What do we know about the dying process?
The biology of dying – a systematic review

Séamus Coyle1, Rachael McDonald2, Amara Nwosu1, Richard Latten1, Stephen Mason1, John Ellershaw1

1Marie Curie Palliative Care Institute Liverpool, University of Liverpool 2Southport Hospital

BACKGROUND
Diagnosing when a patient with advanced disease is in the last months, weeks, days of their life is an ongoing difficulty for the medical teams involved in their care. There are no precise ways of telling accurately when a patient is in the last days of life: Thus there is often significant clinical uncertainty towards the end of a patient’s life.

AIMS
To review the literature to assess the knowledge of the biology of dying – except sudden death.

METHODS
A systematic review of the biology of dying was performed following PRISMA guidelines. Titles and abstracts from each database were examined independently for relevance. Two search strategies were performed:

Search strategy 1
(Death OR Dying* AND (physiol* OR patho*) OR pathophysiol*)

Search strategy 2
(Terminal*, Terminally* AND (patient* OR Patient*) AND (physiol* OR patho*) OR pathophysiol*)

Our search strategy included a systematic search of databases (EMBASE and MEDLINE) and hand searching of reference and citation lists of relevant papers. 2322 articles on MEDLINE and 3016 articles (EMBASE and MEDLINE) were identified.

SYSTEMATIC REVIEW FLOW CHART

DISCUSSION
Although a number of papers describe a process of dying, it is evident from the review that incredibly little is known about the biology of dying. There were no prospective studies investigating biochemical changes during dying.

Perry et al1 investigated brain biochemical activities in relation to agonal status in order to establish if agonal status affected neurochemical activities in general, and if suitable ‘chemical markers’ of the pre terminal or terminal state could be identified. Cases were divided into those dying after a period of normal or near normal health Category A - where death occurred relatively quickly e.g. due to ischaemic heart disease and Category B, those dying after a prolonged period of severe illness including bronchopneumonia, renal and hepatic failure, which frequently terminated in coma. 23 neurochemicals and 13 amino acids were investigated. Contrasted with Category A, patients in Category B showed highly significant reductions in glutamate decarboxylase, phosphofructokinase and tissue pH and increases in the amino acids phenylalanine, lysine, leucine, and most extensively in tryptophan.

Kadhim et al3 have shown in autopsy studies that Interleukin-2 (IL-2) is preferentially expressed in brainstem neuronal centres implicated in cardio-respiratory control mechanisms in critically ill aging adults as well as young infant patients4 who died from various conditions. However, the adult sample size was very small (n=2).

A number of core themes within the literature were identified. These can be classified as:

• Prognostication
• Common terminal symptoms (cachexia, anorexia, fatigue, dyspnoea, terminal secretions, delerium, agitation and dehydration)
• Signs of death in the last 2 weeks of life
• Postmortem studies including causes of death
• Animal studies of terminal senescence

CONCLUSION
1. There are few studies investigating the biological changes during dying and there are no studies prospectively investigating biochemical changes during the dying process.
2. A number of authors postulate a common final dying pathway.
3. Research into the biological changes at the end of life could develop a greater understanding of the dying process. This research would have the potential to significantly impact the care future dying patients receive.

REFERENCES