education

FROM THE JOURNALS Edited highlights of weekly research reviews

Migraine infusiasm

You never have to wait too long for a trial of a new drug for migraine. The latest one is Lu AG09222, a monoclonal antibody to pituitary adenylate cyclase-activating polypeptide (PACAP). The phase 2 trial recruited adults with migraine with an average of 16.7 migraine days per month and for whom two to four preventive treatments had failed. Those given a single infusion of Lu AG09222 750 mg had an average of 6.2 fewer migraine days over the following month, compared with 4.2 fewer in the placebo group (a between-group difference of two days (95% confidence interval −3.8 to −0.3)). With this positive phase 2 result, it's time for Lu AG09222 to PACAP its bags and go to phase 3.

N Engl J Med doi:10.1056/NEJMoa2314577

Keeping viruses ticking over

Infectious disease specialists like to keep fit by lifting heavy parcels of Lyme disease vectors—it might sound odd, but it's just a tick box exercise. But ticks don't just carry the dreaded *Borrelia burgdorferi*, they've also been found to carry the newly coined "wetland virus."

The *New England Journal of Medicine* reports the virus was found in 17 patients in hospitals in north eastern China and was associated with non-specific symptoms including fever, headache, malaise, and myalgia. Wetland virus belongs to the Orthonairovirus genus in the Nairoviridae family—which includes various viruses that can infect humans and other animals through arthropod vectors.

N Engl J Med doi:10.1056/NEJMoa2313722

Triple whammy for blood pressure

I can see the appeal of an antihypertensive that contains low doses of three medications over taking doses of a single drug: leg swelling with 10 mg amlodipine seems so common the tablets should come with a free shoe horn. An open-label randomised controlled trial in Nigeria recruited 300 people with hypertension and blood pressure ≥140/90 mm Hg who were receiving either one antihypertensive medication or none at all. The researchers found that those allocated to a protocol that began with a three-in-one pill containing low dose telmisartan, amlodipine, and indapamide had slightly better blood pressure after six months than those who were treated according to national guidelines (amlodipine 5 mg).

More real-world data would be helpful, particularly given the large reduction in blood pressure seen in both arms of the study (systolic blood pressure was, on average, 31 mm Hg lower and 26 mm Hg lower in the respective groups, from a baseline of 156/97) and low rates of adverse events (none of the trial participants stopped any medications due to adverse events).

JAMA doi:10.1001/jama.2024.18080

GLP1 receptor antagonists and risk of suicide death

Case reports submitted to the US Food and Drug Administration and European Medicines Agency have raised concerns about glucagon-like peptide-1 (GLP-1) receptor antagonists, such as semaglutide and liraglutide, and risk of suicide. A post-hoc analysis of the STEP 1, 2, 3, and 5 trials (looks like they missed a step) has found no important worsening of patient health questionnaire-9 (PHQ9) scores during treatment with semaglutide compared with when they enrolled on the trial or with placebo. However, the trials excluded anyone who had ever made a suicide attempt, was currently at high risk of suicide, or was recently diagnosed with major depressive disorder. Participants were also a remarkably happy bunch, with a mean PHQ9 score of around 2.

JAMA Intern Med doi:10.1001/jamainternmed.2024.4346

Trying the cohort approach

So, if the STEP trials don't tell us whether GLP-1 receptor antagonists are safe in people with pre-existing mental health problems, perhaps a large cohort study using nationwide datasets will? This one in *JAMA Internal Medicine* used an active comparator design to compare rates of suicide death in new users of semaglutide and liraglutide with new users of sodium-glucose cotransporter-2 (SGLT2) inhibitors in Denmark and Sweden between 2013 and 2021.

The authors found that suicide death in people starting GLP-1 receptor antagonists had a weighted incidence rate of 0.23 per 100 000 patient years compared with 0.18 for SGLT2 inhibitors, giving a hazard ratio of 1.25 (95% CI 0.83 to 1.88). Low rates of suicide mean the study lacked the power to detect small differences in suicide death, and the study didn't capture suicide attempts, self harm, or symptoms of depression or anxiety. A linked editorial to these two studies of GLP-1 receptor antagonists concludes that they are pieces of a still incomplete puzzle.

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Bisphosphonates

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Practical Prescribing is a series produced in conjunction with the *Drug and Therapeutics Bulletin* to highlight important issues for prescribers to consider and prompts for shared decision making between prescribers, patients, and their carers. Targeted at all medical and non-medical prescribers, particularly doctors in training, the series covers medicines commonly prescribed in primary and secondary care.

0.5 HOURS

See learning.bmj.com for linked learning module

A 70 year old white woman presented to her general practitioner for her annual check-up. She weighs 62 kg and is 164 cm tall. She is a tobacco user (20 pack-year) with prior wrist fracture three years ago after a fall on ice. Dietary history revealed low calcium intake, and she does not take vitamin D supplements. Her mother had a hip fracture at age 74 years. Given these risk factors, you order a bone density scan (DEXA), which shows a femoral neck T-score of −2.6. A fracture risk assessment tool (FRAX) estimates she has a 10-year hip fracture risk of 18% with 10-year major fracture risk of 36%. You consider prescribing a bisphosphonate.

How often are bisphosphonates prescribed and how do they work?

From February 2023 to January 2024, UK primary care data for England showed that about 6.2 million prescriptions for oral bisphosphonates (alendronate or risedronate) were made.[1] Almost all patients who are treated for postmenopausal osteoporosis are prescribed oral bisphosphonates,[2] and in a review of nearly half a million treated patients with osteoporosis from seven European countries, 84% were prescribed bisphosphonates.[3] There are four licensed preparations commonly available worldwide, alendronate, risedronate, ibandronate, and zoledronate (zoledronic acid).

Bisphosphonates have been introduced for a range of additional indications including Paget disease of bone, prevention of skeletal-related events in advanced malignancies, hypercalcaemia of malignancy, and osteoporosis in men. Secondary care guidelines also recommend bisphosphonate use in patients taking chronic glucocorticoid therapies or with oncology-related conditions such as osteolytic metastases.[7 8]

Taken orally, bisphosphonate bioavailability is low (about 1%), and even lower if taken within 30-60 minutes of food intake.[9] After administration, bisphosphonates are incorporated into the crystalline mineral structure of bone, particularly at sites of active resorption. The drug is then taken up by the osteoclast (bone-resorbing) cell where it inhibits an enzyme, farnesyl pyrophosphate synthase, essential to osteoclast survival and function. Consequently, osteoclast activity is inhibited, and bone resorption is reduced.[10] Despite their low oral bioavailability, bisphosphonates have proved effective at reducing bone loss and thereby maintaining bone density.

WHAT YOU NEED TO KNOW

- For patients with osteoporosis, assess patient eligibility for treatment with bisphosphonate therapy by using a fracture risk assessment tool
- Oral therapy should be taken on an empty stomach with high adherence
- Check renal function prior to prescribing intravenous therapy
- Treat for at least five years (oral) or three years (annual intravenous) before consideration of hiatus
- A shared decision making approach is highly valued by patients who are considering treatment

What should I discuss with patients before starting treatment?

Ask the patient about previous bisphosphonate use. If they have previously taken a bisphosphonate, review the indication, the effects of taking the medication, any adverse effects, and the reason it was stopped. Discuss the purpose of treatment, anticipated magnitude of effectiveness and potential benefits, mode of administration, duration of therapy, and potential risks of bisphosphonate therapy. Also discuss alternative options and the anticipated risks of doing nothing.

When prescribed in primary care, the primary purpose of bisphosphonates is to prevent fractures in disease processes that lead to osteoporosis. The major trials used for the regulatory approval of bisphosphonates evaluated anti-fracture efficacy of three to five years of continuous therapy with oral bisphosphonates in postmenopausal osteoporosis,[11 12] and three years of therapy with intravenous zoledronate in postmenopausal women with osteoporosis.[13] These data demonstrated reductions in both vertebral and non-vertebral fractures, beginning approximately one year after treatment initiation. A 2019 network meta-analysis including 26 studies of bisphosphonates versus calcium, vitamin D, or placebo suggested that bisphosphonates reduce the relative risk of any non-vertebral osteoporotic fracture by approximately 20% (95% confidence interval 10% to 30%), and the relative risks of vertebral and hip fractures by about 40% and 30%, respectively.[14] Among women with a major fracture risk (on FRAX fracture risk assessment tool) of ≥20%, 33 need to be treated with bisphosphonates for three years to prevent one osteoporotic fracture.[6]

Personalise the anticipated risk reduction to the patient's absolute 10 year fracture risk, using positive and negative framing (that is, present both the likelihood of not having a fracture and the likelihood of having a fracture), and provide a visual depiction of risk.[19] For some patients, it may be helpful to discuss the role of non-prescription strategies such as calcium and vitamin D supplementation[20] and exercise to reduce falls,[21] though these strategies should not be viewed as equal alternatives to medications for fracture prevention.

Where possible, provide this information within the context of shared decision making, potentially using patient oriented decision aids.[22] Bisphosphonates cannot prevent all fractures, and so a single fracture occurring within one year of regular use does not imply therapy failure. However, patients may see it as a failure, and a drop in continued adherence may be avoided by a pre-emptive discussion about therapy purpose and expectations.

Compared with newer parenteral drugs for fracture prevention, such as denosumab, once-weekly oral bisphosphonate therapy is usually the least expensive option. However, once-yearly intravenous infusion of bisphosphonate may be more convenient and thereby enhance long term persistence. A recent randomised controlled trial in postmenopausal women showed that intravenous zoledronic therapy every 18 months was still effective in reducing fractures by 37%.[25] Parenteral bisphosphonate may be suitable for patients with malabsorption or intolerance to oral formulations. The optimal duration of therapy remains controversial, with some guidelines recommending 3-6 years[6] and others saying up to 10 years is acceptable.[5] Counsel patients about the expected duration of treatment and the importance of having a scheduled visit at the end of that time to discuss a drug hiatus.

What are the important adverse events to discuss?

Oral bisphosphonates may cause upper gastrointestinal side effects such as nausea, reflux, or oesophagitis; these are common reasons for discontinuation, affecting about 7% of patients in a retrospective study of over 5000 users.[26] However, a case-control study of bisphosphonate users versus non-users showed that use was not associated with increased risk for hospitalisation due to serious upper gastrointestinal events such as oesophageal ulcer or bleeding.[27] Oral bisphosphonates should be avoided in patients with oesophageal disorders or hypocalcaemia, or if they are unable to follow the dosing requirements (that is, remain upright for at least 30-60 minutes after treatment).

Intravenous bisphosphonate therapy can cause cytokine mediated acute phase reactions, manifesting as low grade fever, myalgia, and arthralgia, usually within 24-72 hours of infusion. This was demonstrated in one third of patients after their first infusion in a trial of over 3000 recipients.[13] Symptoms typically last two to three days and decrease in frequency and severity with subsequent infusions.

Less commonly, intravenous bisphosphonates may be associated with transient, mild hypocalcaemia in patients with vitamin D deficiency. Therefore, these patients should receive calcium and vitamin D supplements in accordance with guideline recommendations.[5] If severe vitamin D deficiency is suspected or discovered, this must be corrected with therapeutic doses of vitamin D before bisphosphonate treatment. Other uncommon but treatment-interrupting side effects of oral and intravenous therapy include musculoskeletal pain (bone, joint, and/or muscle pain, 5%), ocular side effects (pain, blurred vision, conjunctivitis, uveitis, and scleritis, ~1%).[28]

Bisphosphonates are not recommended for use in patients with creatinine clearance <30 mL/min. Safety among patients with less severe renal impairment remains unknown and has been difficult to assess in the context of comorbidities and varying degree of chronic kidney disease.[29 30] Before starting oral bisphosphonate and before each infusion of zoledronic acid, in our practice we check patients' creatinine and calcium levels and ensure adequate oral hydration.

Osteonecrosis of the jaw is a rare complication of bisphosphonates,[31] characterised by pain, swelling, exposed bone, and local infection. The estimated risk is about 1-6 per 10 000 person-years in those taking oral bisphosphonates for osteoporosis.[32] Risk factors include cancer and anticancer therapy, high dose and long duration of exposure to bisphosphonates, substantial dental work (extractions, implants, dentures), taking glucocorticoids, smoking, diabetes, and pre-existing dental disease.[32] If osteonecrosis of the jaw occurs, discontinue therapy.[33]

Atypical femur fracture is another rare complication of bisphosphonate use.[34] Estimated risk is 3-50 cases per 100 000 person-years, although risk increases with longer duration of therapy (for example, beyond three to five years of use, up to 100 cases per 100 000 person-years).[35] Other risk factors include glucocorticoid use for more than a year, shorter stature, overweight, and East Asian ethnicity.[36] Atypical femur fractures develop over time and typically present as dull or aching pain in the groin or thigh. In our practice, we recommend an x ray for patients with new onset groin or thigh pain who have been taking bisphosphonates for more than three years. If signs of atypical femur fracture are confirmed, stop bisphosphonate therapy and seek urgent orthopaedic and/or bone specialist consultation.

Given their potential teratogenicity and placental permeability, bisphosphonates are not recommended without specialist input in women who are pregnant or who could become pregnant.

What to consider when prescribing?

Using bisphosphonate therapy to delay or prevent fractures requires continuous drug exposure and adherence to medication long term. Observational data indicate there may be minimal clinical fracture reduction unless long term medication adherence exceeds

60-70%.[37] In addition, a time-to-benefit meta-analysis of clinical trial data showed that a treatment duration of >12 months was required to observe any reduction in clinical fractures.[38] Together, these suggest that maximal benefit will be achieved in those who take the medication regularly for at least one year. With advanced age, many patients may accumulate multimorbid conditions, which may function as real or perceived barriers to bisphosphonate treatment. At the same time, real-world data show that the presence of multiple chronic conditions or recurrent hospitalisations identify patients at 30-50% higher risk of fracture than predicted by models, and so the decision to treat or defer therapy must be weighed carefully.[39]

What should I monitor during the prescription?

Many patients like to have bone mineral density (via DEXA scan) and bone turnover markers (such as the bone resorption marker C-telopeptide) monitored during therapy to provide an indication of effect. However, there is little evidence that routine measurement of these reduces fracture incidence or corresponds with individual drug effect.[41] This can leave physicians in the challenging situation of balancing patient preferences for monitoring versus evidence based allocation of resources. While there is no clear consensus, monitoring recommendations published by the UK National Osteoporosis Guidelines Group and the International Osteoporosis Foundation acknowledge the limited utility of serial DEXA scans during treatment, advocating instead for clinical review and fracture risk re-evaluation (with or without DEXA) after three to five years of therapy.[5 42]

What other concerns might my patient have while on treatment?

Deciding, implementing, and monitoring a comprehensive osteoporosis treatment plan can be overwhelming for patients, particularly those with multiple comorbidities. Clinicians can mitigate this by offering patients a collaborative approach, in which they feel supported in all aspects of the decision making process. Optimise the support and experience for patients using a patient-family approach, including, where available, support by a physician, nurse, pharmacist, dietitian, exercise therapist, and dentist. Before starting treatment, ask patients about their preferences and values, and provide them with the information they require to make autonomous decisions in the context of their comorbidities and lifestyle. Time is a limiting factor to incorporating any new lifestyle change, including the addition of taking a bisphosphonate. When something new is added into one's daily routine, something else is to be deleted.

Changes in bone mass and bone quality are asymptomatic, and the effects of bisphosphonates will not be subjectively sensed, nor are they expected to ameliorate physical symptoms such as pain. It may be helpful to explain the difference between osteoporosis and osteoarthritis to ensure appropriate treatment expectations.

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

An osteoporosis patient partner from our Osteoporosis Self-Consult Program (shared decision making program), Elaine Skulsky, is coauthor of the manuscript. Invited to review the article and contribute a patient perspective, she emphasised the importance of shared decision making with patients and additional concerns patients may raise with respect to initiating therapy.

EDUCATION INTO PRACTICE

- How do you estimate baseline fracture risk in an older-aged individual?
- Think about the last time you prescribed bisphosphonate therapy. When did you reassess the patient, and how did you encourage long term adherence?

When should I stop the prescription?

A controlled extension study of the pivotal registration trial for alendronate indicated that continuing this agent for a total of 10 years is associated with a cumulative clinical vertebral fracture incidence of 2.4%, compared with 5.3% among those who transition from alendronate to placebo after five years.[43] Similarly, six years of continuous intravenous zoledronate was associated with reduced incidence of x ray detected (but not clinical) vertebral fractures compared with three years of therapy (x ray fracture incidence 3.0% *v* 6.2%, odds ratio 0.51 (95% CI 0.26 to 0.95).[44]

While some high risk individuals may benefit from a longer duration therapy, the most substantial benefits are demonstrated in the first three to five years, and enthusiasm for long term therapy (>5 years) has been tempered by concern about the rare but serious side effects of osteonecrosis of the jaw and atypical femoral fractures. While the risk of osteonecrosis of the jaw does not seem to increase substantially with duration of therapy,[33] the likelihood of experiencing an atypical femoral fracture does increase with continuous bisphosphonate use, although the absolute risk remains low and drops substantially within a year of treatment cessation.[45]

Our practice is to prescribe oral bisphosphonates for a duration of five years and intravenous bisphosphonates for a duration of three years for most patients. As bisphosphonates have a long half life in bone and can maintain bone mass and possibly provide some residual anti-fracture effect for months to years after treatment cessation,[43] we consider interrupting treatment ("drug holiday") after completing a course of therapy.

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STATE OF THE ART REVIEW

Evaluation and management of hypertensive emergency

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State of the Art Reviews are commissioned on the basis of their relevance to academics and specialists in the US and internationally. For this reason they are written predominantly by US authors.

Hypertensive emergencies are defined by accelerated and severe elevations of blood pressure associated with acute organ injury and have high morbidity. While no uniform threshold exists, blood pressure elevations typically exceed 180 mm Hg systolic and/or 110 mm Hg diastolic. Hypertensive disorders of pregnancy, for which a recent state of the art review was published,[1] are not covered in this review.

Sources and selection criteria

We searched Medline, Embase, and Google Scholar databases for studies published between November 2008 and October 2023 for synonyms of hypertensive emergency and related disorders, including "malignant hypertension," "hypertensive crisis," "hypertensive urgency," "accelerated hypertension," and "hypertensive encephalopathy." When original research was lacking, we also assessed relevant professional guidelines.

Epidemiology

Hypertension affects nearly 1.3 billion people worldwide, of whom as few as 20% have adequate control.[2] In the ambulatory and hospital settings, it is common to evaluate patients with hypertensive crisis, yet the diagnosis of hypertensive emergency is rare.

Men account for a modestly higher proportion of cases of hypertensive emergency than women (52.5% *v* 47.5%) and have a lower mean age on presentation (55 years *v* 62 years).[6] Black patients account for the highest proportion of admissions for hypertensive emergency (42.6%) compared with white (40.1%) or Hispanic (11.3%) patients.

WHAT YOU NEED TO KNOW

- Hypertensive emergencies cause substantial morbidity and mortality, particularly when acute organ injury is present
- While the selection of specific antihypertensive medications varies little across different forms of hypertensive emergencies, the intensity of blood pressure reduction differs substantially
- Treatment hinges on balancing the positive effects of lowering blood pressure with the potential for organ hypoperfusion in patients with altered autoregulatory mechanisms

Risk factors for hypertensive crisis

Risk factors for hypertensive crisis include chronic kidney disease, renovascular hypertension, coronary artery disease, heart failure, stroke, alcohol use, and recreational drug use.[8] Hypertensive emergencies are associated with comorbid diabetes, hyperlipidaemia, and chronic kidney disease. Rare conditions such as pheochromocytoma or inflammatory vascular disease can also lead to hypertensive crisis.

Classification of hypertensive emergency

Hypertensive emergencies are defined as having evidence of new or substantially worsening organ injury and commonly occur with blood pressure levels above 220/110 mm Hg.[4 12-14] Hypertensive emergencies may occur with lower blood pressures in the setting of an accelerated rise from low baseline blood pressure levels. It is important to differentiate hypertensive emergencies from longstanding, poorly controlled, but asymptomatic and clinically stable elevations in blood pressure. It is also key to differentiate this diagnosis from transient reactive elevations in blood pressure, such as can occur with severe white coat effect, pain, anxiety/stress responses, and exaggerated exercise-induced elevations.

Acute end-organ injury occurs primarily in the cerebrovascular, cardiovascular, ophthalmologic, haematologic, and renal systems.[15 16] Without evidence of substantial new or worsening organ injury, patients with severely elevated blood pressures are classified as having markedly elevated or acute severe hypertension.

Pathophysiology

Uncontrolled hypertension is associated with long term endothelial damage, including oxidative stress and impaired production of nitric oxide.[28] Arteriole thickening and atherosclerosis lead to narrowing and diminished compliance, including in the cerebral circulation.

The process of cerebral autoregulation maintains constant blood flow across a broad range of systemic arterial pressures. For normotensive patients, the upper threshold of this range is a mean arterial pressure (MAP) of approximately 150 mm Hg.[29 30] However, in patients with uncontrolled hypertension over long periods of time, the cerebral vasculature undergoes pathological remodelling.[31] Hence, patients in hypertensive emergency may be tolerant of MAP values well above 150 mm Hg.[32]

Because of these adaptations, many patients are at low risk of immediate cerebral injury. Rather, there exists potential for harm with over-aggressive treatment. Rapid lowering of blood pressure has the potential to cause adverse cerebrovascular effects, particularly in patients with chronic, uncontrolled hypertension. Such changes are reversible with treatment, and, over time, patients reset their cerebral autoregulatory curve towards normal levels.

Diagnostic evaluation of suspected hypertensive emergency

The first step in evaluation is proper blood pressure measurement. Remeasurement with an appropriately sized and positioned cuff and ensuring that the patient is seated and relaxed can exclude the need for further evaluation.[37] Furthermore, remeasurement after adequate analgesia for patients with severe pain often ameliorates markedly elevated blood pressure measurements. In conditions where intensive treatment is warranted, such as aortic dissection, invasive arterial blood pressure monitoring allows for continuous measurements.

Clinical evaluation

The clinical history includes previous diagnosis of hypertension, cardiovascular disorders, cardiometabolic disorders, endocrine disorders, pheochromocytoma, and chronic kidney disease. Furthermore, history includes recent alcohol intake (or cessation), sympathomimetic drugs, supplements, and medication adherence.[42] Drugs containing amphetamines, methamphetamine, and cocaine may precipitate hypertensive emergencies. In females of reproductive age, the history should include current or prior pregnancy.

A focused neurological and ophthalmic history and examination are valuable in the evaluation of severe hypertension. Seizures and altered consciousness can be indicative of hypertensive encephalopathy. Focal neurological deficits point to intracerebral haemorrhage or ischaemic stroke. Fundoscopic examination determines severity of hypertensive retinopathy.[43] Arteriole tortuosity and arteriovenous nipping are indicative of mild hypertensive retinopathy and are chronic findings. New flame haemorrhages, cotton-wool spots, or microaneurysms suggest more acute injury and are consistent with moderate or grade 3 retinopathy. The added finding of papilloedema is consistent with severe retinopathy and requires immediate blood pressure lowering.

Cardiovascular symptoms such as chest pain (26%), shortness of breath (29%), palpitation, and claudication are common in patients with hypertensive emergency.[44] Examination can reveal clear signs of acute heart failure and pulmonary oedema or less common findings of vascular pathology such as abdominal bruits or discordant peripheral pulses. Diaphoresis, palpitations, frequent headaches, and autonomic instability could prompt further evaluation for pheochromocytoma.

True hypertensive emergency is uncommon among asymptomatic individuals even when they present with severe hypertension.

Diagnostic testing

Laboratory testing

Most patients will require an electrocardiogram, a complete blood count with differential, and a metabolic profile assessing sodium, potassium, creatinine, and estimation of glomerular filtration. The presence of acute kidney injury and fragmented red blood cells are important markers of hypertensive emergencies. Other laboratory studies can include thyroid function studies, urine analysis for protein, and urine sediment for erythrocytes, leucocytes, and casts.[37 47]

Some experts advocate laboratory evaluation of secondary causes of hypertension, including plasma renin activity, aldosterone, and catecholamines.[42] However, these tests for secondary causes are rarely evaluated in the emergency department setting.

Circulating biomarkers such as brain natriuretic peptide (BNP) or NT-proBNP and high sensitivity troponin are valuable in evaluation of cardiovascular symptoms, ruling out myocardial damage and heart failure, and provide important prognostic information. Lactate dehydrogenase (LDH), which reflects thrombotic microangiopathy, may also have value.[53]

Imaging

Imaging is tailored to symptoms and suspected organ injury. Head computed tomography (CT) is insensitive for the diagnosis of hypertensive encephalopathy and should not be used to rule out this emergency. Non-contrast head CT in patients with severely elevated blood pressure and altered mental state is critical for determining the presence or absence of intracerebral haemorrhage.

Hypertensive encephalopathy remains a clinical diagnosis and does not require imaging. If available, magnetic resonance imaging (MRI) can solidify the diagnosis when uncertainty is present. Brain MRI may reveal microhaemorrhages in patients with hypertensive encephalopathy.[55] Brain MRI is also critical in differentiating hypertensive encephalopathy from acute stroke.

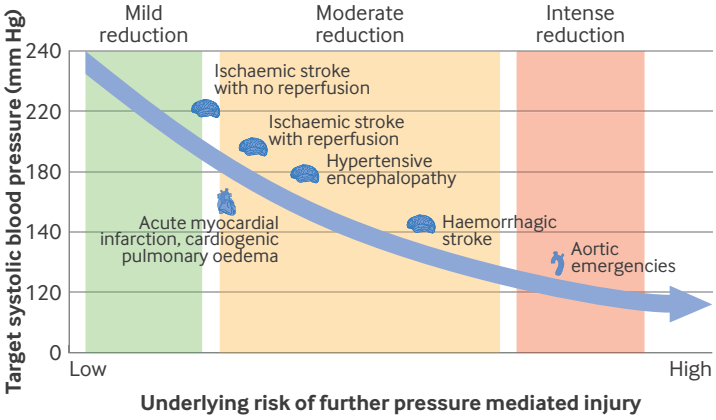
Echocardiography can be useful for assessing left ventricular hypertrophy, systolic and diastolic dysfunction, atrial dilation, and aortic coarctation. While not sensitive, bedside point-of-care ultrasonography has good specificity for the diagnosis of acute aortic dissection, particularly when the dissection extends into the abdominal aorta.[56] Lung ultrasonography is an accurate method of diagnosing acute pulmonary oedema through detection of B-lines.[57]

Other forms of ultrasonography can confirm longstanding effects of uncontrolled hypertension on vascular damage.

Management

Severely elevated blood pressure without emergency

Most patients evaluated for hypertensive emergency have a negative work-up for acute organ injury and are diagnosed with acute severe hypertension. They may often be managed as an outpatient. Their risk of long



Recommended intensity of blood pressure lowering target relative to the underlying risk of further pressure-mediated injury in hypertensive emergency syndromes

term cardiovascular disease is substantial, but short term adverse cardiovascular events have not been demonstrated.[3 38]

When it is unclear if this is a hypertensive emergency, clinicians may consider a period of observation. In patients at low risk for hypertensive emergency, a period of quiet resting has been shown as effective as medication in lowering blood pressure over two hours.[60] Mindfulness combined with slow breathing may be effective.[61] Anxiolytics lower blood pressure in this scenario as well.[62 63] Resumption of outpatient oral antihypertensive medications is appropriate. In patients without known outpatient medications, initiation of an oral antihypertensive medication according to guidelines is reasonable while awaiting additional testing.[17 18] In all patients discharged to outpatient follow-up, barriers to ongoing antihypertensive management must be addressed.

When patients require inpatient hospital admission for diagnoses other than hypertensive emergencies and have acute severe hypertension during their hospital stay there is significant heterogeneity in management.

The optimal approach to managing patients with acute severe hypertension in the hospital is gradual and stepwise titration of guideline recommended oral antihypertensive agents. Intravenous treatment is rarely, if ever, indicated. Treating pain often ameliorates severe rises in blood pressure. Efforts to address anxiety or withdrawal states are also indicated.[40] Many of these patients will continue to have elevated blood pressure as an outpatient and require a coordinated strategy to progressively control blood pressure and prevent long term complications.[38 67]

Management of specific hypertensive emergencies

Guidelines for the management of hypertensive emergency unanimously recommend immediate treatment when organ injury is present. The treatment follows a stepwise pathway, including initial reduction in blood pressure, careful monitoring of the patient's clinical status, and subsequent gradual blood pressure lowering. The figure demonstrates the intensity of lowering relative to the underlying risk of further pressure-mediated injury based on specific syndromes.

We universally recommend intravenous antihypertensive medications and favour continuous infusions for initial management. Intravenous hydralazine and nitroprusside are not recommended. Hydralazine is inconsistent in its effects and difficult to titrate, and both agents can lead to unexpected, sudden drops in blood pressure.[66 76]

Hypertensive encephalopathy

Hypertensive encephalopathy is defined by alterations in mental state with severely elevated blood pressure beyond a patient's limits for cerebral autoregulation. Symptoms may also include seizures, headache, lethargy, and visual disturbances. Blood pressure is commonly >220/110 mm Hg. In young adults or those without a history of chronic hypertension, however, rapid increases in blood pressure to lower elevated ranges are possible. Concomitant findings can include acute hypertensive retinopathy and microangiopathic haemolytic anaemia. The diagnosis remains principally a clinical one and requires exclusion of other acute neurological hypertensive emergencies.

The treatment goal is immediate reduction of blood pressure to restore cerebral autoregulation. Current guidelines recommend reduction of the patient's initial MAP by 20-25% within the first hour of care. First line antihypertensive agents include nicardipine, clevidipine, and labetalol. Given its effectiveness and ease of titration, nicardipine is often preferred.[37 77] After initial lowering of blood pressure, clinicians should maintain the target MAP over the next 2-6 hours to ensure it is well tolerated. If MAP falls beyond the anticipated <25% reduction, fluid resuscitation is indicated. Pressure natriuresis is a consequence of severe arterial hypertension and can lead to intravascular depletion due to increased renal sodium excretion. Once initial blood pressure lowering is tolerated, further gradual reduction towards a blood pressure of 160/110 mm Hg over the next 48 hours is acceptable.[47]

Aortic disease

In the case of aortic dissection and other acute aortic syndromes, standard practice and societal guidelines dictate immediate afterload reduction with systolic blood pressure <120 mm Hg and impulse control with a heart rate <60 beats per minute. US and European professional guidelines recommend beta blockade in conjunction with calcium channel blockers as first line therapy.[77 78]

Acute aortic emergencies are the only category of hypertensive emergencies for which >25% reduction in MAP is indicated, based on the immediate risk of dissection extension and mortality.

Haemorrhagic stroke and subarachnoid haemorrhage

For haemorrhagic stroke, immediate reduction of blood pressure is recommended by the International Society

of Hypertension and European Society of Cardiology to a goal systolic blood pressure <130 mm Hg.[37 45] Current guidelines by the American Heart Association/American Stroke Association (AHA/ASA) target a goal systolic blood pressure of 140 mm Hg, with the caveat that clinicians consider higher targets if patients present with systolic blood pressure >220 mm Hg.[47]

Short acting calcium channel blockers, including nicardipine and clevidipine, are excellent first line antihypertensive medications.

Compared with intracerebral haemorrhage, aneurysmal subarachnoid haemorrhage less commonly has accompanying severe elevations in blood pressure. AHA/ASA guidelines recommend gradual blood pressure lowering when systolic blood pressure >180 mm Hg.[81]

Ischaemic stroke

In the early management of hypertensive emergency and ischaemic stroke, the need for acute reperfusion therapy (thrombolytic and/or endovascular thrombectomy) guides blood pressure targets. In patients with an ischaemic stroke who do not receive acute reperfusion therapy, immediate blood pressure lowering is not indicated unless blood pressure exceeds 220/120 mm Hg. For these patients, gradual antihypertensive titration over several days is appropriate.

For patients receiving acute reperfusion therapy, international guidelines recommend blood pressure goals of systolic <185 mm Hg and diastolic <110 mm Hg.[83] Recommended antihypertensive agents include continuous nicardipine or intermittent intravenous labetalol. The AHA/ASA guidelines also recommend maintenance of blood pressure <180/105 mm Hg for the first 24 hours after reperfusion therapy.[83]

Cardiac emergencies

Cardiac hypertensive emergencies include acute myocardial infarction and cardiogenic pulmonary oedema with blood pressure >180/110 mm Hg. In these presentations, afterload increases myocardial demand and strain, leading to ischaemic symptoms or increased hydrostatic pressure causing pulmonary oedema. Diagnosis requires a rise and fall in cardiac troponin above the 99th centile reference range. It is common for patients with acute severe hypertension to have chronic elevations in cardiac troponin, and these patients do not require immediate blood pressure lowering.

Blood pressure treatment is indicated when acute pulmonary oedema or the less common type 2 myocardial infarction is present. The intensity of treatment is mild to moderate, largely based on expert opinion, and targets a 15-25% reduction in MAP and relief of symptoms.[77] Nitroglycerin is a preferred agent and can be titrated to relief of chest pain and MAP. Beta-blockade can reduce tachycardia and myocardial oxygen demand. Unless contraindicated, esmolol and intravenous labetalol are good second line agents. For patients with acute cardiogenic pulmonary oedema, nitroglycerin is also a preferred agent as it provides venodilation and preload reduction and afterload reduction at higher doses. Nicardipine and clevidipine used in conjunction with a loop diuretic can provide rapid relief of symptoms due to pulmonary oedema.

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Patients with hypertensive emergency or suspected hypertensive emergency participated in informal interviews with the writing team. Patients conveyed a common sense of anxiety and fear of stroke when they had severe blood pressure elevations. They also discussed frustrations related to transitions of care between the emergency department, hospital, and outpatient settings. These discussions particularly informed the writing and editing of the section on severely elevated blood pressure without emergency.

Uncommon causes of hypertensive emergencies

Pheochromocytomas release excess catecholamines leading to uncontrolled hypertension and can precipitate hypertensive emergency. Paroxysmal elevations in blood pressure are common in patients with pheochromocytoma.[86] The diagnosis of a pheochromocytoma is difficult.[49 50] In patients with newly identified or known pheochromocytoma, initial treatment with alpha antagonists or calcium channel blockade is preferred.[87] Phentolamine is a preferred agent.[88] Initial treatment with beta blocking antihypertensive agents is contraindicated because of the low risk of paradoxical hypertension.

Sympathomimetic drugs can also lead to hypertensive emergencies. In cases of suspected amphetamine, methamphetamine, or cocaine overdose, benzodiazepines should be considered as first line treatment to control clinical symptoms and secondarily to reduce blood pressure. Selective beta-1 blockers are contraindicated.

Guidelines

The American Heart Association (AHA)/American College of Cardiology (ACC),[17] the European Society of Cardiology/European Society of Hypertension,[18] the British and Irish Hypertension Society,[77] and the International Society of Hypertension[37] have published guidelines about the management of severe hypertension and hypertensive emergencies. The above guidelines are unanimous in their emphasis on titratable blood pressure reduction for hypertensive emergencies, which includes an immediate reduction <25% followed by more gradual reduction. These guidelines agree that patients with severe elevations in blood pressure without signs of acute organ injury do not need emergency department evaluation or immediate blood pressure reduction with intravenous medications.

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Reducing drug waste in hospitals

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CPD READING

0.5 HOURS

EDUCATION INTO PRACTICE

- What opportunities are available to you to reduce unnecessary waste of medications in your clinical practice?
- What policies could be adjusted or improved to optimise medicines management in your hospital?

Pharmaceutical manufacturing, packaging, and distribution are carbon intensive processes, accounting for an estimated 12% of healthcare's global carbon footprint.[2 3] Despite the costs of production and procurement in terms of carbon emissions, considerable financial burden on health systems, and ongoing challenges with drug shortages, some medicines ultimately enter the waste stream as expired or unused products.[4 5]

In hospitals, drug waste can occur because of challenges with inventory management, including overstocking and product expiry.[8-13] Waste also occurs in clinical care during dispensing, preparation, and administration of medicines.[13-18] Although the full magnitude of hospital drug waste is not well studied, existing literature identifies potentially avoidable waste of various medication types across many inpatient settings.

Evidence for the solution

Improvements to pharmacy inventory management processes and inter-hospital collaboration, through medication inventory pooling and exchange, can facilitate efficient use of near-expiry medications.[8-20] Implementation of automated dispensing systems across three intensive care units in a French hospital facilitated inventory tracking, and combined with staff education, expiry date monitoring, and stock rotation, was found to eliminate waste of expired drugs, saving €14 772 (£12 437) per year.[12] A US hospital used lean methodology to improve central pharmacy purchasing, staffing, and workflow for drug preparation and distribution, which reduced waste from sterile compounding, drug expiry, and missing doses, and resulted in an annual cost savings of $289 256.[13]

Monitoring drug utilisation and stocking product type, quantity, and package sizes to match clinical usage patterns can also mitigate waste. Replacing 50 mL and 100 mL bottles of propofol with 20 mL bottles in a US surgical suite reduced waste from 29.2 mL/day/bin to 2.8 mL/day/bin.[14] By applying stewardship principles to target unnecessary use, inefficient vial sizes, and vial loss, another US hospital decreased monthly spending on suggamadex from $70 777 to $33 821 (£53 910 to £25 757) while increasing its availability in operating theatres.[15] In a Dutch intensive care unit, switching from syringes prepared by staff in the hospital pharmacy to pre-filled, sterilised syringes with longer shelf life significantly reduced the total waste of syringes.[21]

Patients can assist in efforts to reduce waste by bringing medicines from home for inpatient use. Use of patients' own medication schemes consistently show financial savings, but data related to impact on absolute quantity of waste are limited.[22]

WHAT YOU NEED TO KNOW

- Drug waste is an important source of financial and environmental waste within healthcare systems
- Audit and analysis of drug inventory management, hospital policies on medicines, and prescribing and utilisation in clinical practice offer opportunities to reduce medicines waste
- Engaging in multidisciplinary collaborations and partnering with patients are useful strategies for promoting sustainable medicines use

What you can do

Medicines stewardship principles can guide efforts to adjust practices and promote efficient use of resources.[11-26] Efforts to reduce waste require systematic and coordinated strategies across the medicines management lifecycle adapted to specific hospital settings and local needs.

Pharmacy staff can contribute to waste mitigation by adjusting procurement and inventory management processes and reviewing drug preparation and utilisation, to reduce waste resulting from loss, expiry, or inefficient use of medicines. Optimising inventory tracking, storage, and ward distribution can facilitate this by ensuring appropriate products and quantities are stocked and rotated using "first expired, first out" principles.

Clinical staff can evaluate contributions to drug waste in their practice from prescribing, inventory use, preparation, and administration. Staff should take steps to avoid loss or unnecessary disposal of usable medicines and should ensure that available products reflect patterns of clinical use.[14-21]

Health professionals can partner with patients to promote sustainable use of medicines by engaging them in discussions about their therapy and tailoring medication regimens for individuals. Deprescribing interventions can minimise unnecessary treatments, and shared decision making can both improve patient education and demonstrate a common preference for fewer medications.[27 28]

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MINERVA

An oral complication of bisphosphonate therapy

During a routine dental examination, a 69 year old man was found to have multiple areas of exposed bone on the lingual aspect of the right mandible. He had a history of myeloma and was being treated with lenalidomide and monthly infusions of 4 mg zoledronic acid for chronic pain secondary to multiple spinal compression fractures. He had no known dental disease before starting therapy, or history of trauma or radiation. Computed tomography showed heterogeneous cortical bone destruction suggesting osteonecrosis but no evidence of osteomyelitis or odontogenic infection.

Bony complications of bisphosphonates include osteonecrosis of the jaw and atypical femoral fractures. Patients taking high dose bisphosphonates, in the absence of trauma or radiation, carry a much higher risk of osteonecrosis than the general population. Dental evaluation is therefore recommended before starting and during bisphosphonate therapy. This patient's bisphosphonates were stopped, but, due to poor healing and spontaneous tooth loss, he underwent subsequent tooth extraction, necrotic bone debridement, and soft tissue reconstruction with an anterolateral thigh fascia lata flap. At three months, there was no osteolysis with complete mandibular soft tissue coverage.

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Patient consent obtained.

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If you would like to write a Minerva picture case, please see our author guidelines at bit.ly/29HCBAL and submit online at bit.ly/29yyGSx

Timing of anticoagulation in stroke

Earlier this year, a large randomised controlled trial reported that early anticoagulation in people with atrial fibrillation who had sustained a stroke probably carried a small benefit over delayed anticoagulation. However, the confidence intervals around the estimated treatment effects were too wide to make definite recommendations (*N Engl J Med* doi:10.1056/NEJMoa2303048). A re-analysis finds that this conclusion isn't changed when infarct size is taken into account. The important finding is that early treatment with direct acting oral anticoagulants doesn't carry a higher risk of bleeding complications, intracranial haemorrhage, or other adverse events, even when the infarct is large (*JAMA Neurol* doi:10.1001/jamaneurol.2024.1450).

New treatments for dementia

Lecanemab and donanemab, both monoclonal antibodies that target the accumulation of amyloid protein in the brains of people with Alzheimer's disease, have been shown to slow the progression of dementia in clinical trials. This of course is welcome news, but it's important to ask both how large the benefit is and whether it might be rather smaller when the drugs are used beyond the carefully selected groups of patients who took part in the trial. A sceptical piece in *Unherd* reckons that the benefits of these new drugs are more likely to be felt by the companies that make them than by people with Alzheimer's disease (https://unherd.com/2024/01/the-false-hope-of-the-new-alzheimers-drugs/).

Arts and crafts

Among 7000 respondents in the *Taking Part Survey*, a household inquiry conducted by the UK's Department for Culture, Media and Sport, more than a third said that they had taken part in at least one arts and crafts activity in the past 12 months. They reported higher levels of happiness and life satisfaction, as well as a stronger sense of life being worthwhile, than people who didn't take part in that sort of activity. Minerva found it hard to interpret these findings usefully. Does engagement with a creative activity improve mental outlook? Or is it that happier people are more likely to be creative? (*Front Public Health* doi:10.3389/fpubh.2024.1417997).

Revascularisation for intermittent claudication

Seven years' follow-up of a series of patients with intermittent claudication treated at a centre in the US suggests that a conservative approach should be preferred over surgical or endovascular intervention (*J Vasc Surg* doi:10.1016/j.jvs.2024.03.455). Patient reported outcomes concerning level of function and satisfaction in social roles and activities were no better among 89 patients who underwent a revascularisation procedure than among 136 who were managed conservatively. This conclusion echoes European guidelines, published earlier this year, which recommend that revascularisation procedures should be undertaken only when there is no improvement with conservative treatment (*Eur J Vasc Endovasc Surg* doi:10.1016/j.ejvs.2023.08.067).

Alcohol consumption and gout

James Gillray drew his famous cartoon, *The Gout*, which depicts a black demon sinking its fangs into a red and swollen first metatarsophalangeal joint, in the 18th century, when the condition was prevalent among those who could afford a rich diet and a heavy intake of fortified wines. Data on 400 000 participants in the UK Biobank study who were free of gout at the time of recruitment show that the link with heavy drinking persists. In both men and women, higher alcohol consumption was linked to a higher incidence of gout. The relation was stronger for men than women, and stronger for beer and cider than champagne or white wine (*JAMA Netw Open* doi:10.1001/jamanetworkopen.2024.30700).

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