

Clinical signs suggest impending death in patients with cancer

A new study has revealed eight highly specific physical signs associated with death within 3 days in patients who have cancer (Hui et al, 2015).

Very few studies have exam-

Dr David Hui, Assistant Professor, MD Anderson Cancer Center, Houston, Texas



ined the signs of impending death, making it difficult for health-care professionals to confidently diagnosis death and to communicate this with the family.

To address this, Dr David Hui of the MD Anderson Cancer Center, and his colleagues recorded the physical changes in the final days of life in 357 cancer patients who were admitted to acute palliative care units in two cancer centres: MD Anderson Cancer Center in Houston and Barretos Cancer Hospital in Brazil. The investigators systematically documented 52 physical signs every 12 hours from admission to death or discharge.

During the study, 57% of the patients died. The research-

ers identified eight bedside physical signs that, if present, strongly suggest that a patient will die within 3 days.

The signs are non-reactive pupils, decreased response to verbal stimuli, decreased response to visual stimuli, inability to close eyelids, drooping of the nasolabial fold (which makes the face appear more relaxed), hyperextension of the neck, grunting of vocal cords, and upper gastrointestinal bleed. These signs may help doctors and nurses to make the diagnosis of impending death.

‘This study shows that simple bedside observations can potentially help us to recognize if a patient has entered the final days of life,’ said Dr Hui. ‘Upon further confirmation of the usefulness of these “tell-

tale” signs, we will be able to help doctors, nurses and families to better recognize the dying process, and in turn, provide better care for the patients in the final days of life.’

While the findings are relevant for clinicians who care for dying cancer patients, it is unclear whether they also translate outside of cancer centres. Therefore, the investigators are now validating their results in other settings, such as home and the inpatient hospice.

Hui D, Dos Santos R, Chisholm G, Bansal S, Souza Crovador C, Bruera E (2015) Bedside clinical signs associated with impending death in patients with advanced cancer: Preliminary findings of a prospective, longitudinal cohort study. *Cancer* (doi: 10.1002/cncr.29048)

Cell cultures may not accurately mimic human tissue

Researchers from the MRC Human Genetics Unit at the University of Edinburgh, UK, and Linköping University, Sweden, have revealed just how quickly cells change their identity when grown in the laboratory (Nestor et al, 2015). They found that cells adapt to cell culture systems within 1 week of growth in a laboratory dish. The analysis provides new insight into how faithfully these cells mimic real tissue, and how models of human disease can still be improved.

Study author Professor Richard Meehan from the MRC Human Genetics Unit at the University of Edinburgh, said: ‘We were astonished by the speed and spread of the changes. Many

cultured cells used in research have been grown for decades and as a result are likely to have very different properties from the cells they are supposed to model.

He continued: ‘Our findings suggest that we have to be circumspect about the interpretation of some previous experiments, and our data reinforce a growing realisation that cell line models of human diseases, particularly cancer, can be poor surrogates for many aspects of in-vivo biology.’

Nestor CE, Ottaviano R, Reinhardt D et al (2015) Rapid reprogramming of epigenetic and transcriptional profiles in mammalian culture systems. *Genome Biol* 16(1): 11 (doi: 10.1186/s13059-014-0576-y)

Diet affects the nutrient composition of uterine fluid

A study undertaken to assess the influence of various factors on the make up of human uterine fluid found that only maternal diet affected the levels of 18 amino acids (Kermack et al, 2015).

Uterine secretions were aspirated from 56 women aged 18–45 years and analysed using reverse phase high performance liquid chromatography. The results were analysed against the women’s stage of menstrual cycle, age, body mass index and diet.

Dr Franchesca Houghton, Associate Professor at the University of Southampton, and senior author commented: ‘At this stage, our findings are not trying to give dietary advice to women but further

research is now required to determine the impact of diet around the time of conception, on the uterine environment and embryo development.’

This information may help in the development of nutritional interventions aimed at optimizing the preimplantation phase of human embryo development in vivo, although the authors caution that the study may not have had sufficient numbers to detect mild effects of body mass index or age.

Kermack AJ, Finn-Sell S, Cheong YC, Brook N, Eckert JJ, Macklon NS, Houghton FD (2015) Amino acid composition of human uterine fluid: association with age, lifestyle and gynaecological pathology. *Hum Reprod* (doi:10.1093/humrep/dev008)

Losing a spouse too often linked to depression

A new study has found that loneliness brought about by the death of a spouse can trigger a wider network of depression-like symptoms – but that doctors are often too quick to attribute these symptoms to depression (Fried et al, 2015).

The study examined depression symptoms in recently widowed elderly people. The researchers followed 515 mar-

ried men and women age 65 years or older. A total of 241 individuals who lost a spouse during the course of the study were invited to follow-up interviews 6 months after loss, together with an equally large still-married control group. The researchers then examined and compared the depression symptoms reported by patients in the two groups.

This produced two key findings, explained lead author Dr Eiko Fried: ‘First, we found that spousal loss causes a very small number of specific depression symptoms, the most important of which was loneliness. Second, we observed that these few initial depression symptoms in turn trigger a specific network of subsequent depression symptoms.’

‘This has implications for prevention and intervention in elderly bereaved people,’ said Dr Fried. ‘Instead of targeting

depression in general, specifically targeting key symptoms such as loneliness may prevent the activation of further symptoms in a person’s psychopathological network and prevent the development of a full-fledged depression.’

Adding to the researchers’ concern is the fact that the newest edition of the *Diagnostic and Statistical Manual* (5th edn), published in 2013, removed the distinction between depression and bereavement. ‘This has been a topic of huge debate, and we fear that in many people who exhibit a normal grief response after losing their partner, normal sadness may be misdiagnosed as having pathological depression,’ said Dr Fried.

Fried EI, Bockting C, Arjadi R et al (2015) From loss to loneliness: the relationship between bereavement and depressive symptoms. *J Abnorm Psychol* (doi: 10.1037/abn0000028)

Dr Eiko Fried, Postdoctoral Research Fellow, University of Leuven, Belgium



Apremilast oral treatment for chronic plaque psoriasis

Apremilast (Otezla) is licensed in the EU for the treatment of specific groups of adult patients with moderate to severe chronic plaque psoriasis or active psoriatic arthritis. Apremilast reduces the activity of phosphodiesterase 4, helping to control associated inflammation, and thereby reducing the signs and symptoms of these conditions.

Breast cancer diagnostic test available in England

The Oncotype DX breast cancer diagnostic test is available across England for the first time. This tests the likely benefit for patients with early-stage, hormone receptor-positive, HER2 negative, invasive breast cancer of undergoing chemotherapy and the risk of recurrence.

9-valent vaccine increases protection against HPV infection

Nine sub-types of the human papillomavirus (HPV) cause 85% of pre-cancerous cells of the cervix. A randomized controlled international trial (doi: 10.1056/NEJMoa1405044) of a new 9-valent vaccine means that these infections could now largely be prevented.

Endovascular treatment of ischaemic stroke

The ESCAPE trial (Goyal et al, 2015) was a multicentre, prospective, randomized, open-label, controlled trial with blinded outcome evaluation.

This trial was designed to answer a practical question regarding a patient with acute ischaemic stroke who has just undergone neurovascular imaging with non-contrast computed tomography and computed tomography angiography: ‘Should this patient undergo endovascular thrombectomy?’

Participants were assigned, in a 1:1 ratio, to receive endovascular treatment plus guideline-based care (intervention group) or guideline-based care alone (control group).

Participants in both groups received intravenous alteplase within 4.5 hours of the onset of stroke symptoms if they met accepted local guidelines for this. For those in the intervention group the neurointerventionist used available thrombectomy devices to achieve reperfusion.

The primary outcome (score on the modified Rankin scale at 90 days after randomization) was assessed by trained personnel who were unaware of the treatment group assignments.

An unplanned interim analysis was conducted after the release of the MR CLEAN results, which showed efficacy of endovascular therapy. The ESCAPE trial was stopped

early on the advice of the data and safety monitoring board because the prespecified boundary for efficacy had been crossed.

The researchers concluded that among participants with acute ischaemic stroke with a small infarct core, a proximal intracranial occlusion in the anterior circulation, and moderate-to-good intracranial collateral circulation, rapid endovascular treatment improved the clinical outcome and reduced mortality.

Goyal M, Demchuk AM, Menon BK et al for the ESCAPE Trial Investigators (2015) Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med* (doi: 10.1056/NEJMoa1414905)

Physical and psychosocial factors trigger low back pain

New research reveals the physical and psychosocial factors that significantly increase the risk of low back pain onset (Steffens et al, 2015). The results show that being engaged in manual tasks involving awkward positions will increase the risk of low back pain by eight times. Those who are distracted during activities or fatigued also significantly increase their risk of acute low back pain.

At some point, nearly 10% of the world's population experience

back pain, which is the leading cause of disability according to the World Health Organization.

'Understanding which risk factors contribute to back pain and controlling exposure to these risks is an important first step in prevention,' explains Associate Professor Manuela Ferreira, from The George Institute for Global Health and Sydney Medical School at The University of Sydney in New South Wales,

Australia. 'Our study is the first to examine brief exposure to a range of modifiable triggers for an acute episode of low back pain.'

For this case-crossover study, researchers recruited 999 participants from 300 primary care clinics in Sydney, Australia, who had an acute low back pain episode between October 2011 and November 2012. Study subjects were asked to report exposure to 12 physical or psychosocial factors in the

96 hours before the onset of back pain.

The risk of a new episode of low back pain significantly increased as a result of a range of triggers, from an odds ratio of 2.7 for moderate to vigorous physical activity to 25.0 for distraction during an activity. Researchers found that age moderated the effect of exposure to heavy loads, with odds ratio for individuals 20, 40 or 60 years of age at 13.6, 6.0 and 2.7 respectively. A new finding not reported previously was that back pain risk was highest between 7:00 am and noon.

'Understanding which modifiable risk factors lead to low back pain is an important step toward controlling a condition that affects so many worldwide,' concluded Professor Ferreira. 'Our findings enhance knowledge of low back pain triggers and will assist the development of new prevention programmes that can reduce suffering from this potentially disabling condition.'

Steffens D, Ferreira ML, Latimer J et al (2015) What triggers an episode of acute low back pain? A case-crossover study. *Arthritis Care Res (Hoboken)* (doi: 10.1002/acr.22533)

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Royal College makes recommendations for tackling exit block in emergency departments

Exit block accounts for hundreds of deaths per year. The Royal College of Emergency Medicine (2015) has published a new report *Exit Block in Emergency Departments – 6 month review*, which brings together the latest research on crowding and exit block in emergency departments, including national statistics on the impact of exit block. It also includes personal accounts from emergency medicine consultants of the impact of crowding and exit block on their departments.

The Royal College of Emergency Medicine has made eight specific recommendations to hospital trusts to assist them in dealing with crowding and exit block in emergency departments:

1. Emergency department capacity should be capable of meeting demand
2. Non-emergency department staff should not 'gate-keep' access to the emergency department
3. A patient who attends an emergency department is

entitled to an assessment by a clinician

4. Emergency departments should have systems that can monitor the degree and impact of crowding
5. Streaming patients does not help with emergency department crowding if the cause of crowding is inadequate hospital capacity
6. Investigations should be 'front loaded' to reduce delay to disposition decisions
7. Senior doctors of all specialities should be involved with rapid assessment and treatment
8. Hospitals with emergency departments should have a hospital-wide escalation policy for when the emergency department becomes crowded with locally agreed triggers.

Dr Cliff Mann, President of the Royal College of Emergency Medicine, said:



'Exit block remains a serious problem and is continuing to impact severely on patient safety. We know that where exit block occurs, mortality rates increase, operations are delayed, and

overworked staff in emergency departments experience stress and burnout. We're calling on hospital chiefs across the country to implement our recommendations for tackling this pernicious problem.'

Dr Mark Porter, British Medical Association council chair, commented: 'Problems at the hospital front door are often linked to delays at the back door. Delays in discharging patients, often as a result of a lack of available care in the community, have a knock on effect on patient flow across a hospital.'

Royal College of Emergency Medicine (2015) *Exit Block in Emergency Departments. 6 month review.* <http://secure.collemergencymed.ac.uk/CEM/document?id=8263> (accessed 25 February 2015)

Inquiry finds avoidable deaths in detention of people with mental health conditions

Repeated basic errors, a failure to learn lessons and a lack of rigorous systems and procedures have contributed to the non-natural deaths of people with mental health conditions detained in psychiatric hospitals, prisons and police cells in England and Wales, according to a new Inquiry by the Equality and Human Rights Commission (2015).

During 2010–13 367 adults with mental health conditions died of non-natural causes while detained in psychiatric wards and police cells and

Preventing Deaths in Detention of Adults with Mental Health Conditions

An Inquiry by the Equality and Human Rights Commission

Equality and Human Rights

another 295 adults died in prison, many of whom had mental health conditions.

The Inquiry found failures by institutions to bring in processes to learn from lessons and implementation recommendations. As a result, the Commission has created an easy-to-follow Human Rights Framework, aimed at policy makers and front-line staff across all three settings, which includes 12 practical steps to help protect lives.

Professor Swaran Singh, Lead Commissioner on the Inquiry, said: 'Human rights are for all

of us and nothing is more fundamental than our right to life. When the state detains people for their own good or the safety of others it has a very high level of responsibility to ensure their life is protected. For people with mental health conditions that is a particular challenge with a large number of tragic cases over the past few years where that responsibility has not been met.'

Equality and Human Rights Commission (2015) Preventing Deaths in Detention of Adults with Mental Health Conditions. An Inquiry by the Equality and Human Rights Commission. www.equalityhumanrights.com/publication/preventing-deaths-detention-adults-mental-health-conditions (accessed 25 February 2015)

Role of family in deciding on cancer treatment

Shared decision-making is an important component of patient-centred care and is associated with improved outcomes. However, little is known concerning the extent and predictors of the involvement of a patient's family in decisions regarding cancer treatments.

The Cancer Care Outcomes Research and Surveillance (CanCORS) Consortium is a large, multi-regional, prospective cohort study of the cancer care and outcomes of patients with lung and colorectal cancer. Multinomial logistic regression was used to assess patient factors associated with family roles in decisions (Hobbs et al, 2015).

Among 5284 patients, 80 (1.5%) reported family-controlled decisions, with the highest adjusted rates (12.8%) noted among non-English-speaking Asians. Among the 5204 remaining patients, 49.4% reported equally sharing decisions with family, 22.1% reported some family input, and 28.5% reported little family input.

In adjusted analyses, patients who were married, female, older and insured more often reported equally shared decisions with family (all $P < 0.001$). Adjusted family involvement varied by race, ethnicity and language.

Hobbs GS, Landrum MB, Arora NK et al (2015) The role of families in decisions regarding cancer treatments. *Cancer* (doi: 10.1002/cncr.29064)

Increased risk of dementia with higher use of anticholinergic medications

A prospective population-based cohort study was undertaken (Gray et al, 2015) using data from the Adult Changes in Thought study in Group Health, in Seattle, Washington. It included 3434 participants 65 years or older with no dementia at study entry.

Computerized pharmacy dispensing data were used to ascertain cumulative anticholinergic exposure, which was defined as the total standardized daily doses dispensed in the past 10 years.

The main outcome measures were incident dementia and Alzheimer's disease using standard diagnostic criteria. Statistical analysis used Cox proportional hazards regression models adjusted for demo-

graphic characteristics, health behaviours and health status, including comorbidities.

The most common anticholinergic classes used were tricyclic antidepressants, first-generation antihistamines, and bladder antimuscarinics. During a mean follow-up period of 7.3 years, 797 participants (23.2%) developed dementia (637 of these (79.9%) developed Alzheimer's disease).

A 10-year cumulative dose-response relationship was observed for dementia and Alzheimer disease (test for trend, $P < 0.001$). Results were robust in secondary, sensitivity and post hoc analyses.

The researchers concluded that higher cumulative anti-



Dr Shelly Gray, Professor, University of Washington School of Pharmacy, Seattle, Washington

cholinergic use is associated with an increased risk of dementia. Efforts to increase awareness among health-care professionals and older adults about this potential medication-related risk are important to minimize anticholinergic use over time.

Gray SL, Anderson ML, Dublin S et al (2015) Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. *JAMA Intern Med* (doi: 10.1001/jamainternmed.2014.7663)