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Cover picture

JAMES LIND: CONQUEROR OF SCURVY

Surgeon of Britain's Royal Navy aboard H.M.S. Salisbury, in the English Channel in 1747, James Lind conducted a series of clinical experiments that definitely proved citrus fruits or their juices would cure scurvy, dread dietary-deficiency disease that killed a million seamen between 1600 and 1800. Dr. Lind's work, at sea, in Edinburgh, and at Haslar Naval Hospital, plus his three books, on scurvy, on care of sailors' health, and on tropical diseases, had much to do with reforming naval health practices, saving lives both on sea and land, and shaping destinies of nations, as world commerce increased.

Robert A. Thom, Artist

Fluid management in the adult patient

Introduction

Intravenous fluid therapy is commonly instituted in an acute care setting. Although intravenous fluid therapy is considered as a routine with few consequences, it carries many risks as well as benefits. Fluids should be regarded as drugs, as any fluid can be harmful if dosed and chosen incorrectly. The differences in efficacy between administering crystalloids and colloids are modest; however, the cumulative differences in safety appear to be significant.

Due to limited evidence, recommendations regarding fluid have historically been opinion based. Since acutely ill patients have a variety of conditions that alter body water homeostasis, the selection of intravenous fluids is largely individualised and should be based on physiological principles, and clinical practice will be determined by the clinician's preference.

Steps in prescribing intravenous fluids

It is vital to administer the right amount of fluid of the right type at the right time. The following questions will need to be addressed before prescribing fluids for adult patients [1].

1. Is the patient euvolaemic, hypovolaemic or hypervolaemic?
2. Does the patient need intravenous fluids, if so why?
3. How much fluid is required? When prescribing intravenous fluids and electrolytes it is important to consider all other intakes of fluids, electrolytes, oral or enteral intake, and intake from drugs, intravenous nutrition, blood and blood products.
4. What type of fluids does the patient need?

5 Rs in prescribing intravenous fluids

It is essential to assess and manage a patient's fluid and electrolyte needs as a part of every ward review. Intravenous fluids should be prescribed only for patients whose needs cannot be met by oral or enteral routes. When prescribing intravenous fluids it is worthwhile to remember the 5 Rs [2].

- Resuscitation
- Routine maintenance
- Replacement
- Redistribution
- Reassessment

Resuscitation

Patients in need of intravenous fluids for resuscitation should be given crystalloids that contain sodium in the range of 130-154 mmol/l. This is administered as a bolus of 20-30 ml/kg (about 250-500 ml) over 15 minutes [2]. Avoid

Table 1. Assessment of fluid status

Volume status of the patient	*Clinical findings*
Euvolaemic patient	Veins are well filled and extremities will be warm. Blood pressure and pulse rate will be normal.
Hypovolaemic patient	Cool peripheries with postural hypotension. Systolic blood pressure will be <100mmHg, pulse rate>90 beats per minute, respiratory rate>20 breaths per minute and the early warning score will be>5. Haemodynamic improvement with the passive leg raising test suggests fluid responsiveness in a hypovolaemic patient. History suggests an ongoing fluid loss or low fluid intake. Signs of hypovolaemia may be unreliable in elderly patients.
Hypervolaemic patient	Appears oedematous with inspiratory crackles on auscultation and a raised JVP. History as well as fluid balance charts will indicate fluid overload.

using tetrastarch for fluid resuscitation. Large randomised trials have shown that crystalloids are superior to colloids for fluid resuscitation, and there is limited data on the use of gelatins for fluid resuscitation [2]. Human albumin solution can be considered for fluid resuscitation only in patients in septic shock.

Response to treatment should be assessed using patient's cardiac output and stroke volume measured by flow based technology whenever possible. Alternatively the clinical response may be monitored by the pulse rate and volume, capillary refill time (normal <2 seconds), blood pressure before and 15 minutes after receiving the infusion, and trends in central venous pressure [3]. Assessment should be repeated until there is no further increase in stroke volume and improvement is observed in clinical variables.

Hypovolaemia predominantly due to blood loss should be treated with crystalloids until packed red blood cells are available. The ideal fluid resuscitation strategy in trauma patients remains a debated topic [4]. Clinical evidence emphasizes that a restrictive fluid resuscitation before surgery, referred to as damage control resuscitation, aiming for a systolic blood pressure of 90 mmHg improves outcome in patients with penetrating trauma [4]. Fluid management of blunt trauma patients, especially with coexisting brain injury, remains unclear.

Hypovolaemia due to severe inflammation such as infection, peritonitis, and pancreatitis should be treated with balanced crystalloids to normalise haemodynamic variables and to minimize overload [3]. It is important to bear in mind that critically ill patients are unable to excrete sodium and water, placing them at high risk of severe interstitial oedema.

Routine maintenance

If a patient requires intravenous fluids for maintenance alone, restrict the initial prescription to 25-30 ml/kg/day of water, 1mmol/kg/day of sodium, potassium and chloride, and about 50-100 g /day of glucose to prevent starvation ketosis [2]. The routine maintenance is calculated as 1.5 ml/kg/hour. Avoid prescribing routine maintenance fluids at a rate of >100 ml/hour [1].

For patients who are obese the prescription has to be adjusted according to their ideal body weight. For patients who are old and frail, or having renal and cardiac failure the 24-hour fluid requirement is best calculated at 20-25 ml/kg, with close monitoring of vital signs to avoid fluid overload [2].

Replacement and redistribution

Patients receiving intravenous fluids for replacement and redistribution problems may need frequent monitoring, unlike a patient on long term fluid therapy who is stable. Large cohort and small randomised studies have shown that balanced crystalloids may be superior to 0.9% sodium chloride during treatment of surgical patients [2].

Table 2. Types of crystalloid and colloid formulations

Solution	*PH*	*Na^+*	*Cl^-*	*K^+*	*Ca^{++}*	*Lactate*	*Glucose*	*Osmolality*	
0.9% Na Cl	5.0	154	154	0	0	0	0	308	
Hartmann (CSL)	5-7	130	110	5	2	28	0	278	
Plasmalyte	7.4	140	98	5	0	0	0	294	
5% Dextrose in water (DSW)	4.0	0	0	0	0	0	50g/l	252	
Dextrose (D1/2 NS)	4.5	77	77	0	0	0	50g/l	406	
Albumin (4%)	6.7-7.3	140	128	0	0	0	0	260	40g/l albumin
Albumin (20%)	6.4-7.3	48-100	130-160	0	0	0	0	130	200g/l albumin
Hetastarch 6%	5.5	154	154	0	0	0	0	310	60g/l starch
Pentastarch 10%	5.0	154	154	0	0	0	0	326	100g/l starch
Dextran 40	3.5-7.0	154	154	0	0	0	0	311	100g/l dextran
Dextran 70	3.5-7.0	154	154	0	0	0	0	310	60g/l dextran
Haemaccel 3.5%	7.4	145	145	5	6.35	0	0	293	35g/l gelatin
Gelofusine	7.4	154	125	0	0	0	0	308	40g/l gelatin

Fluid prescription needs to be adjusted for existing fluid or electrolyte deficits or excess and ongoing losses (high output drainage from fistula, copious nasogastric drainage). Similarly, in situations where there is gross oedema, hypo- or hypernatremia, renal, cardiac, hepatic failure, post-operative fluid retention, and malnourished patients with re-feeding issues require expert opinion [2].

Reassessment

Patients receiving intravenous fluids should be re-assessed using the ABCDE approach. It is important to monitor the haemodynamic variables (blood pressure, pulse rate, capillary refill time, and urine output, aiming for 0.5-1ml/kg/hour), and measure the venous lactate, arterial pH and base excess.

Clinical monitoring should also include the current status and trends in early warning scores, fluid balance charts, and ideally the weight of the patient. This could be further supplemented by laboratory investigations such as full blood count (packed cell volume), serum electrolytes, blood urea and creatinine [2].

Individualised goals integrating functional haemodynamic variables should be used to assess for fluid responsiveness. Serial measures that are superior to blood pressure, CVP and urine output are available, such as pulse pressure variation and variation in sonographic readings which can be readily assessed with limited training at the bedside.

Types of Fluids

Fluids are broadly classified as crystalloids or colloid solutions. Crystalloids are solutions of ions that are freely permeable but contain varying concentrations of sodium, chloride and other cations that determine the osmolality of the fluid.

Colloid solutions are suspensions of molecules within a carrier solution that are relatively incapable of crossing the healthy, semipermeable capillary membrane owing to the molecular weight of the molecules [5].

Most studies indicate that isotonic fluids are most appropriate for the vast majority of hospitalised patients who are at risk for elevated arginine vasopressin (AVP) levels (which place the patient at risk for a plasma sodium concentration that is too low, resulting in hospital acquired hyponatremia) [6]. But this does not mean that isotonic fluids are appropriate in all clinical settings and that they are without risks.

Isotonic (0.9g/dl) saline is found to be unsafe in hyperkalaemic renal failure. This finding comes from a randomized controlled trial comparing isotonic saline with compound lactate solution, in the operating room during renal transplant surgery. Patients who received isotonic saline had higher rates of hyperkalaemia requiring rescue therapy such as insulin [7]. The explanation for this is probably that isotonic saline cause hyperchloraemic acidosis, which shifts potassium out of the cells thereby elevating serum potassium levels. Contrary to prevailing custom, compound lactate solution is safe in hyperkalaemic renal failure.

Isotonic saline is considered non-physiological because of its high chloride content, compared to human plasma. Apart from causing hyperchloraemic metabolic acidosis, it is also responsible for reduction in GFR secondary to renal vasoconstriction, which could result in acute kidney injury with a greater likelihood of requiring renal replacement therapy [8].

Physiologically balanced crystalloid may be the "default" fluid for most patients, and compound lactate solution is a reasonable choice of resuscitation fluid. The only potential contraindications being elevated intracranial pressure and profound liver failure [7].

Colloid solutions do not offer advantages over crystalloid solutions with respect to haemodynamic effects. Albumin is regarded as the reference colloid solution but its cost is a limitation to its use. Albumin has a role to play in resuscitation of septic patients, but its use is associated with mortality in patients with traumatic brain injury [5]. Use of hetastarch solutions is associated with increased rates of renal replacement therapy and a number of adverse events. Hetastarch solutions should not be used in the resuscitation of septic and trauma patients.

Solutions such as 4%/0.18% dextrose/saline and 5% dextrose are important sources of free water for maintenance but are not appropriate for resuscitation and replacement therapy except in conditions such as diabetes insipidus, where there is a free water deficit [3]. Nonetheless 5% dextrose can be used to treat the evaporation loss that occurs during surgery under anaesthesia.

Administration of hypotonic maintenance fluids in both adults and children is associated with a higher incidence of hospital acquired hyponatraemia and more than 100 reports of iatrogenic deaths or permanent neurological impairment related to hyponatraemic encephalopathy have been reported in the literature [6]. Physiologically balanced salt solutions are available but none are perfectly matched with plasma.

Conclusion

Prescribing intravenous fluids is a common medical task and safe and unambiguous fluid prescribing is a required training outcome for all doctors.

Inappropriate fluid management can result in under or over-resuscitation with serious harm to the patient. Hence assessment of fluid requirement needs care and attention, with adjustment to the individual patient for it is easy to give excess salt and water but very difficult to remove them. The prescription of intravenous fluids can be made simple by routinely considering the 5 Rs in fluid management.

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Treating osteoporosis

Summary

Osteoporotic fractures are common resulting in increased morbidity and mortality. Exercise can help prevent osteoporosis. It can also benefit patients with osteoporosis, but the exercises must be tailored to the patient.

Most Australians should be able to obtain adequate calcium in their diet and vitamin D from the sun. Supplements may be needed in some patients and they are recommended for use with other drugs for osteoporosis.

Bisphosphonates, and in some patients denosumab, are first-line drugs for osteoporosis. Raloxifene and strontium ranelate can be considered in patients who cannot take bisphosphonates or denosumab. Teriparatide is reserved for patients with severe osteoporosis and the use of strontium ranelate is declining because of cardiovascular safety concerns.

Key words: bisphosphonates, bone resorption inhibitor, calcium, vitamin D

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Introduction

Osteoporosis is a common systemic skeletal condition among older people. Currently, 2.2 million Australians have osteoporosis and, for those aged 50 and over, up to one in four men and two in five women will experience a minimal trauma fracture.[1] Retrospective data show that fewer than 20% of these patients are investigated or treated for osteoporosis. Fractures cause significant pain, disability, reduced quality of life and even premature death.[2] In economic terms, the cost of osteoporosis to the Australian community is projected to be $33.6 billion in the decade 2012–22.[3] There is some international evidence that early detection and treatment of osteoporosis in both men and women is cost-effective.[4-6]

Exercise

Exercise can delay the onset of osteoporosis. There is strong evidence that 'impact exercises' in children such as hopping, skipping and jumping can lead to higher peak bone mass in adulthood.[7,8] Impact exercises are also beneficial for middle-aged and older adults for increasing or preventing age-related bone loss. Although the gains in bone mass are promising, there is insufficient evidence to suggest exercise might reduce fractures.

The frequency and severity of falls may be reduced by exercises that maintain muscle strength, muscle mass, flexibility, mobility, balance and ease of movement. For people with established osteoporosis, any exercise that promotes these characteristics is recommended. The Box lists exercises according to their 'osteogenic' profile and more detailed information is available at www. osteoporosis. org.au/exercise. Specifically, weight-bearing aerobic exercises and progressive resistance training improve bone mineral density.[7-11]

Box **The impact of exercises on bone health**

Highly osteogenic	Moderately osteogenic	Low osteogenic	Non-osteogenic*
Basketball, netball	Running, jogging	Leisure walking	Swimming
Impact aerobics	Brisk walking, hill walking	Lawn bowls	Cycling
Dancing, gymnastics	Resistance training	Yoga, pilates, tai chi	
Tennis	Stair climbing		
Skipping with a rope			

(Adapted from Osteoporosis Australia with permission)

***** Although non-weight bearing exercises such as swimming and cycling do not increase bone density, they should not be discouraged, as they probably contribute to the overall maintenance of muscular and cardiovascular health.

Any recommendation for exercise must be tailored to the individual. For example, in patients who have already sustained osteoporotic fractures, moderate to high-impact activities may be unsuitable. Patients with asymptomatic vertebral fractures can be at risk of further vertebral fractures and exercises involving forward flexion of the spine should be avoided. However these patients could benefit from postural strengthening exercises.

Calcium

Adequate body calcium is crucial to prevent bone loss and fracture. The recommended dietary intake of calcium is between 1000 and 1300 mg per day, depending on age and sex. It is recommended that people get this through their diet by selecting foods that are naturally high in calcium, and including foods that have had calcium added. A dietary calcium calculator is available on the International Osteoporosis Foundation website.*

Most Australians do not reach the recommended dietary intake so daily supplements of 500–600 mg of calcium are sometimes needed. This is because calcium supplementation, especially when combined with vitamin D, can reduce the rate of bone loss and fracture in people who are deficient in dietary calcium such as the frail elderly. Calcium supplementation in these people is also thought to optimise the effectiveness of osteoporosis treatments including bisphosphonates, strontium ranelate, denosumab, teriparatide and selective oestrogen receptor modulator therapy.

The controversy regarding the safety of calcium supplements has not yet been resolved. There is some concern regarding a possible increase in the rate of myocardial infarction,[12-14] however this has not been confirmed by other research.[15,16] A large European study appeared to show increased rates of myocardial infarction in people taking calcium supplements, but not in people who achieved their calcium intake through diet alone.[17] Taken as currently recommended, combined calcium and vitamin D supplements seem safe and effective for most people who require them. The risk of heart attack and stroke will be the subject of ongoing research.

Vitamin D

Small amounts of vitamin D are found in some foods, but most adults are unlikely to get more than 5–10% of their requirement from food. Australians receive most of their vitamin D from direct sunlight. To maintain adequate vitamin D, those with fair skin need only expose the arms for 6–7 minutes mid-morning or mid-afternoon outdoors on most days during the Australian summer. Up to 30 minutes exposure will be required in winter. Advice regarding time of day and duration of exposure varies with latitude. A randomised trial of sunlight exposure in residential aged-care facilities in Sydney found that compliance with the duration and amount of sunlight exposure required to reach optimal vitamin D concentrations was low.[18] Darker skinned people require 3–6 times longer exposure. Window glass, full-coverage clothing and sunscreen inhibit transmission of ultraviolet B and thus synthesis of vitamin D in the skin. Synthesis of vitamin D in the skin also becomes less efficient in older people.

If indicated, vitamin D is best measured at the end of winter or in early spring, when serum 25-hydroxyvitamin D is lowest. Optimal mineral metabolism, bone density and muscle function are achieved when serum 25-hydroxyvitamin D is greater than 50 nmol/L. If testing is carried out at the end of summer, the concentration should be 10–20 nmol/L higher.

Evidence suggests that 31% of Australians are vitamin D deficient.[19] In older people, deficiency is associated with loss of lower extremity muscle mass, strength and impaired balance. Rates of deficiency are higher in southern Australia compared to northern Australia, and in the winter months, 50% of all Australian women are vitamin D deficient.[19] Improving vitamin D status reduces the risk of falls and fractures in older people,[20,21] particularly when combined with adequate calcium.[22]

Prevention of vitamin D deficiency

To prevent vitamin D deficiency in people who receive less than optimal sun exposure, supplementation is recommended:

- at least 600 IU per day for people under 70
- at least 800 IU per day for people over 70
- 1000–2000 IU per day may be required for sun avoiders or those at high risk of deficiency.

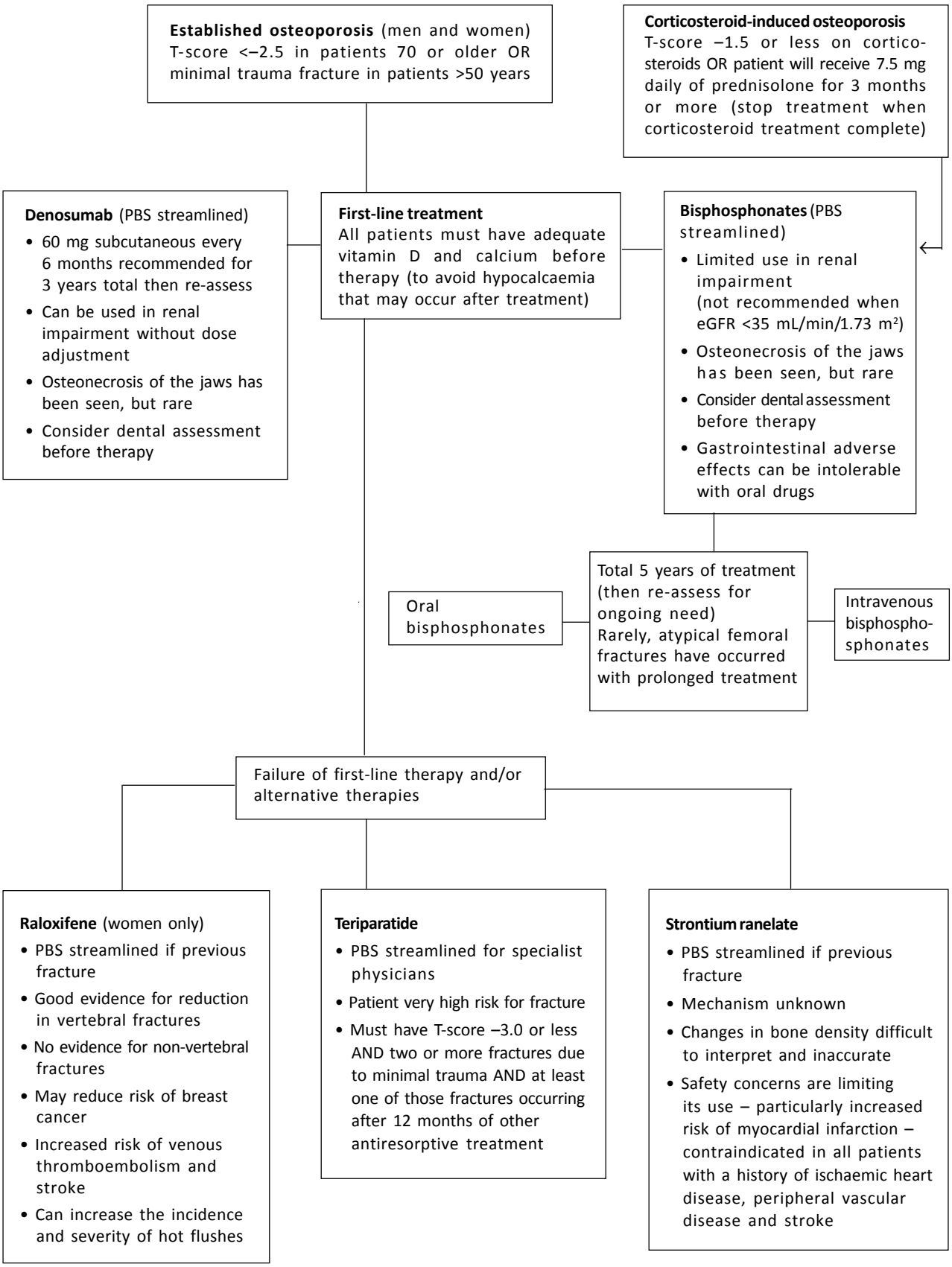
Higher doses are needed if there is vitamin D deficiency (Table 1). For all individuals taking a vitamin D supplement, a daily intake of 1000–1300 mg calcium, ideally dietary calcium, should be encouraged.

Table 1. Treatment of vitamin D deficiency

Vitamin D status	25–hydroxy vitamin D (end of winter)	Recommended vitamin D supplementation
Mild deficiency	30-49 nmol/L	1000-2000 IU per day
Moderate deficiency	12.5-29 nmol/L	3000-5000 IU per day (for 6-12 weeks) followed by maintenance dose of 1000-2000 IU per day
Severe deficiency	<12.5 nmol/L	

* www.iofbonehealth.org/calcium-calculator

Fig. **Osteoporosis drug treatment algorithm**



PBS Pharmaceutical Benefits Scheme (authority prescriptions) eGFR estimated glomerular filtration rate

Vitamin D status should be re-assessed 3-5 months after commencing supplements as the full increase in serum 25-hydroxyvitamin D may not be seen until this time. Although there is no definitive evidence, it is recommended that calcium and vitamin D status be checked annually in patients undergoing treatment for osteoporosis.

There are very few adverse effects related to vitamin D supplementation. When combined with calcium, there is a small risk of hypercalcaemia, which may lead to hypercalciuria and nephrolithiasis.

Drugs for osteoporosis

When considering, and before starting, therapies ensure that all patients have adequate vitamin D and calcium concentrations and that any secondary causes for osteoporosis have been managed. The Figure provides an algorithm for the management of established osteoporosis.

Bone mineral density testing by dual energy X-ray absorptiometry is recommended every 2–3 years to help monitor adherence and response to therapy.[23] More frequent testing every 12 months may be needed if there is a significant change in therapy or the patient's health, or the use of drugs which decrease bone density, for example corticosteroids.[23] The frequency of bone density testing has come under question. Given that changes to bone density generally occur slowly and allowing for measurement error of the testing, there is little evidence to support annual testing unless there have been major changes in treatment or health status. Some would argue that, once a diagnosis has been made and treatment started, no further testing is necessary given the weak concordance between fracture risk reduction and bone density changes, together with the lack of clear evidence that monitoring improves compliance.[24] However, most specialists still monitor bone mineral density to gauge adherence and response to treatment after two years and then again at five years to aid decisions about treatment duration.

Table 2 shows the number of patients that must be treated for 36 months in order to prevent one fracture.[25-28]

Oral bisphosphonates

Bisphosphonates block osteoclast activation and thus slow bone resorption. They slow bone loss, improve bone mineral density and reduce fracture rates. Most bisphosphonates have similar degrees of efficacy, whether they are used intravenously or orally. Head-to-head evidence for oral bisphosphonates is lacking. Oral drugs alendronate and risedronate are the preferred first choice due to their low cost and ease of use with once-weekly dosing. There are other oral bisphosphonates, however they are uncommonly used in the treatment of osteoporosis.

The use of oral bisphosphonates is limited by their adverse effects in renal impairment and they are absolutely contraindicated if the estimated glomerular filtration rate

Table 2. Efficacy of antiresorptive drugs

Drug	Vertebral fractures (NNT)	Hip fractures (NNT)	Patient population studied (to determine NNT)
Oral bisphosphonates[25]	15–20	91	Bone mineral density (T-score –2.0 to –4.0) Low-trauma fracture
Intravenous bisphosphonates[25]	14	91	Bone mineral density (T-score –2.0 to –4.0) Low-trauma fracture
Raloxifene[26]	29	n/a	Low bone mineral density (T-score less than –2.5) Low-trauma fracture
Denosumab[27]	21	200	Bone mineral density only (T-score –2.5 to –4.0)
Teriparatide[28]	11	n/a	Low bone mineral density (mean T-score –2.6) Low-trauma fracture

NNT number needed to treat for three years to prevent fracture (all estimates based on drug effect compared placebo)

(eGFR) is below 35 mL/minute/1.73 m^2. They also have significant upper gastrointestinal adverse effects. Dysphagia, achalasia, or an inability to remain upright for 30 minutes after tablet ingestion, are absolute contraindications.

Intravenous bisphosphonates

Intravenous bisphosphonates can overcome the gastro-intestinal limitations, however this therapy has other potential adverse effects, notably the risk of flulike reactions with intravenous infusions of zoledronic acid. Other symptoms such as joint and muscle pains can be prolonged. Patients with renal impairment can be at greater risk of these reactions, and in such cases the infusion rate could be reduced. Intravenous bisphosphonates are not recommended when the eGFR is below 35 mL/minute/ 1.73 m^2. Zoledronic acid has not been tested to any great extent in people with eGFR below 30 mL/minute/1.73 m^2. It may be directly nephrotoxic or may worsen already low bone turnover, however these issues do not appear to be of concern when using the osteoporosis regimen of 5 mg annually. Some clinical experience with zoledronic acid was reported in a cohort with eGFR in the 20-30 mL/minute/1.73 m2 range without untoward effects although reduced dosing was recommended. As zoledronic acid is renally cleared it has generally been recommended to use a reduced dose or a slower infusion rate in older patients with reduced renal function but no sound evidence exists for this.[29] A different class of drug that is not affected by renal function, such as denosumab, should be considered. There may also be a slight risk of atrial fibrillation with intravenous zoledronate.

The recommended duration of therapy with oral bisphos-phonates is five years and perhaps less (3 years) for intravenous bisphosphonates.[30-35] Safety data are robust for up to five years of treatment, but extending treatment beyond this has questionable benefit and possible harm. Harms such as osteonecrosis of the jaws and atypical femoral fractures occur very infrequently but are more likely with longer periods of antiresorptive treatment. Osteo-necrosis of the jaws is more likely to be seen in patients with cancer receiving frequent doses of bisphosphonates, but other risk factors include dental extractions, dental implants, poorly fitting dentures, and pre-existing dental disease, glucocorticoid use and smoking (see Dental note in this issue).

More research is required to determine optimum duration of bisphosphonate therapy. Each patient should be reviewed after five years and a decision regarding ongoing treatment based on their individual needs and fracture risk profile. If they remain at high risk, most specialists would continue treatment.

Treatment may be safely extended or alternative treatments used if:

- the femoral neck T-score** is less than –2.5 without prevalent vertebral fractures
- the femoral neck T-score is less than –2.0 with prevalent vertebral fractures
- there has been a recent fracture.

Denosumab

Denosumab is a monoclonal antibody that reversibly inhibits bone resorption by reducing osteoclast formation and differentiation while increasing osteoclast apoptosis. It increases bone mineral density at the lumbar spine and hip, and reduces vertebral, non-vertebral and hip fractures. In contrast to bisphosphonates, denosumab can be used in chronic kidney disease, however these patients are particularly at risk of hypocalcaemia so baseline assessment of calcium and vitamin D status should be undertaken before starting therapy. Denosumab's effect will wear off as it does not accumulate. It is therefore given regularly as a six-monthly subcutaneous injection.

Raloxifene

Raloxifene is a selective oestrogen receptor modulator that reduces postmeno-pausal bone loss. It reduces the risk of vertebral fractures, but it does not reduce non-vertebral fractures. Raloxifene is an alternative to bisphosphonates or denosumab (if they cannot be tolerated) for women with postmenopausal osteoporosis and is most appropriate for treating younger postmenopausal women with spinal osteoporosis. It increases the incidence of hot flushes, which can be a significant problem in young postmeno-pausal women. Raloxifene reduces the risk of breast cancer, so it can be considered in women with a high risk of breast cancer. It is, however, known to increase the risk of deep venous thrombosis and other evidence suggests a slightly increased mortality after stroke.

Strontium

Strontium ranelate reduces bone resorption but its mechanism of action is unknown. A 2008 Cochrane systematic review[36] of three randomised controlled trials reported a 37% reduction in vertebral fractures and a 14% reduction in non-vertebral fractures over three years when strontium was used for established osteoporosis. However, monitoring of bone mineral density while on therapy is difficult to interpret. Up to 50% of any increase in spinal bone mineral density is due to the atomic weight of strontium and the distribution across the skeleton can be highly variable.

** T-score: the number of standard deviations that bone mineral density differs from that of a young adult of the same sex

Recent data have raised significant safety concerns, particularly the risk of myocardial infarction. This has curtailed the use of strontium with contraindications in patients with a history of ischaemic heart disease, venous thromboembolism, peripheral vascular or cerebrovascular disease. Strontium use is declining in Australia, but it remains an option for people unable to tolerate other drugs and who have a low cardiovascular risk.[37]

Teriparatide

Teriparatide is a synthetic form of parathyroid hormone and is the only currently available drug that increases bone formation. As a last line of therapy, teriparatide is used to treat severe osteoporosis and is subsidised in Australia when people continue to fracture despite receiving at least 12 months treatment with first-line therapies. The rate of vertebral fractures may be reduced by up to 65%. There is an overall reduction in nonvertebral fractures, but the rate of hip fractures is not reduced.

Contraindications include patients younger than 25 years, known or suspected Paget's disease or previous radiotherapy to bone. Additional contraindications include pre-existing hypercalcaemia, malignancy, kidney disease and primary hyperparathyroidism. Rat studies have shown a risk of bone sarcomas and this is the only basis for the recommended lifetime exposure to teriparatide being limited to 18 months. Following a course of teriparatide, patients should receive antiresorptive therapy (e.g. raloxifene, a bisphosphonate, denosumab, strontium ranelate) to further increase bone mineral density and maintain the anti-fracture effect.

New drugs

There are some drugs in development, but their role is currently uncertain. Cathepsin K is elevated in women with postmenopausal osteoporosis. It is a cysteine protease that cleaves collagen 1, the major collagen type in bone. Bone mass can therefore be preserved by inhibiting cathepsin. Clinical trials with cathepsin K inhibitors, such as odanacatib, have shown improvements in bone mineral density at the spine and hip. These trials have also found a reduction in bone resorption markers with minimal effect on bone formation.

Another target for therapy is sclerostin. It is produced by osteocytes as a glycoprotein inhibitor of osteoblast signalling. Romosozumab is an anti-sclerostin monoclonal antibody that increased bone formation and bone mineral density in phase I and phase II trials. Further evaluation of the efficacy and safety of this drug in a large phase III controlled study is awaited. These interventions appear to be promising drugs for the treatment of osteoporosis.[38,39]

Conclusion

As our population ages, osteoporotic fractures are likely to occur more frequently. While preventive measures in the form of exercise are ideal and lifestyle measures play their role, they have limited efficacy in established osteoporosis. There are readily available screening tests along with effective treatments to prevent fractures. All men and women over the age of 50 who sustain a fracture should be assessed for antiresorptive therapy.

Therapy can and should be tailored to the individual. Bisphosphonates are by far the preferred treatment from a cost-effectiveness perspective. Newer treatments are available for patients who cannot use bisphosphonates. Surveillance for the potential adverse effects of therapy and the need for the continuation of therapy is essential.

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Further Reading

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Self-assessment questions

Question 1

A 69-year-old woman was admitted to the ETU of a General Hospital with a history of sudden visual deterioration and severe headache. Her medical history is diabetes for 12 years and hypertension for 8 years. She has had a mastectomy for carcinoma of the left breast 24 years ago. She is on Human Mixtard insulin 15 units s.c. twice a day, enalapril 5 mg twice a day, and atenolol 50 mg twice a day. Examination by the Resident Physician revealed a BP of 170/95 mmHg, pulse 66 bpm, oral temperature 37° Celsius, a palpable spleen and liver 3 cm below the costal margins, and a left homonymous hemianopia. She was rational and conscious, and funduscopy showed only bilateral diabetic retinal changes. Blood tests results at 24 hours are given below, along with the ECG and CXR findings.

Hb	17.5 g/dl	(12.0 – 15.5)	MCV	75 fl	(80 – 96)
Haematocrit	55%	(37 – 47%)	ESR	5 mm one hour	(< 20)
WCC	11.8×10^9/1	(4 – 11)	Creatinine	140 µmol/l	(75 – 115)
Neutrophils	8.5×10^9/1	(2 – 7.5)	Urea	11.0 mmol/I	(2.5 – 6.5)
Lymphocytes	2.6×10^9/1	(1.5 – 4.0)	ALP	145 u/1	(35 – 115)
Eosinophils	0.04×10^9/1	(0.04 – 0.4)	Glucose (random)	7.0 mmol/l	(< 8.75)
Basophils	0.04×10^9/1	(0.01– 0.1)	HbA 1c	10%	(< 7.0)
Platelets	480×11^9/1	(150 – 400)			

CXR – Cardiac silhoutte widened, left ventricular profile suggestive

ECG – Sinus rhythm, rate 68 bpm. Left ventricular hypertrophy

1. What is the most likely diagnosis at this stage?
2. What confirmatory test should be done?
3. What is the likely aetiology of the homonymous hemianopia?
4. What confirmatory test should be done?

Question 2

A 45-year-old unkempt man was referred to an epilepsy clinic for poor control of seizures and vague pains in all four limbs for 1 year, with seizures occurring at least twice a month. He had been stabilised on phenytoin sodium 300 mg a day 20 years ago, and had continued on this medication thereafter, without attending any clinic. He consumed arrack with lunch and dinner every day, estimated at 100 ml of ethanol by the S.H.O. The clinical examination was normal except for a fine tremor, gross periodontitis, and a recent memory deficit. Initial in-ward results are as follows,

Hb	12.0 g/dl	(14.0 – 15.5)	ALT	45 IU	(< 40)
MCV	99 fl	(80 – 96)	AST	38 IU	(12 – 40)
MCHC	32 g/dl	(32 – 36)	ALP	740 IU	(40 – 110)
Creatinine	100 micromol/l	(75 – 115)	Bilirubin	20 micromol/l	(< 17)
E. GFR	60 ml/min		Calcium (corrected)	1.9 mmol/l	(2.20 – 2.67)
Glucose (fasting)	6.2 mmol/l	(4.5 – 5.6)	Phosphate	0.6 mrnol/l	(0.80 – 1.5)
			Albumin	30 g/l	(35 – 50)

1. What are the significant biochemical abnormalities?
2. What are the likely diagnoses?

Answers to self-assessment questions

Question 1

1. This woman has polycythaemia vera. The raised haemoglobin content, haematocrit and platelet count, hypertension, hepato-splenomegaly, and sudden onset of homonymous hemianopia put the diagnosis almost beyond doubt.

2. JAK2, V 617 F or the functionally similar JAK 2 exon 12 mutation.

3. An infarct in the right occipital lobe or right optic tract.
   A CT-scan showed an infarct in the right occipital lobe.

Question 2

1. The striking biochemical abnormalities are a raised ALP, hypocalcaemia, hypophosphataemia, hypoalbuminaemia, and macrocytic anaemia.

2. The clinical picture is of self-neglect in a boozer. The likely diagnoses are macrocytic anaemia from folate deficiency (alcohol plus diet), osteomalacia (prolonged phenytoin use plus diet), protein malnutrition (diet) and gum hypertrophy and consequent periodontitis (phenytoin).

   The raised ALP is not of hepatic origin (AST, ALT, bilirubin are normal). Isoenzyme studies confirmed bony origin of ALP, and bone biopsy confirmed osteomalacia. The fasting blood glucose became normal with a full and balanced diet (never heard of "starvation diabetes"?)

   The patient responded to oral folic acid, calcium lactate and colecalciferol. The epilepsy medication was changed to topiramate, and he was referred to counselling for the alcohol problem.

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