● Create a quiet, safe environment</td>
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<td>● Enlist the aid of the patient’s family</td>
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<td>● Optimal level of stimulation with fixed day/night rhythm</td>
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<td>● Promotion of mobility</td>
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<td>● Relaxing music and smells (aromatherapy)</td>
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<td>● Touch by persons with whom the patient feels at ease</td>
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Conflict of interest statement

Prof. Lorenz serves as a paid consultant for Boehringer and UCB Pharma and has received research support from Teva and Allion.

Prof. Noachtar has served as a paid consultant for UCB, Pfizer, Eisai, and Desitin. He has received honoraria from GlaxoSmithKline, Destin, Eisai, and UCB. He has been paid for preparing scientific continuing education sessions and manuscript states that he has no conflict of interest.

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REFERENCES


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Further information on CME

This article has been certified by the North Rhine Academy for Postgraduate and Continuing Medical Education. Deutsches Ärzteblatt provides certified continuing medical education (CME) in accordance with the requirements of the Medical Associations of the German federal states (Länder). CME points of the Medical Associations can be acquired only through the Internet, not by mail or fax, by the use of the German version of the CME questionnaire within 6 weeks of publication of the article. See the following website: cme.aerzteblatt.de

Participants in the CME program can manage their CME points with their 15-digit “uniform CME number” (einheitliche Fortbildungsnummer, EFN). The EFN must be entered in the appropriate field in the cme.aerzteblatt.de website under “meine Daten” (“my data”), or upon registration. The EFN appears on each participant’s CME certificate. The solutions to the following questions will be published in issue 29–30/2012.

The CME unit “The Treatment of Climacteric Symptoms” (Issue 17/2012) can be accessed until 8 June 2012. For issue 25/2012, we plan to offer the topic “The Acute Scrotum in Childhood and Adolescence.”

Solutions to the CME questions in issue 13/2012:
Przybilla B, Ruëff F: Insect Stings—Clinical Features and Management.
Solutions: 1b, 2c, 3c, 4b, 5a, 6d, 7d, 8e, 9c, 10a.
After discussion with the certifying agency (the North Rhine Medical Association), we have decided to count all answers to Questions 4 and 6 as correct.
Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the answer that is most appropriate.

**Question 1**
What instrument is most commonly used to diagnose delirium in the German-speaking countries?
- a) Memorial Symptom Assessment Scale
- b) Dementia Rating Scale
- c) Schedule for Meaning in Life Evaluation
- d) Confusion Assessment Method
- e) Montgomery Depression Scale

**Question 2**
Which of the following is a common cause of delirium in women with breast cancer?
- a) Hypoglycemia
- b) Hypernatremia
- c) Hypercalcemia
- d) Diminished cortisol secretion
- e) Dehydration

**Question 3**
Which of the following classes of drugs carries a high risk of causing delirium in elderly patients?
- a) Antispasticity drugs
- b) Homeopathic drugs
- c) Anticholinergic drugs
- d) Muscle relaxants
- e) Low-molecular-weight heparins

**Question 4**
Approximately what percentage of patients aged 65 are in delirium on admission to the hospital?
- a) 5%
- b) 20%
- c) 40%
- d) 60%
- e) 80%

**Question 5**
Which of the following typically precipitates delirium?
- a) Chronic hepatitis C infection
- b) An insect bite
- c) An acute illness
- d) Dysphagia
- e) Urticaria

**Question 6**
What study that is suitable for the evaluation of confusion of acute onset is usually readily available and can be performed at the bedside?
- a) EEG
- b) MRI of the head
- c) Cystoscopy
- d) Abdominal ultrasonography
- e) Pleural tap

**Question 7**
A dying patient whose pain is well controlled becomes delirious in the final, agonal phase of his illness. What should be done?
- a) An MRI scan
- b) A CT scan
- c) Sedation with opioids
- d) Symptomatic treatment, e.g., with anxiolytic drugs
- e) An EEG

**Question 8**
What is the usual indication for treating delirium with clomethiazole?
- a) Delirium due to nicotine withdrawal
- b) Hypoglycemic delirium
- c) Hypoactive delirium
- d) Delirium due to alcohol withdrawal
- e) Drug-induced delirium

**Question 9**
How does postoperative delirium differ from postoperative cognitive dysfunction?
- a) In its duration
- b) In its etiology
- c) There are sex-specific differences
- d) There are differences in diagnostic assessment
- e) Different types of operation are responsible

**Question 10**
What is poriomania?
- a) A method of neuropsychological assessment
- b) An apathetic state
- c) A state in which the patient sees holes in the wall
- d) The pathological urge to punch holes in things
- e) The tendency to run away
Continuing Medical Education

Acute Confusional States in the Elderly—Diagnosis and Treatment

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eReferences
