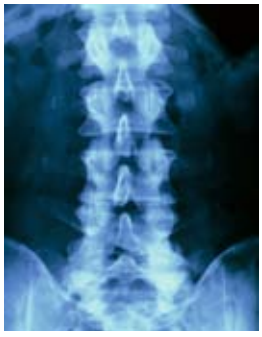
Epidural steroid injections for low back pain

Overall the evidence of benefit is weak, but some may benefit



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RESEARCH, p 573

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In the linked randomised trial, Iversen and colleagues assess the efficacy of caudal epidural steroid and caudal epidural saline injection in the treatment of chronic (>12 weeks' duration) lumbar radiculopathy.[1] Low back pain is the leading cause of disability in the world and a major contributor to a wide range of other problems, such as substance misuse and depression.[2] Perhaps the most important distinction to make when categorising low back pain is to distinguish between neuropathic and mechanical causes, because this informs treatment.[2 3] Recent studies show that about a third of patients with chronic low back pain have predominantly neuropathic pain.[3] Sciatica responds better than non-specific low back pain to interventions, but treating any form of low back pain is challenging.

Epidural steroid injections have been used for more than 50 years to treat low back pain and are the most common intervention in pain clinics throughout the world.[4] Yet despite their widespread use, their efficacy is unclear. Of around 35 controlled studies evaluating such injections, slightly more than half show some benefit. Moreover, systematic reviews written by authors who perform epidural steroid injections are more likely to conclude that it is effective than reviews written by those who do not use such injections.[5-7] Reasons for these discrepancies include differences in methodology, treatment characteristics, and perhaps most importantly, patient selection.

Iversen and colleagues' study had three intervention groups, each of which received two injections with a two week interval: subcutaneous sham injections superficial to the sacral hiatus and not into the spinal canal; caudal epidural injections with saline alone; and caudal epidural injections with a combination of saline and triamcinolone acetonide. All groups improved after the intervention, but no significant difference was seen in the primary outcome (as measured by the Oswestry disability index) between the groups over time.

The decision to use a second control group that received epidural saline was a shrewd addition because evidence suggests that the epidural administration of non-steroid solutions may provide benefit.[7] This may be due to the washout of inflammatory cytokines, lysis of scar tissue, and the effects of local anaesthetic. Yet this strategy, designed to distinguish between the effects of perineural steroids and the epidural route itself, is futile if a treatment benefit is not shown, as was the case for Iversen and colleagues' study. A similar study found that epidural steroid injections provided better pain relief than either epidural saline or intramuscular steroids, which in turn were both more effective than intramuscular saline.[8]

How can these differences be explained? Overall, epidural steroid injections seem to be beneficial, but only provide modest improvement in carefully selected patients with predominantly radicular symptoms. There are several potential reasons why Iversen and colleagues' study failed to show a benefit. Firstly, the authors injected steroids via the caudal root, which means that the area(s) they were targeting (for example, L4-S1) were far removed from the site of injection. Although caudal injections can be effective for neuropathic back pain, site targeted injections that deposit the steroid directly over the affected nerve root and into the ventral epidural space (transforaminal injections) are superior.[5] Secondly, part of the effect of caudal epidural steroid injections stems from the large volume injected, which increases the likelihood of spread to the area of pathology, and may itself afford benefit.[9] However, any benefits conferred by this were negated by the combination of the low dose of steroid (40 mg triamcinolone) used and high volume (30 mL), which significantly diluted the steroid bathing the nerve roots. In addition, most studies use a local anaesthetic to break the cycle of pain, increase blood flow to ischaemic nerve roots, and possibly reverse the processes of central sensitisation, but the authors did not do this. A final shortcoming lies in the randomisation, which resulted in the sham group having experienced a significantly shorter duration of pain. Studies conducted in multiple populations with back pain have found an inverse correlation between the duration of symptoms and treatment outcomes.[2 10]

So where do we go from here? After around 35 studies have failed to provide a definitive answer regarding the efficacy of epidural steroid injections, it is unlikely that future trials will do so. This poses a dilemma for researchers designing clinical studies for low back pain. Generally, efficacy studies command stringent inclusion and exclusion criteria (such as short duration of pain, less disease burden), which maximises the chances for pain relief. However, these conditions also increase the likelihood of the control group improving. The placebo response is stronger for pain than for almost any other non-psychiatric medical condition. Whereas the response of the control groups can be reduced by liberalising the selection criteria, the treatment response will invariably also be reduced. More inclusive selection criteria tend to be used for comparative-effectiveness studies because they enhance external validity, but this will in turn reduce the chance of demonstrating efficacy. For a study with relatively liberal selection criteria that used a less effective injection route, Iversen and colleagues' study was probably underpowered.

Despite the negative findings, the current study should not be misinterpreted as suggesting that epidural steroid injections are of no use in neuropathic back pain. Even if only a

small proportion of people return to work[11] or can avoid surgery—as a randomised study performed by spine surgeons found[12]—this suggests that epidural steroid injections may be an effective adjunct when used judiciously.

Although these findings do not provide a definitive answer regarding the effectiveness of epidural steroids, they do fit neatly into an increasingly complex puzzle. In patients with acute or subacute radiculopathy secondary to a herniated disc in whom more conservative measures have failed, epidural steroid injections should be considered as part of a multidisciplinary treatment plan (including exercise and physiotherapy). People with chronic or non-remitting pain, non-radicular pain, and spinal stenosis may also benefit, but the number needed to treat is considerably higher. Fluoroscopy should always be used to ensure proper needle placement, and the transforaminal approach seems to provide better relief than the caudal or conventional interlaminar method.

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Co-prescription of co-trimoxazole and spironolactone in elderly patients

Should be used with caution because of the risk of hyperkalaemia

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Although much effort goes into understanding the risks and benefits of recently licensed drugs, less is known about many of the older drugs that are prescribed widely. For example, the phrase "safe as aspirin" is often used to extol the safety virtues of a drug, even though aspirin is one of the main culprits when it comes to hospital admissions related to an adverse drug event.[1] Spironolactone and trimethoprim-sulfamethoxazole (co-trimoxazole) are two "older" drugs about which we should know more. In the linked case-control study, Antoniou and colleagues assess the risk of admission to hospital for hyperkalaemia in elderly patients treated with co-trimoxazole in combination with spironolactone.[2]

Spironolactone works well in congestive heart failure,[3] resistant hypertension,[4] hyperaldosteronism,[5] and hypertension in general.[6] Despite hypertension being an unlicensed indication in the United Kingdom, the new guidelines from the National Institute for Health and Clinical Excellence (NICE) on hypertension name spironolactone as an option for fourth line treatment.[7] Because of these benefits, the use of spironolactone in the UK and elsewhere has increased greatly over recent years, mainly for the above indications, but also for secondary aldosteronism resulting from cirrhotic liver disease.[8]

The down side of spironolactone is the risk of hyperkalaemia, which is increased in older people; those with renal impairment, diabetes, or a high pretreatment serum potassium; and when it is co-administered with potassium supplements and drugs that reduce potassium excretion. Hyperkalaemia with spironolactone has been reported in patients with congestive heart failure,[9] but this has not been a major problem in the UK because of the cautious prescribing and frequent monitoring of renal function within the NHS.[8] The more selective aldosterone antagonist, eplerenone, may be less toxic than spironolactone, but it is also less effective, at least in patients with hypertension and aldosteronism.[10]

In Canada, co-trimoxazole is the most commonly prescribed antibiotic for urinary tract infection. This is unlike the UK, where the use of co-trimoxazole is restricted because of concerns about serious cutaneous adverse reactions and blood dyscrasias. In the UK, trimethoprim, a component of co-trimoxazole, is much more commonly used for this indication. Hyperkalaemia is also a risk with co-trimoxazole, probably because of the potassium sparing action of trimethoprim.

Given the benefits and potential for toxicity with spironolactone and trimethoprim or co-trimoxazole, any new data that will inform the risk-benefit balance of these drugs are welcome. Antoniou and colleagues' study shows an important adverse pharmacodynamic interaction between co-trimoxazole and spironolactone in elderly patients that can lead to hospital admission for hyperkalaemia—a relatively "hard" biochemical end point. There was also a smaller risk of hyperkalaemia with co-prescription of nitrofurantoin. The same authors have previously reported serious hyperkalaemia associated with co-prescription of co-trimoxazole and angiotensin converting enzyme inhibitors or angiotensin receptor blockers (adjusted odds ratio 6.7, 95% confidence interval 4.5 to 10.0), which is thought to be caused by a similar pharmacodynamic interaction.[11]

In the current study, Antoniou and colleagues reported that patients taking spironolactone and co-trimoxazole were about 12 times more likely to be admitted to hospital for hyperkalaemia (12.4, 7.1 to 21.6) than those taking spironolactone with amoxicillin.[2] The risks of co-trimoxazole were also dose related. The population attributable fraction suggests that

around 60% of admissions to hospital for hyperkalaemia in elderly patients taking spironolactone and an antibiotic for a urinary tract infection could be avoided if co-trimoxazole was not co-prescribed with spironolactone.

As with all observational studies, various factors might confound the outcomes of interest because of the co-linearity of some variables in the study. However, the greatly increased risk (around 12-fold) suggests that minor problems with data adjustments would not have changed the overall finding of an increased risk of hyperkalaemia for co-prescribing co-trimoxazole and spironolactone.

To set the results in a UK context, trimethoprim is prescribed to about 60 per 1000 of the UK population each year, co-trimoxazole to 0.8 per 1000, nitrofurantoin to 18 per 1000, and spironolactone to 7 per 1000 (data for 2010 from the MEMO database[12]). The co-prescription of spironolactone with trimethoprim is therefore likely to occur infrequently but is set to increase as spironolactone is used more often and broad spectrum antibiotics for urinary tract infection are avoided to mitigate the development of *Clostridium difficile* colitis.

We need to know if trimethoprim alone will cause a similar adverse drug interaction as co-trimoxazole (as seems likely), whether these risks extend to younger people, and whether other factors increase the risks. So, as always, more research is needed. In the interim, a cautious approach is needed and the use of alternative antibiotics should be considered where appropriate. Monitoring for hyperkalaemia should be increased, and temporarily reducing the dose of spironolactone or angiotensin converting enzyme inhibitors or angiotensin receptor blockers might be useful in patients receiving these drugs in combination with trimethoprim, co-trimoxazole, or even (until further data are available) nitrofurantoin.

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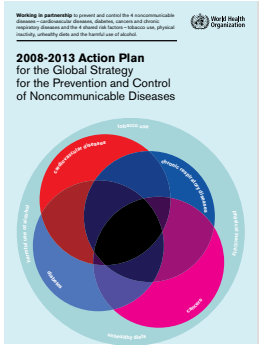
UN meeting for non-communicable diseases

Long term commitment within countries is needed, with support from global development partners and strong leadership from the UN



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On 19-20 September 2011, the United Nations will host a general assembly high level meeting on the control and prevention of non-communicable disease (NCD). Although the meeting will be held in New York, the eyes of developing country leaders, decision makers, civil society groups, industry, non-governmental organisations, and researchers will be focused on the event and its outcomes. Previous UN summits have provided the catalyst for change. The summit on HIV/AIDS in 2001 resulted in substantial funding and political commitments.[1]

The UN meeting is a crucial moment. This is especially true because it developed in the shadow of global efforts to achieve the millennium development goals, which do not include NCD. NCD is by far the largest killer on the planet and has continued to advance in low and middle income countries, so that the cause of 63% of all global deaths receives less than 3% of international development assistance for health.[2] About 80% of deaths caused by NCD occur in developing countries and generally in a younger population than in high income countries.[3 4] Over the next 10 years, the World Health Organization predicts that deaths from NCD will increase by 17% globally, with the greatest increases in the African (27%) and the Eastern Mediterranean (25%) regions. In terms of the highest absolute number of deaths, the Western Pacific and South East Asian regions are projected to lead the field.[1] Because of the scope of the problem, predicted economic impact, and general lack of preparedness to tackle it in many countries, health ministers from low and middle income countries have been the major catalyst for the meeting.

As we head into the final days before the meeting, there is much wrangling over the outcomes document, particularly over targets and resources, and some fear that if world leaders do not turn up with open minds and potentially open chequebooks that NCD might drop off the agenda for 10 years, especially with such tough economic times in so many high income countries. However, it seems unlikely that NCD will disappear from the global health agenda now. Whatever happens at the UN meeting, it has led to the creation of the NCD Alliance and has begun to increase public consciousness about these diseases.

Some claim that NCD may be one of the greatest hindrances to development and alleviation of poverty.[3 5] In that light the UN should learn from the models of AIDS and tobacco control. Perhaps the central message that must emerge from the UN meeting is that a "whole of government and whole of society" approach is needed to tackle NCD.[6]

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Only limited progress can be made if action is expected only from within the health system. This is an important message for low and middle income countries. We need to prepare national plans and create partnerships with all stakeholders and emphasise the importance of public health measures beyond the service provision level; we also need to look beyond health policy and include urban planning, agriculture, taxes, indoor air pollution, trade, finance, public transportation, civil society, education, and more. Recommendations for food and agriculture sectors to work on NCD are emerging along with the UN meeting.[7]

WHO needs to act as the conductor of the UN family and bring together the Food and Agriculture Organization (vital if agriculture is to be transformed to tackle undernutrition and overnutrition better); UN Habitat (to build urban design into its work with a focus on restoring mobility, and safe walking and cycling into everyday lives); Unicef (to use its powerful Convention on the Rights of the Child to tackle many aspects of NCD and move beyond a sole focus on health matters that affect survival in under 5 year olds); the World Bank and International Monetary Fund to ensure that fiscal policy and development finance support NCD goals, and more. The model for this leadership comes to us from tobacco prevention through the Ad Hoc Committee of the UN Economic and Social Council.

Although our governments might need technical help for some of the needed steps, they can also identify focal points for NCDs at the national level, along the model of national tobacco control programmes. Considering the burden of disease for NCDs, a heart disease focal point or a diabetes focal point should not be considered out of the question. Physical activity is another area that may require a focal point to build it into health prevention among adults and into health education for children, as well as planning for safe places to engage in sport or even pavements for safe walking.

Outside of the UN meeting there must be a global commitment, a global partnership, and a global plan, preferably with targets and some resources such as the Stop NCDs Partnership.[8] The encouragement of global support for research and networks must continue to build so that we can figure out what works and how to apply it across settings. The United Health-National Heart, Lung and Blood Institute Centers of Excellence network is a comparably small but important example of how research can be funded and capacity can be built across developing countries, but these 11 centres alone cannot reach every country and population that is in need.

In addition to leadership at the UN and national levels, technical support from WHO, the World Bank, and other UN bodies will be needed, along with the provision of more resources for NCDs; not just financial resources, but also investment in knowledge generation, synthesis, and translation. Experts need to be available to help countries with implementing situation assessments of burden, policy, and programmes that may already exist; planning; developing multisectoral approaches and interventions; and training field workers even for deceptively simple tasks like conducting a WHO-STEPS survey.

The strengthening of health systems, although necessary, will not be a sufficient solution for this pressing development problem. Long term commitment within countries is needed now to create change, and countries should demand technical support and financing from global development partners along with strong leadership from the UN.

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UN's dietary policies to prevent cardiovascular disease

Modest diet changes could halve the global burden

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On 19 September 2011, the United Nations General Assembly convenes a landmark high level meeting on non-communicable diseases. Cardiovascular disease will be high on the agenda. The potential health and financial benefits of cardiovascular disease prevention are astonishing. Each year, cardiovascular disease kills about 20 million people, including 10 million prematurely (before age 65 years) and inflicts high morbidity, disability, and socioeconomic costs.[1] In high income countries, preventing or postponing 100 cases saves about $1m (£0.6m; €0.7).[2]

The relative socioeconomic savings of prevention are even higher in low and middle income countries, in which cardiovascular disease strikes at younger ages and there are fewer resources for care; this results in familial burdens, lost productivity, and cyclical escalation of poverty, which in turn contributes to cardiovascular disease.[1]

Diet is a powerful common determinant of cardiovascular disease, obesity, diabetes, and several cancers.[3-6] Natural experiments have shown rapid reductions in cardiovascular disease after dietary improvements in populations.[7] Unfortunately, both the optimal dietary targets and evidence based interventions to achieve them have been unclear for decades. Numerous arrays of specific nutritional factors have been considered over time. This has caused confusion and often misguided dietary priorities. These challenges, compounded by resistance and misdirection by industry, have to date produced a relative dearth of effective dietary policies.

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Recent scientific advances allow eight dietary targets to be prioritised for the prevention of cardiovascular disease (fruits, vegetables, whole grains, nuts, vegetable oils, seafood, omega-3 fatty acids, sodium, and industrial trans fats; see web table).[4 5] Six are aimed at increasing consumption of healthy foods and two at limiting specific harmful nutrients. The proposed targeted changes are modest, reflect changes achieved in population based interventions, and are supported by observed consumption distributions within and across countries. Meeting any one target would produce substantial benefits. The eight targets together could halve global cardiovascular disease, annually preventing more than five million premature deaths from cardiovascular disease (and 10 million deaths from cardiovascular disease overall), while simultaneously reducing obesity, diabetes, and common cancers.[4 5] Over just a few years, these modest dietary improvements could prevent one million deaths from cardiovascular disease in the US and 30 million worldwide (table).

New policy research also allows prioritisation of specific interventions, optimally as multicomponent strategies.[2 8-10] These include pricing policies to subsidise healthier foods and drinks and tax less healthy ones, as well as long term agricultural-government strategies to promote the infrastructure needed for the production, transportation, and marketing of healthier foods. Salt and industrial trans fat content should be limited by direct restrictions that drive product reformulations, and strict guidelines should govern marketing of foods and drinks to children. In addition, sustained and focused media and education campaigns should encourage specific healthy foods, and mandatory product and menu labelling—with an emphasis on the appropriate dietary priorities above—should also stimulate product reformulations. Neighbourhood design and policy should increase the availability of local markets that provide healthier food. Workplaces should incorporate healthier food options in cafeterias and vending machines and have comprehensive wellness programmes with a strong dietary focus. School based interventions should incorporate dietary curriculums, training for teachers, parental and family components, supportive school policies, and the availability of healthy food and drink.

Inevitably, most evidence for the effectiveness of these strategies comes from high and middle income, rather than low income, countries.[2 8-10] Nonetheless, although absolute rates vary across populations, the relative impact of major cardiovascular risk factors is shared across nations.[11] Similarly, the relative benefits of these population strategies will inform policy priorities across many nations.

Drug based and hospital based prevention approaches that target those at highest risk reduce cardiovascular disease but can be relatively costly, which limits their applicability and sustainability in many countries. In contrast, modest population-wide behavioural changes can produce larger benefits.[12] Effective population-wide prevention programmes are generally highly cost effective or even cost saving.[2 8-10] One analysis estimated nearly $6 return per $1 spent on population approaches to improve nutrition and other health behaviours.[2] Recent modelling studies showed net cost savings with any population-wide interventions that achieved even modest reductions in cardiovascular risk.[2 8 10]

The specific dietary priorities and applicable population level interventions are clear, providing a road map for governments to prevent cardiovascular disease. The UN must provide clear leadership to prioritise these dietary targets and policies across multiple stakeholders representing economic (for example, the World Bank), agricultural (for example, Food and Agriculture Organization), and health (for example, World Health Organization) domains. Comprehensive initiatives in member countries should complement this global strategy and tackle region specific gaps and priorities. New strategic initiatives must translate this evidence into political action, bringing together policymakers, researchers, political scientists, economists, advocacy groups, and other stakeholders. Efforts should be supported by recruitment of legislative champions, public awareness campaigns to garner momentum for policy improvements, and development of public-private partnerships focused on population health rather than profit margins alone.

None of the available evidence is flawless. However, imperfect evidence does not condone inaction, as painfully learnt from decades of delays in tobacco control. For any public health intervention, probabilities of benefits and risks must be balanced. The overall scientific rationale for prioritising these dietary targets and specific population-wide strategies is now sufficient.

The UN meeting offers a unique opportunity to review and set these priorities, share best practices, and coordinate global polices. Currently disparate organisations can become natural allies with shared dietary goals for preventing chronic non-communicable diseases. Preparatory work has identified the powerful logic of realigning all such organisations around diet and other major lifestyle behaviours. An internationally coordinated and promoted initiative to improve these dietary targets would powerfully reduce the risk of cardiovascular disease and promote public and economic health. The Framework Convention on Tobacco Control was a major global health achievement, and the UN and member countries could do even better with diet.

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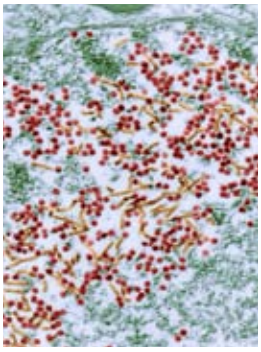
Infection with polyomavirus JC

Is highly prevalent, and can be fatal in immunocompromised people



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The recent discovery of new neurological syndromes that result from neuronal infection with polyomavirus JC, also known as JC virus, and the presence of this virus in the grey matter are currently under debate.[1] It has been suggested that JC virus is associated with cognitive decline, dementia, strokes, and brain tumours,[2] and this hypothesis has been commented on in the *BMJ*.[3]

JC virus is a causal agent implicated in a rare but often fatal infection known as progressive multifocale leucoencephalopathy (PML).[4] JC virus was first isolated in 1971 from the brain of a patient with PML; JC are the patient's initials.[5]

PML is a demyelinating disease of the central nervous system that results from lytic JC virus infection of glial cells in immunosuppressed patients.[1] It was first described as a complication of immune suppression 50 years ago and emerged as a major complication of HIV infection in the 1980s.[6] PML has recently become topical because it is a side effect of some newly developed immunomodulatory drugs for autoimmune diseases, including natalizumab for multiple sclerosis and Crohn's disease, rituximab for systemic lupus erythematosus, and efalizumab for psoriasis.[1 4 6] PML has had a dramatic effect on the use of these drugs—efalizumab was withdrawn from the market in April 2009 and natalizumab was transiently withdrawn in February 2005 after three confirmed cases of PML.[7]

New neurological disorders—including granule cell neuropathy, encephalopathy, and meningitis—have also been recently attributed to JC virus,[1] and the virus has also been associated with some tumours.[8]

JC virus is one of the most prevalent viruses worldwide, and the seroprevalence in healthy people ranges from 50% to 86%.[1 9] Aerosol inhalation and ingestion of contaminated water or food have been suggested as major modes of human transmission.[10] After asymptomatic primary infection, which occurs in childhood, the virus remains quiescent (latent state) in the kidney, bone marrow, lymphoid tissues, and tonsils.[1 4] Recent studies suggest that the virus can remain latent in the brains of healthy people.[11]

Asymptomatic reactivation of latent JC virus is common in immunocompetent people, and the virus can be detected in the urine of about 30% of healthy people.[7] In people who are immunosuppressed, JC virus can reactivate and cause PML. The proportion of people affected depends on the underlying pathology and the treatment. Before the advent of combined antiretroviral therapy, PML developed in 3-7% of HIV infected patients. With current treatments the frequency has decreased to 0.07% per person year of follow-up.[10] In patients with multiple sclerosis, the risk of developing PML is now 1.56 cases per 1000 patients with 25-36 infusions of natalizumab.[1]

PML usually presents insidiously with focal neurological deficits that vary according to the location of the lesion[10] and include muscle weakness, sensory deficits, hemianopsia, cognitive dysfunction, aphasia, and problems with coordination and gait.[1]

PML is normally diagnosed on the basis of distinguishing neurological features at presentation, characteristic changes on brain magnetic resonance imaging, and the presence of JC virus DNA in cerebrospinal fluid. Histologically, the brain shows multiple areas of demyelination caused by productive lytic infection of oligodendrocytes with JC virus. Gliosis and giant multinucleated astrocytes may be seen.[1 10]

Even though survival has increased over the past 10 years, the prognosis remains poor. PML has a three month mortality rate of 20-50%, so prompt intervention is essential.[10 12] Unfortunately, there is no specific antiviral drug against JC virus. The current treatment goal is to restore the patient's adaptive immune response.[1] Antiretroviral treatment is started immediately in HIV infected patients,[10] and immunosuppressive drugs are reduced if possible in recipients of organ transplants.[1] Nevertheless, rapid improvement in immune function may be associated with clinical worsening, a phenomenon known as immune reconstitution inflammatory syndrome.[1 10] This syndrome accounts for up to 23% of PML cases diagnosed in HIV positive patients. The frequency of this syndrome in other populations has yet to be established.[1]

Moreover, PML has occasionally been diagnosed in patients without apparent immunosuppression.[13] Thus, to develop efficient therapeutic strategies a better understanding of the immune control of JC virus is needed. Many important aspects of JC virus biology and its pathogenesis, including the site of latency and the mechanisms and site of reactivation, are still unclear. This is crucial because of the absence of specific antiviral drugs. The pathogenesis of the association between PML and monoclonal antibody treatments is also unclear.[14] Methods are needed to help identify patients at higher risk of PML.

One important biological question is the relation between the two genetic variants of JC virus.[4] One variant is found in the urine of healthy and immunocompromised people, whereas the other is most often isolated from the cerebrospinal fluid and brain tissue of patients with PML.[1 4] Understanding the mechanism of JC virus transformation from one form to the other is crucial and might have therapeutic implications.[4]

Future research is needed to understand the biology of JC virus and host immune responses, and subsequently to develop predictive markers to identify patients at risk of PML, new treatments, and reliable methods of monitoring therapeutic response.

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