Death rattle is defined as noisy breathing in the last few hours or days of life. It likely arises from the flow of air through accumulated secretions in the oropharynx and bronchia. The secretions are produced in normal or in increased amounts and not effectively removed.

In the last days and hours of life, death rattle is one of the most common symptoms. According to Ellershaw et al., respiratory tract secretions and the resulting death rattle is—even more than agitation and pain—the most difficult symptom to treat in the final 48 h.

In the first part of this article, death rattle is described (incidence, risk factors, significance, pathophysiology, measurement instruments, and common treatments). The second part provides a systematic literature review on treatment recommendations that was performed within the framework of the project to develop treatment recommendations in palliative medicine commissioned by the “Arzneimittelkommission der deutschen Ärzteschaft” (AkDÄ, Drug Commission of the German Medical Association; see article Radbruch et al., this issue).

Incidence

In the literature, the incidence of death rattle ranges widely between 23% [42] and 92% [15] in palliative care patients in the dying phase. Once death rattle starts, it can be used to predict imminent death. In a prospective study with 100 patients, the median time from onset of death rattle to death was 23 h (average 57±82 h) [30]. In a retrospective study, duration of treatment for death rattle prior to death ranged from 15 min to 25 days [42].

Impact

Death rattle is significant for several reasons. Although the patients are themselves generally drowsy or even unconscious, death rattle can disturb sleep, induce coughing, predispose to infections and increase dyspnea. In the few cases in which the patients are conscious and alert, it can lead to unrest and fear of suffocation. Some authors explain that death rattle causes intensive stress in patients. Furthermore, relatives and medical and nursing staff perceive this symptom as distressful. Nurses and physicians feel obliged to treat it. The sound itself gives the impression that the patient is drowning or suffocating. However, not all relatives are burdened to the same extent. Wee et al. found in a qualitative study that some relatives perceived death rattle neutrally, while they found other events in the process of dying to be substantially more distressful. For others, it was a natural signal of the final hours of life.

Pathophysiology

The cause of death rattle is not completely understood. Various mechanisms can contribute to death rattle: in the dying phase, when patients are often very weak or unconscious, adequate coughing and swallowing reflexes are impaired; thus, normal or excessive amounts of secretion in the hypopharynx and bronchial tree can not be expectorated, which leads to the characteristic death rattle during normal inspiration and expiration.

Excessive respiratory secretions. Excessive respiratory secretions are caused by parasympathetic activation of the salivary glands and bronchial mucosa, which lead to mucus accumulation in the respiratory tract. It is also presumed that brain controlling functions between the sympathetic and parasympathetic systems fail due to general lack of oxygen. Parasympathetic neurons continue to excrete acetylcholine uncontrolled and stimulate the muscarinigenic receptors (M3) in the salivary and bronchial glands, which leads to increased secretions. In addition, the production of thick mucus, functional dysfunction of cilia, and the patient’s supine position are mentioned as further causes for death rattle.

Apart from these, other causes, e.g., respiratory infection, pulmonary embolism, tumor growth, or heart failure can lead to increased secretion accumulation in the lung. These can also result in death rattle in the final phase.

Bennett distinguished between two forms of terminal death rattle, i.e., (real) death rattle (type I) which is caused by increased respiratory tract secretions, and pseudo death rattle (type II) which has different causes:
In palliative medicine, there are no accept-

Pharmacological treatment options

Based on experience from anesthesia and other treatment observations, anticholin-

Scopolamine. The structure of scopol-

Anticholinergics. Atropine was the first anticho-

Dehydration. Decreased fluid intake is regarded to be appropriate and effective [15, 35]. However, the presumption that dehydration can improve the symptom [2] has not been confirmed [15, 29]. Another publication postulates that an existing parenteral fluid administration should be reduced to a minimum or stopped [18].
neous administration is not possible [12]. The dose of 0.5 mg/72 h appears helpful for some patients, while other patients require a higher dose. Harlos [17] anecdotically reported the use of three patches simultaneously in one patient. Onset is slow—approximatively 8 h after administration [32, 36]—and the effect continues for approximately 12 h after removal of the patch [17].

**Butylscopolamine.** Butylscopolamine (Buscopan®) is a quaternary ammonium compound, semisynthetically derived from scopolamine. It is readily available and inexpensive in many countries. This is a reason why it is commonly used in outpatient treatment [5]. However, its efficacy on salivary glands is shorter than scopolamine and its complete pharmacodynamics are relatively unknown [4].

**Glycopyrrolate.** Glycopyrrolate (Robi-nul®) is a synthetic inhibitor of acetylcholine at muscarinic receptors. In anesthesia, it is commonly administered and compared to atropine it is selective and 6-times more potent and has a longer effect (up to 6 h) on salivary excretions in bronchial glands [26, 27]. It dilates smooth muscles in the bronchia, which results in less mucus formation and lower breathing resistance. Furthermore, tachycardia occurs less often than with scopolamine or atropine [42] and it has a longer effect [13]. Glycopryrolate and butylscopolamine (both quaternary amines, hydrophilic) are only able to cross the blood–brain barrier to a limited extent [42]; thus, agitation and sedation seldom occur [13].

**Side effects**

Anticholinergic medicines can result in unpleasant or even dangerous side effects. Systematic effects can lead to the following symptoms: dry mouth, urinary complaints, decreased sweating and hyperthermia, erythema, tachycardia and psychological disturbances [9], reduction of peristalsis and of gastrointestinal secretions [1]. At the end of life these undesired effects are very difficult to differentiate and sometimes do not have much clinical importance any more. In other clinical situations, they can even be partially desired (e.g., in complete gastrointestinal obstruction).

**Literature review**

In our systematic literature review, we searched for experimental studies supporting the efficacy for treatment of death rattle. The PRISMA statement recommendations were observed ([3, 21, 28], also see article by Radbruch et al. this issue). Searches were performed in two databases (Embase and Medline) through the end of 2010. For the search strategy, terms in association with palliative care, death rattle, pharmacological and no pharmacological treatment were used (Tab. 1, see article by Radbruch et al., this issue). Studies included were those fulfilling the inclusion criteria (Tab. 2).

The information from the selected articles was extracted and combined in a database. Thereby, the following information was taken into consideration: authors, publication year, methods, participants, interventions, results, and comments.

**Results**

A total of 134 hits were identified in the search (Fig. 1); after removal of dupli-
Two cohort studies were identified [4, 20].  

Fourteen articles were selected for detailed evaluation. Based on detailed evaluation, six studies fulfilled the inclusion criteria and abstracts, 20 articles were selected. Based on titles and abstracts, 84 titles remained. Based on titles and abstracts, 20 articles were selected. Six studies fulfilled the inclusion criteria (Tab. 3) and are discussed in more detail below.

**Cohort studies**

Two cohort studies were identified [4, 20]. Back et al. compared [4] scopolamine 0.4 mg s.c. (108 patients) and glycopyrrolate 0.2 mg s.c. (62 patients) in a palliative care unit. The assessment was performed using a scale from 0 to 3 (similar to a staged VRCS) by the nursing staff. The study consisted of 2 phases: during phase 1 (11 months), all patients with death rattle (n=129, 44%) received scopolamine. In phase 2 (9 months), 75 patients (36%) with death rattle received glycopyrrolate (0.2 mg s.c., bolus, repeated after 30 min, and finally followed by a continuous s.c. infusion of glycopyrrolate 8 mg/24 h).

The authors found a significant difference between the two medicines after 30 min (statistically significant), addition in the second phase (glycopyrrolate), it was observed that larger doses of diamorphine (statistically significant), midazolam, and levopromazine were administered. The onset of glycopyrrolate occurred later than in scopolamine. Especially Murtagh et al. [33] criticized this study: “research laziness” appears to have occurred in the second phase. Furthermore, the equivalence of both doses are
doubted (it was suggested that glycopyrrolate was underdosed). Finally, the comparability of the two groups being studied was questioned [26].

Hugel et al. [20] came to other conclusions. They examined 36 patients at the end of life in a pairwise comparison (selected with respect to gender, age, and diagnosis). Scopolamine was administered as a 0.4 mg s.c. bolus, which was followed by 1.2 mg/24 h as a continuous subcutaneous infusion. If death rattle persisted, another bolus was administered (time point not clearly defined) and the infusion was doubled to 2.4 mg/24 h. In comparison, glycopyrrolate was administered as 0.2 mg s.c., followed by 1.2 mg/24 h as a continuous subcutaneous infusion. All patients reacted positively to glycopyrrolate, 78% of patients to scopolamine. Of the patients receiving glycopyrrolate, 72% died symptom free compared to 58% with scopolamine. If death rattle persisted, another bolus was administered and the infusion was doubled to 2.4 mg/24 h. This difference was statistically significant. The authors found no difference between side effects and concluded from the study that glycopyrrolate was at least as effective as scopolamine in controlling death rattle.

Experimental studies

Four experimental studies were identified [11, 23, 24, 41].

In a study with 31 cancer patients, Likar et al. [23] compared scopolamine (0.5 mg i.v. or s.c. then 2 additional doses of 0.5 mg administered every 4 h) vs. placebo (after 12 h, the study was performed in an open manner with 0.5 mg/4 h s.c. or i.v.). For the evaluation of death rattle, the trained nursing personnel used a scale from 1 to 5 (1= noisy breathing, 5= very strong death rattle). The authors found no significant difference of scopolamine compared to placebo; however, there were statistically significant more complaints of pain and unrest in patients treated with scopolamine. The authors concluded that scopolamine at this dosage was not the ideal medicine for the treatment of death rattle. As a criticism of this study, Radbruch [34] said that the underlying disease in half of the patients was bronchial carcinoma. Thereby, it may be possible that the death rattle was type II, which in turn could be the reason for the poor response to scopolamine treatment.

In another study with a similar design (13 patients with cancer), scopolamine (0.5 mg i.v. or s.c. every 6 h) was compared with glycopyrrolate (0.4 mg i.v. or s.c. every 6 h; [24]). The authors found better efficacy with glycopyrrolate (statistically significant after 2 and 12 h). In addition, there was no difference in restlessness and complaints of pain. The advantage of both studies was the methodology (RCT); however, the number of patients was only small.

In an open, prospective, randomized, multicenter study, Wildiers et al. [41] examined the efficacy of atropine (0.5 mg s.c. bolus, followed by 3 mg/24 h, i.e., 0.5 mg every 4 h or as a continuous infusion i.v. or s.c.), scopolamine (0.25 mg s.c. bolus, followed by 1.5 mg/24 h, i.e., 0.25 mg every 4 h or continuous infusion i.v. or s.c.), and butylscopolamine (10 mg s.c. bolus, followed by 60 mg/24 h, i.e., 10 mg every 4 h or continuous infusion i.v. or s.c.). They found no relevant differences in the efficacy of these three anticholinergics in the treatment of death rattle (efficacy in 42%, 37%, and 42% of patients, respectively, after 1 h). During the study period, an increase in relief was observed over time.

Although not an accepted treatment for death rattle, but due to the wide distribution of somatostatin receptors in salivary glands and the lungs, 0.2 mg s.c. octreotide (a synthetic analog of the peptide hormone somatostatin) was compared in a cross-over study with 0.4 mg s.c. scopolamine in 10 patients [11]. Octreotide was not more effective and was also not recommended by the authors due to its high cost.

In 2008 with an update in December 2009, Wee and Hiller [40] performed a systematic Cochrane review with the goal of describing the evidence for the efficacy of pharmacological and nonpharmacological interventions in the treatment of death rattle. They searched various databases (Medline, Embase, CINAHL, the Cochrane Pain, Palliative and Supportive Care Trials Register and Cochrane Central Register of Controlled Trials) for RCTs and quasi-experimental studies. They identified 32 studies, but only 4 studies fulfilled the inclusion criteria. These 4 studies [11, 23, 24, 41] were included in our review. The authors concluded that there is currently no proof that pharmacological or nonpharmacological interventions are superior to placebo.
Conclusions from the studies

Concerning the treatment of death rattle in the dying phase, there are only few evidence-based studies, especially concerning the administration of anticholinergics. Performed were either cohort studies with larger numbers of patients and, thus, weaker evidence or comparison studies without sufficient numbers of participants in order to achieve statistically significant results. A placebo group was only used in the study by Likar et al. [23]. Thus, it cannot be determined how death rattle would have developed in patients not receiving treatment with anticholinergics.

A further problem was that in the studies different methods were used to evaluate the treatment of death rattle and the corresponding success criteria. This makes comparison of the studies difficult. In addition, the comparability of the results within studies was also a problem. For example, in the multicenter study by Wildiers et al. [41] it was difficult to determine whether ‘mild’ noise had the same meaning in all centers. Furthermore, the evaluation was performed by the person who provided the medicine (i.e., health care personnel [11, 23, 24, 40]). The evidence base for such open studies is problematic.

The patients included were predominantly adults with cancer. Whether the results can be transferred to other palliative care situations remains to be studied.

Conclusion

There are few studies that have examined the efficacy of treatment, although death rattle is a common problem. Nonpharmacological treatment is still the treatment of choice. If anticholinergics are taken into consideration, the selection is dependent on whether simultaneous sedation is desired.

Anticholinergic treatment of marked death rattle is more effective if it is start-
ed early, because no medicine is able to dry out secretions that have already been produced [16, 42]. However, not all patients develop a death rattle which required pharmacological treatment. At the time that death rattle develops, the patient is often not conscious and alert. We do not know whether the patient suffers from death rattle or whether pharmacological treatment represents an additional burden, or whether it only improves the situation for the relatives. However, because the duty of palliative medicine includes the care of the patient as well as the care of the relatives [10, 17], the pharmacological treatment of death rattle can be reasonable, if it results in a calming of the latter. Providing information to the relatives about the whole situation is, however, absolutely essential. Further studies are needed in order to better understand the pathogenesis and treatment possibilities of death rattle. Ethical and methodological problems in performing studies should, however, not be underestimated.

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**References**