

Management of Hyperphosphataemia in Chronic Kidney Disease: Summary of National Institute for Health and Clinical Excellence (NICE) Guideline

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Key Words

Phosphate · Hyperphosphataemia · Chronic kidney disease · Guideline · National Institute for Health and Clinical Excellence

Abstract

Bone disease and ectopic calcification are the two main consequences of hyperphosphataemia of chronic kidney disease (CKD). Observational studies have demonstrated that hyperphosphataemia in CKD is associated with increased mortality. Furthermore, the use of phosphate binders in dialysis patients is associated with significantly lower mortality. The UK Renal Registry data show significant underachievement of phosphate targets in dialysis patients. It is believed to be due to wide variation in how management interventions are used. The National Institute for Health and Clinical Excellence (NICE) has developed a guideline on the management of hyperphosphataemia in CKD. This is based on the evidence currently available using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. This review outlines the recommendations including research recommendations and discusses methodology, rationale and challenges faced in developing this guideline and the health economic model used to assess the cost-effectiveness of different phosphate binders.

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Introduction

In chronic kidney disease (CKD) there is derangement of phosphate homeostasis. The serum phosphate level is maintained by a balance between absorption of ingested phosphate, excretion by the kidney and the reservoir function of the skeletal system. The kidney is the key regulator of this homeostasis. As CKD progresses, phosphate excretion by the kidney diminishes, which raises the serum phosphate level. This positive phosphate balance is further exacerbated by the impairment of the reservoir function of the skeleton in advanced CKD [1]. The two main consequences of a high serum phosphate level are increased parathyroid hormone secretion that starts a cascade of events leading to bone disease and ectopic calcification in the soft tissue and blood vessels.

Cardiovascular morbidity and mortality are high in CKD and the risk increases progressively with the progression of CKD [2]. Those with end-stage kidney disease have a greatly increased risk of cardiovascular mortality [3]. Vascular stiffness and calcification related to the positive phosphate balance are thought to contribute significantly to this high cardiovascular risk [4–6]. Observational studies in end-stage kidney disease show a graded relationship between serum phosphate level and cardiovascular events [7, 8]. Similar observations have been made in patients with advanced CKD who are not on di-

alysis [9, 10]. On the other hand, using an instrumental-variable analysis adjusted for case-mix and nutritional indicators, the Dialysis Outcomes and Practice Patterns Study (DOPPS) demonstrated facility percentage of phosphate binder prescription was associated inversely with mortality [HR for 10% more phosphate binders: 0.95 (95% CI: 0.92–0.99)] [11]. Furthermore, even in people with normal kidney function, a relative increase in serum phosphate within the normal range has been linked to cardiovascular disease in a number of observational cohorts, prompting some to suggest phosphate may be the ‘the new cholesterol’ [12–14].

Paediatric studies have also shown that serum phosphate causes thickening and stiffness of the arteries [15, 16] resulting from a deposition of calcium and phosphate in the vessel wall [17] as well as left ventricular hypertrophy [18]. A key risk factor highlighted by virtually all of the paediatric studies is the strong linear association between deteriorating vascular measures and high serum phosphate levels [16, 19, 20], suggesting that dysregulated mineral metabolism is central to the vasculopathy of childhood CKD.

The UK Renal Registry data (2011) show that only 56% of adult haemodialysis and 69% of adult peritoneal dialysis patients achieve the recommended serum phosphate level of 1.1–1.7 mmol/l. Among the paediatric patients, only 51% of haemodialysis and 74% of peritoneal dialysis patients achieve the age-related targets [21]. It is believed that this may be because of wide variation between units and practices across the UK in how management interventions are used.

In view of the untoward effects of hyperphosphataemia alluded to above, it is important to manage hyperphosphataemia in CKD effectively. This guideline [22] offers best practice advice on the care of adults, children and young people with stage 4 or 5 CKD, including those on dialysis, who have or are at risk of hyperphosphataemia.

Methodology

The guideline was developed according to National Institute for Health and Clinical Excellence (NICE) guideline methodology [23], which involves systematically searching, critically appraising and summarising the evidence. Papers were identified from a number of different databases (Medline, Embase, Medline in Process, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials and the Centre for Reviews and Dissemination) using a broad search strategy. Of the 16,463 abstracts and titles, 1,288 full texts were reviewed, of which 79 were

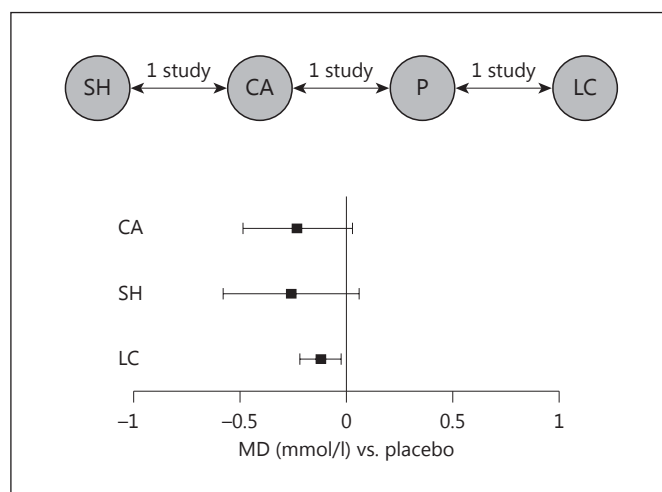


Fig. 1. Multiple treatment comparison network: serum phosphate in adults with stage 4 or 5 CKD who are not on dialysis [3 RCTs; 28–30]. Relative effectiveness compared to placebo: serum phosphate. MD = Mean difference; CA = calcium acetate; LC = lanthanum carbonate; P = placebo; SH = sevelamer hydrochloride.

included. Meta-analyses were performed to answer individual questions. Only randomised controlled trials (RCTs) were included (except for patient education review protocol and sequencing of binders in the absence of RCT evidence) in accordance with NICE policy. Grading of Recommendations Assessment, Development and Evaluation (GRADE) profiles suggested that the quality of the available evidence was either low or very low in almost all cases.

As there was a lack of evidence allowing a direct comparison between all of the possible treatments, a series of multiple treatment comparisons were carried out to aid the guidelines development group’s (GDG) decision-making process. Due to the use of continuous measures and the wide range of follow-up times presented within the evidence base, it was not possible to develop a single network which assessed all of the treatments at the various different time-points. Therefore, a series of network analyses were carried out at 3 months (90 days), 6 months (180 days) and 12 months (360 days). Figures 1–5 are examples of multiple treatment comparisons for phosphate. Calcium acetate performed consistently well in all of the analyses at various time-points, which supports the recommendations. Further details are available in the guidance [22] (<http://guidance.nice.org.uk/CG157>).

A multidisciplinary guideline development group discussed the evidence and formulated clinical recommendations. An economic model was developed to identify the most cost-effective strategies for treating hyperphosphataemia with different phosphate binders in children, young people and adults. The model used an individual patient (‘discrete event’) simulation approach, capturing costs and effects associated with a series of discrete health states (fig. 6). The cost utility plane for first-line phosphate binder use (fig. 7) supports the use of calcium acetate. The cost utility plane for sequential use (switch), from calcium acetate to

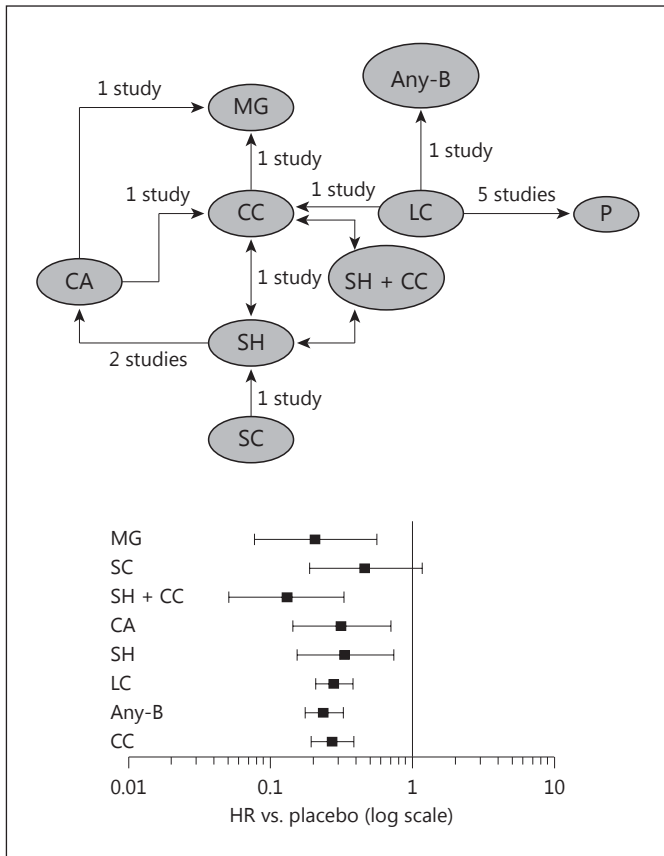


Fig. 2. Multiple treatment comparison network: proportion of patients achieving phosphate control [15 RCTs; 31–45]. Relative effectiveness compared to placebo: proportion achieving phosphate control. Any-B = Any binder; CA = calcium acetate; CC = calcium carbonate; LC = lanthanum carbonate; MG = magnesium carbonate; P = placebo; SC = sevelamer carbonate; SH = sevelamer hydrochloride.

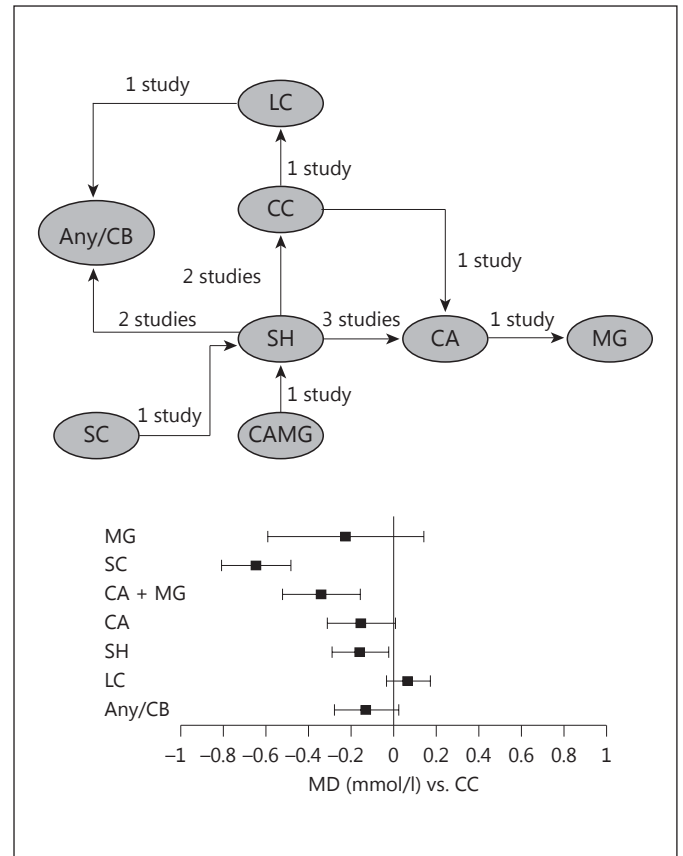


Fig. 3. Network binder map of serum phosphate at 90 days for patients with CKD stage 5 on dialysis [13 RCTs; 34, 37–39, 44, 46–53]. Relative effectiveness compared to calcium carbonate: serum phosphate at 90 days. MD = Mean difference; Any/CB = any calcium binder; CA = calcium acetate; CAMG = calcium acetate and magnesium carbonate; CC = calcium carbonate; LC = lanthanum carbonate; MG = magnesium carbonate; SC = sevelamer carbonate; SH = sevelamer hydrochloride.

either sevelamer hydrochloride or lanthanum carbonate, supports the use of either treatment taking into account the NICE threshold for the incremental cost effectiveness ratio per quality of life years gained (fig. 8). The full details of these analyses are available in NICE guidance [22] (<http://guidance.nice.org.uk/CG157>).

The guideline went through an external consultation with stakeholders. The development group assessed the comments, re-analysed the data where necessary, and modified the guideline. The GDG made recommendations based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. The wording used in the recommendations in this guideline denotes the strength of a recommendation, i.e. certainty with which the recommendation is made. Where the word ‘offer’ has been used in the recommendation, it suggests that the intervention will benefit the vast majority of patients and is cost-effective. This is a strong recommendation. The word ‘consider’ is used where the GDG is confident that an

intervention will do more good than harm for most patients and be cost-effective, but other options may be similarly cost-effective. In this situation, the choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient’s values and preferences; the healthcare professional should consider the options and discuss these with the patient. The full guideline contains details of the methods and evidence used to develop the guideline [22].

NICE has produced four different versions of the guideline: a full version; a NICE Pathway; a version known as the ‘NICE Guideline’, which summarises the recommendations, and a version for patients and the public. NICE has also developed implementation tools. All these documents are available from the NICE website (www.nice.org.uk). Future updates of the guideline will be published according to the NICE guideline development programme.

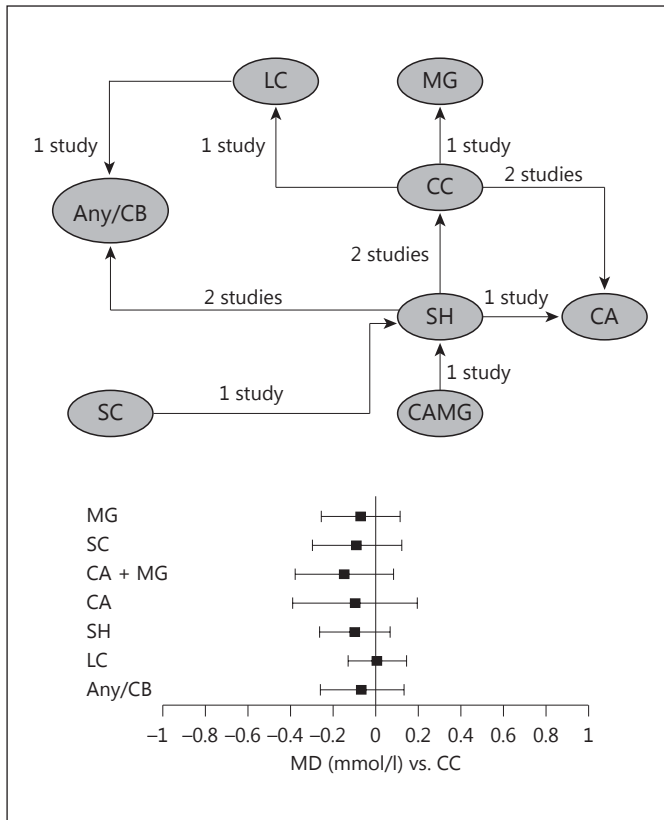


Fig. 4. Network binder map of serum phosphate at 180 days for patients with CKD stage 5 on dialysis [12 RCTs; 37–39, 45–52, 54]. Relative effectiveness compared to calcium carbonate: serum phosphate at 180 days. MD = Mean difference; Any/CB = any calcium binder; CA = calcium acetate; CAMG = calcium acetate and magnesium carbonate; CC = calcium carbonate; LC = lanthanum carbonate; MG = magnesium carbonate; SC = sevelamer carbonate; SH = sevelamer hydrochloride.

Recommendations

Dietary Management: Children, Young People and Adults

A specialist renal dietitian, supported by healthcare professionals with the necessary skills and competencies, should carry out a dietary assessment and give individualised information and advice on dietary phosphate management.

Advice on dietary phosphate management should be tailored to individual learning needs and preferences, rather than being provided through a generalised or complex multicomponent programme of delivery.

Give information about controlling intake of phosphate-rich foods (in particular, foods with a high phos-

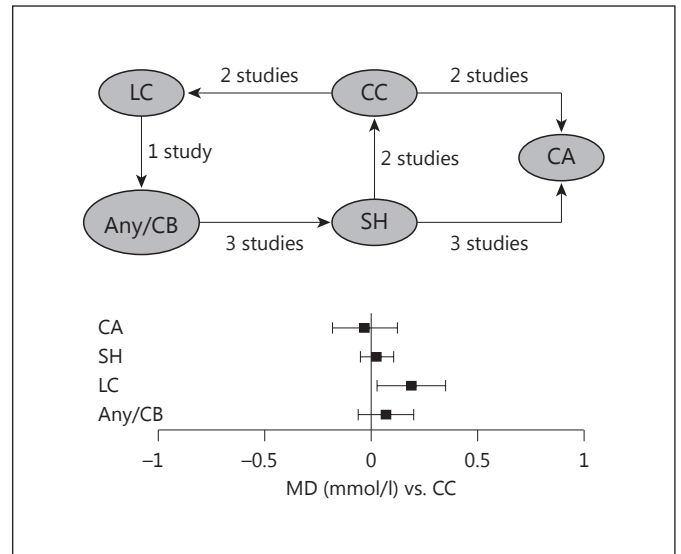


Fig. 5. Multiple treatment comparison network: serum phosphate at 360 days [13 RCTs; 39, 46–48, 51, 52, 54–60]. Relative effectiveness compared to calcium carbonate: serum phosphate at 360 days. MD = Mean difference; Any/CB = any calcium binder; CA = calcium acetate; CC = calcium carbonate; LC = lanthanum carbonate; SH = sevelamer hydrochloride.

phate content per gram of protein, as well as food and drinks with high levels of phosphate additives) to control serum phosphate, while avoiding malnutrition by maintaining a protein intake at or above the minimum recommended level. For people on dialysis, take into account possible dialysate protein losses.

If a nutritional supplement is needed to maintain protein intake in children and young people with hyperphosphataemia, offer a supplement with lower phosphate content, taking into account patient preference and other nutritional requirements.

Phosphate Binders: Children and Young People

Offer a calcium-based phosphate binder as the first-line phosphate binder to control serum phosphate in addition to dietary management.

If a series of serum calcium measurements shows a trend towards the age-adjusted upper limit of normal, consider a calcium-based binder in combination with sevelamer hydrochloride, taking into account other causes of rising calcium levels.

If the child or young person remain hyperphosphataemic despite adherence to a calcium-based phosphate binder, and whose serum calcium goes above the age-adjusted upper limit of normal, consider either combining

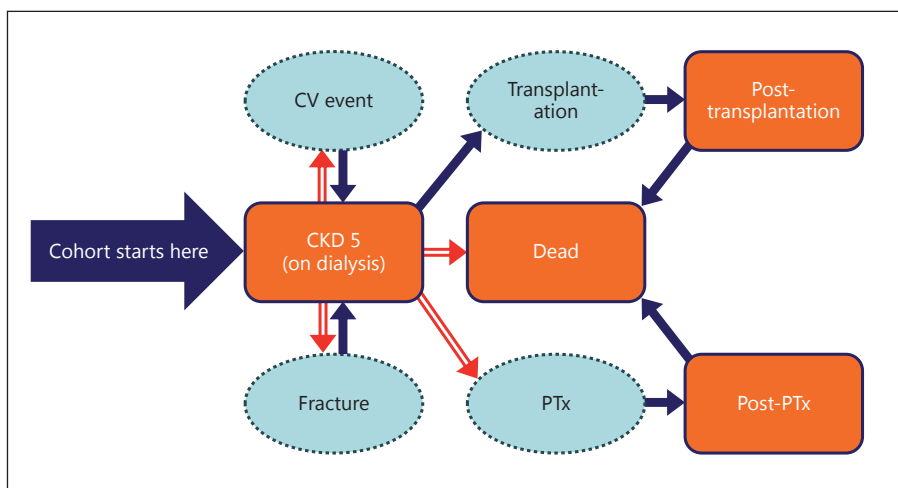


Fig. 6. Health economic model structure: an individual patient ('discrete event') simulation approach. PTx = Parathyroidectomy.

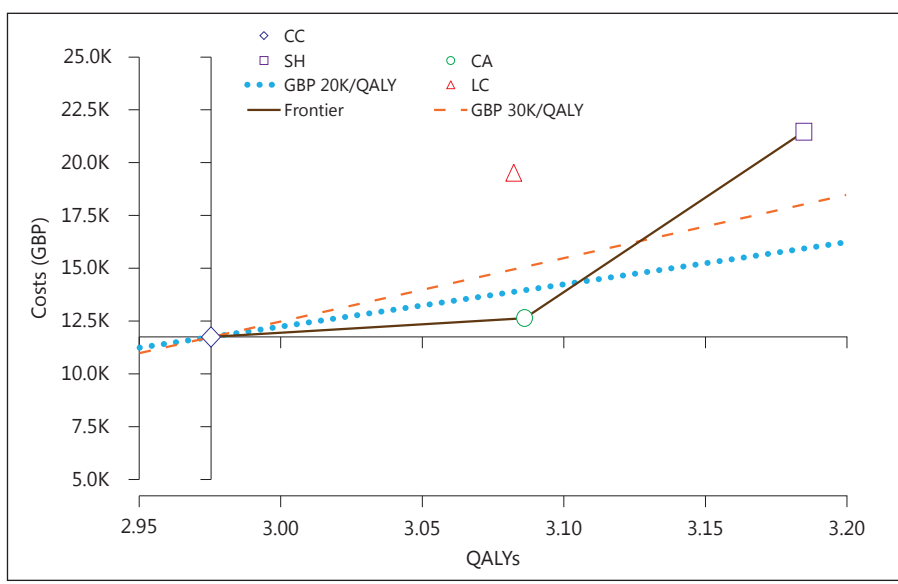


Fig. 7. Cost utility plane for first-line phosphate binder use. CA = Calcium acetate; CC = calcium carbonate; LC = lanthanum carbonate; SH = sevelamer hydrochloride; QALYs = quality-adjusted life years. Calcium acetate: an incremental cost effectiveness ratio (ICER) of GBP 8,000 per QALY gained compared to calcium carbonate (approx.). Sevelamer HCL: ICER of GBP 90,000 per QALY compared to calcium acetate (approx.)

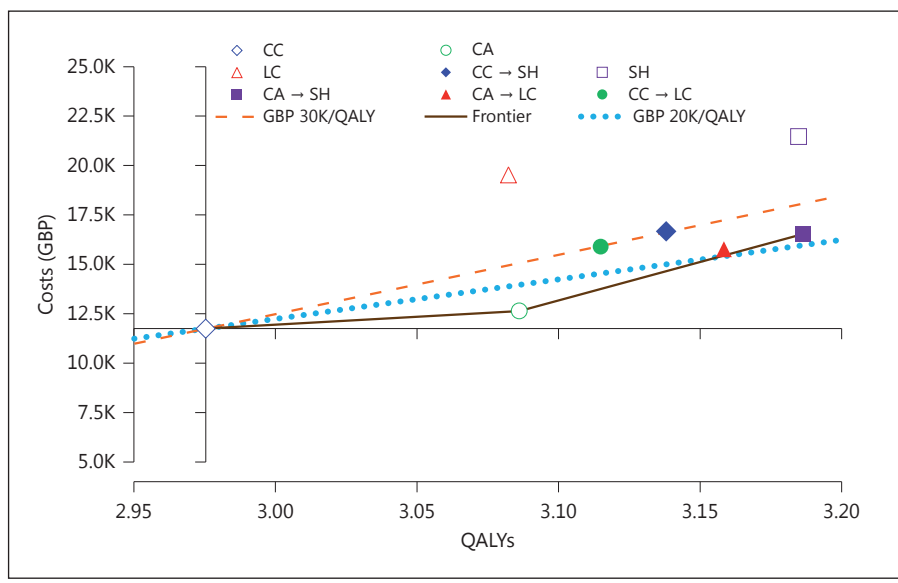


Fig. 8. Cost utility plane for sequential phosphate binder use. CA = Calcium acetate; CC = calcium carbonate; LC = lanthanum carbonate; SH = sevelamer hydrochloride; QALYs = quality-adjusted life years. Compared with a common baseline of indefinite calcium-acetate treatment: GBP 38,078 per QALY gained for switching to sevelamer hydrochloride, GBP 42,683 per QALY gained for switching to lanthanum carbonate.

with, or switching to, sevelamer hydrochloride, taking into account other causes of raised calcium.

Phosphate Binders: Adults

Offer calcium acetate as the first-line phosphate binder to control serum phosphate in addition to dietary management.

Consider calcium carbonate if calcium acetate is not tolerated or found unpalatable.

For those with stage 4 or 5 CKD not on dialysis who are taking a calcium-based binder:

- consider switching to a non-calcium-based binder if calcium-based binders are not tolerated
- consider either combining with, or switching to, a non-calcium-based binder if hypercalcaemia develops (taking into account other causes of raised calcium), or if serum parathyroid hormone levels are low.

For those with stage 5 CKD on dialysis who remain hyperphosphataemic despite adherence to the maximum recommended or tolerated dose of calcium-based binder, consider combining with, or switching to, a non-calcium-based binder.

For those with stage 5 CKD on dialysis who are taking a calcium-based binder, if serum phosphate is controlled by the current diet and phosphate binder, but serum calcium goes above the upper limit of normal, or serum parathyroid hormone levels are low, consider either combining with, or switching to, sevelamer hydrochloride or lanthanum carbonate, having taken into account other causes of raised calcium.

Phosphate Binders: Children, Young People and Adults

If a combination of phosphate binders is used, titrate the dosage to achieve control of serum phosphate while taking into account the effect of calcium-based binders on serum calcium levels.

Take into account patient preference and the ease of administration, as well as the clinical circumstances, when offering a phosphate binder.

Advise patients (or their parents and/or carers) that it is necessary to take phosphate binders with food to control serum phosphate.

Review of Treatments: Children, Young People and Adults

At every routine clinical review, assess the patient's serum phosphate control, taking into account: dietary phosphate management, phosphate binder regimen, adherence to diet and binder, and other factors that influence phosphate control such as vitamin D or dialysis.

Overcoming Barriers

The GDG faced a number of challenges in developing the guideline on management of hyperphosphataemia. As has been alluded to above, control of serum phosphate depends on diet, excretion and bone homeostasis, which are together controlled by a complex interplay of hormonal and metabolic mechanisms. The guideline was developed using the shorter of the NICE guideline development processes, with only 15 months from the first meeting to publication; the scope was limited to phosphate control only, with little or no reference to related physiological processes such as parathyroid hormone activity or the effects of vitamin D analogues or dialysis. Furthermore, many of the publications on which current practice is based, particularly in relation to the cardiovascular effects of raised calcium and phosphate levels in the blood, were not considered because they failed to reach the standard required for inclusion using the GRADE methodology [24]. Consequently, in considering the evidence, members of the GDG found it necessary to question some of the concepts on which standard practice is currently based, such as the assumption that only calcium-containing phosphate binders cause a detectable increase in serum calcium levels. A rise in plasma calcium concentration is seen, albeit to a lesser extent, with non-calcium-containing binders. It then becomes necessary to quantify the differential increase in serum calcium and to extrapolate the predicted effect on cardiovascular mortality. When the calculated effect on predicted mortality is then incorporated into the health economic model, predicted life expectancy compares very closely to that seen in the longest available empirical follow-up of trials comparing sevelamer hydrochloride with calcium-based binders [25]. Modelled survival gains are more modest than those seen in the longest available follow-up of people treated with lanthanum carbonate [26]; this may be caused or exacerbated by differences between the trial population and the modelled cohort.

Another subject for debate was the inclusion or exclusion of aluminium hydroxide in the guideline. The GDG was conscious that this potent and inexpensive phosphate binder is in widespread use in many parts of the world [27]. There was detailed discussion about interpretation of studies describing the severe consequences of aluminium toxicity, which were conducted during a time when water concentrations were much higher and the methodology for removal less refined. Although the evidence that aluminium toxicity arises from pharmacological admin-

istration is weak, there is also very scant published data on its efficacy as a phosphate binder. Consequently, the GDG decided to differentiate the advice that it gave in relation to adults on dialysis, i.e. for whom specific non-calcium-containing binder preparations were recommended, and those not on dialysis, i.e. for whom any non-calcium-containing binder could be used including, by inference, aluminium hydroxide. The GDG consequently gave a high priority in the research recommendations for studies into the efficacy and potential toxicity of aluminium hydroxide preparations.

There is a general paucity of high-quality evidence, particularly in relation to treating children and young adults with hyperphosphataemia, and in adults with CKD 4 or 5 who are not on dialysis. The GDG outlined a number of research recommendations with a view to improving the evidence base and treatment of hyperphosphataemia in the future.

Research Recommendations

The GDG has made the following recommendations for research, based on the paucity of evidence, to improve NICE guidance and patient care in the future:

- Which binders are most effective in controlling serum phosphate in adults with stage 4 or 5 CKD who are not on dialysis?

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- In adults with stage 4 or 5 CKD, including those on dialysis, what is the long-term effectiveness and safety of aluminium hydroxide in controlling serum phosphate?
- In adults with stage 4 or 5 CKD, including those on dialysis, what is the long-term effectiveness and safety of magnesium carbonate in controlling serum phosphate?
- Which binders are most effective in controlling serum phosphate in children with stage 4 or 5 CKD, including those who are on dialysis?
- For adults with stage 4 or 5 CKD, including those on dialysis, what is the most effective sequence or combination of phosphate binders to control serum phosphate?

The GDG and the Project Team

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