SHORT CUTS

ALL YOU NEED TO READ IN THE OTHER GENERAL JOURNALS

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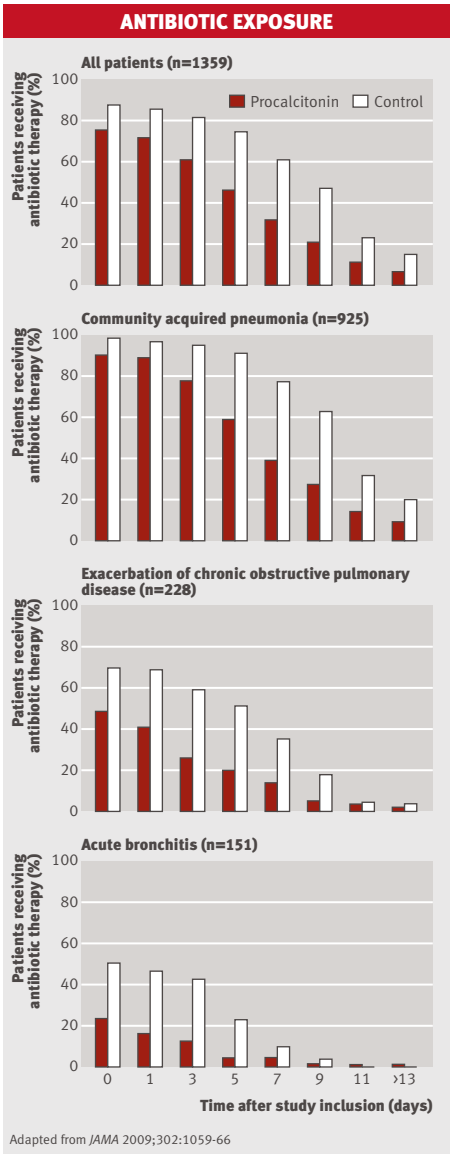
Procalcitonin tests help control antibiotic prescribing

Procalcitonin is a serum marker for bacterial infections and a potentially useful guide to antibiotic prescribing for people with lower respiratory tract infections. The biggest trial so far suggests that treatment informed by a rapid procalcitonin test can reduce patients' exposure to antibiotics and protect them from side effects without adversely affecting clinical outcomes.

All the participating patients presented to Swiss emergency departments with symptoms of lower respiratory tract infection.



Adapted from *JAMA* 2009;302:1059-66

Doctors treating the intervention group used an algorithm based on serum procalcitonin concentration to determine whether to prescribe antibiotics. Doctors treating the control group used one based on current guidelines for antibiotic prescribing. After 30 days, a similar proportion of both groups had died, been admitted to intensive care, had a complication, or had a recurrent infection (15.4% (103/671) of the procalcitonin group *v* 18.9% (130/688) of controls; difference -3.5%, 95% confidence interval -7.6% to 0.4%). Controls received antibiotics for three days longer than patients treated according to the procalcitonin algorithm (8.7 days *v* 5.7 days), and were considerably more likely to experience side effects (28.1% (193/688) *v* 19.8% (133/671); -8.2%, -12.7% to -3.7%). Two thirds of participants in this trial had community acquired pneumonia.

These results are encouraging but preliminary, says an editorial (p 1115-6). Further trials in other populations should be done and should consider costs as well as effectiveness.

JAMA 2009;302:1059-66

Natalizumab linked to more cases of progressive multifocal leucoencephalopathy

Progressive multifocal leucoencephalopathy is a rare but potentially devastating side effect of natalizumab, a monoclonal antibody used to treat multiple sclerosis. It's actually an opportunistic infection caused by a polyomavirus. Demyelination of the central nervous system is the main feature, so it's relatively easy to miss in people with multiple sclerosis.

Two recent case reports of progressive multifocal leucoencephalopathy in patients receiving natalizumab bring the total number of cases to 14 in the United States and Europe. One expert estimates that the risk associated with natalizumab is around one in 1000 (p 1041-3). We have no idea how to identify those most likely to be affected, he adds.

The two new cases developed progressive multifocal leucoencephalopathy after 12 months and 14 months of natalizumab. Both survived after treatment with plasma exchange and immunoadsorption to remove the remaining drug. Both had the causative JC virus in their cerebrospinal fluid.

Natalizumab was taken off the US market in 2005 but relicensed a year or so later after a risk benefit assessment, says the expert. Further cases were anticipated and have duly materialised. We urgently need markers to help predict this complication and diagnose it early. Looking for the JC virus in urine is one option already under study (p 1067-74). Looking for the haematopoietic cells that carry JC viruses from the bone marrow, where they are dormant, to the bloodstream is another.

N Engl J Med 2009;361:1075-80, 1081-7

African children with sickle cell anaemia are dying from preventable infections

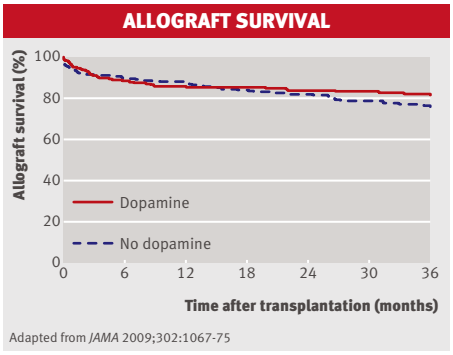
Sickle cell anaemia has a high mortality in sub-Saharan Africa, particularly among children under five years of age. Invasive bacterial infections are at least partly to blame, but which ones? A case control study from Kenya suggests that African children with sickle cell anaemia get the same bacterial infections as affected children living in developed countries, where vaccines have helped to reduce mortality.

Streptococcus pneumoniae, *Haemophilus influenzae*, and non-typhi *Salmonella* species were the commonest pathogens isolated from children admitted to one rural hospital. Bacteraemia of any kind was associated with sickle cell anaemia (odds ratio 26.3, 95% CI 14.5 to 47.6). The association was most powerful for these three familiar infectious agents.

The authors and a linked comment agree that screening African children for sickle cell anaemia should be priority so they can be offered the kind of preventive measures that are taken for granted in developed nations (doi:10.1016/S0140-6736(09)61602-0). These include prophylactic antibiotics and education about complications, as well as the standard immunisations against *Streptococcus pneumoniae* and *Haemophilus influenzae*. Currently, more than 90% of sub-Saharan children with sickle cell anaemia die before they can get a diagnosis. Efforts to reduce the death toll have been hampered in the past by arguments about which infections are killing them. Now we know, says the comment.

Lancet 2009, doi:10.1016/S0140-6736(09)61374-X

Dopamine for kidney donors helps renal recovery in recipients



Adapted from *JAMA* 2009;302:1067-75

Kidneys destined for transplantation must be put in cold storage for transport between donor and recipient. The kidney inevitably deteriorates during this cold ischaemic time, although there's some evidence that pre-treating the kidney with dopamine can reduce the damage.

In one German trial, pre-treating donors with low dose dopamine before organ harvest was associated with faster recovery of renal function in the recipient. Donors, who were brain dead and had stable cardiovascular parameters, had 4 µg/kg/min of dopamine for a median of 344 minutes or no dopamine. Between 75% and 85% of both groups also received noradrenaline and desmopressin.

Recipients of pre-treated kidneys were significantly less likely to need multiple dialysis sessions after their transplant than controls (24.7% (56/227), 95% CI 19.0% to 30.3% *v* 35.4% (92/260), 29.5% to 41.2%; P=0.01). The difference didn't translate into longer survival for the recipients or their kidneys, but the trial may have been too small to detect changes in these important outcomes. Mean cold ischaemic time for all kidneys was 14 hours.

The donors were randomised in this trial but the recipients were not, so the results have an observational element usually missing from randomised trials. Even so, the authors are confident the protective effect of dopamine is real and probably owing to a direct effect on endothelial cells.

JAMA 2009;302:1067-75

Less than half of completed trials are published

Selective publication of clinical trials distorts the literature and denies doctors, patients, and researchers access to essential information about the safety and effectiveness of treatments. The full extent of selective publication is hard to determine, although a recent study of trials registered on ClinicalTrials.gov suggests it is still widespread.

Among a random sample of 677 trials completed by 2005, only 311 (46%) were published and traceable through Medline. Even fewer (96 out of 311 published trials (31%)) provided a citation on ClinicalTrials.gov to allow easy access to published results. Only 66% of trials reported their primary outcomes and 56% reported their secondary outcome. Trials sponsored by government agencies were no more likely to be published than trials sponsored by the drugs industry (47% (57/122) *v* 40% (144/357); P=0.22).

The authors say a greater commitment to timely publication is required from all sponsors and the scientific community in general. A recent ruling by the US Food and Drug Administration may help. The authority now requires researchers investigating drugs and devices to update ClinicalTrials.gov with results for primary and secondary outcomes within two years of trial completion. It's unclear how researchers will be punished if they don't.

PLoS Med 2009;doi:10.1371/journal.pmed.1000144

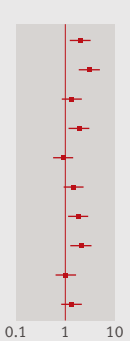
Inflammatory markers predict poor outcome after stroke

High serum concentrations of inflammatory markers were associated with a poor prognosis after stroke in a cohort of 844 patients from Scotland. The association was strongest and most independent for interleukin 6: patients with concentrations in the top third in the immediate aftermath of a stroke were three times more likely to die or be left seriously disabled than patients with concentrations in the bottom third (adjusted odds ratio 3.1, 95% CI 1.9 to 5.0).

Data on disability came from a validated questionnaire completed six months after stroke, whereas data on deaths came from the Scottish national death register. White cell count, C reactive protein, and fibrinogen concentration were also linked to outcome at six months. The authors adjusted analyses for multiple factors that influence outcome including severity of stroke, but they weren't able to exclude patients with infections, a potentially important confounder.

ASSOCIATION BETWEEN INFLAMMATORY MARKERS AND POOR OUTCOME

		Adjusted odds ratio *v* bottom third (95% CI)
Interleukin 6	Middle third	2.0 (1.2 to 3.2)
	Top third	3.1 (1.9 to 5.0)
C reactive protein	Middle third	1.4 (0.9 to 2.2)
	Top third	1.9 (1.2 to 3.0)
Fibrinogen	Middle third	0.9 (0.6 to 1.5)
	Top third	1.5 (1.0 to 2.4)
White cell count	Middle third	1.8 (1.2 to 2.9)
	Top third	2.1 (1.3 to 3.4)
Glucose	Middle third	1.0 (0.7 to 1.7)
	Top third	1.3 (0.8 to 2.1)



Adapted from *PLoS Med* 2009;doi:10.1371/journal.pmed.1000145

Others have also reported a statistical association between interleukin 6 and prognosis after stroke. Could it be useful at the bedside? Probably not, say the authors, who found that adding interleukin 6 made little material difference to the accuracy of a simple clinical prediction tool. The extra information on interleukin 6 concentration reclassified just 5% of patients into a different prognostic group.

PLoS Med 2009;doi:10.1371/journal.pmed.1000145

Two swine flu vaccines seem immunogenic in early trials

Early trials of two swine flu vaccines suggest that both are immunogenic enough to protect recipients from infection. The first trial tested an inactivated monovalent vaccine without adjuvant in 240 Australian adults aged between 18 and 64 years. A single intramuscular injection of the standard 15 µg dose induced a good antibody response in 96.7% of participants (116/120; 95% CI 91.7% to 98.7%), a welcome surprise for the researchers who had assumed that two doses would be required. The 30 µg dose was no more immunogenic than the 15 µg dose.

The second trial, from England, tested a different inactivated vaccine with or without a well established adjuvant. Interim results also suggest that one dose might be enough. The first 100 adults received one or two 7.5 µg doses of the adjuvanted vaccine. Those given two doses had higher antibody titres than those given just one, but titres looked high enough to be protective in all groups.

Safety data from both trials are reassuring so far. Neither trial included an unvaccinated control group.

Any effective vaccine is likely to be in short supply, so a one dose schedule has obvious advantages, says an editorial (doi:10.1056/nejme0908224). The supply would go further, vaccinated individuals would develop immunity faster, and vaccination programmes would be simpler and cheaper. These results need confirming in other populations though. Neither vaccine has yet been tested in children or in adults with underlying health problems—the two groups likely to be vaccinated first.

N Engl J Med 2009;doi:10.1056/NEJMoa0907413, 10.1056/NEJMoa0907650

Cite this as: *BMJ* 2009;339:b3739