

**NHS England**

**Evidence review: Bile acid replacement  
therapy for inborn errors of bile acid  
synthesis**



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# **Evidence review: Bile acid replacement therapy for inborn errors of bile acid synthesis**

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## 1 Introduction

### Introduction

- Bile acids are chemical compounds secreted by the liver that assist in the intestinal absorption of fat and fat-soluble vitamins.
- The objective of this evidence review is to investigate the clinical effectiveness, cost effectiveness and the safety of the primary bile acids cholic acid and chenodeoxycholic acid in the treatment of inborn errors of primary bile acid synthesis.

### Existing guidance from the National Institute for Health and Care Excellence (NICE)

- We found no guidance from NICE about bile acid replacement therapy for inborn errors of bile acid synthesis.

### The indication and epidemiology

- Inborn errors of primary bile acid synthesis are rare congenital genetic disorders which affect enzymes catalysing reactions in the synthesis of the primary bile acids, cholic and chenodeoxycholic acid. They affect approximately 0.6 per 100,000 population in the EU, equivalent to approximately 321 people in England (Balistreri 1999).
- Because affected people do not produce normal bile acids, bile acid intermediates accumulate, along with abnormal bile acids and alcohols derived from these compounds. These can damage the liver and may cause liver failure. Furthermore, the absence of primary bile acids leads to malabsorption of fat and fat-soluble vitamins. Left untreated, these conditions can lead to developmental delay and neurological abnormalities, as a result of malabsorption or other manifestations of the underlying congenital abnormality. They are often progressive and can be fatal (Bove 2000, Bove 2004, Clayton 2006).
- Inborn errors of primary bile acid handling are categorised as primary and secondary.
- Primary metabolic defects involve congenital deficiencies in enzymes required to synthesise the two main bile acids, cholic acid and chenodeoxycholic acid (Clayton 2006). They include
  - disorders of steroid nucleus modification such as deficiency of 3 $\beta$ -hydroxy- $\Delta^5$ -C<sub>27</sub>-steroid dehydrogenase and of  $\Delta^4$ -3-oxosteroid 5 $\beta$ -reductase. These are autosomal recessive disorders presenting with liver disease in infancy or childhood. 3 $\beta$ -hydroxy- $\Delta^5$ -C<sub>27</sub>-steroid dehydrogenase deficiency is the most common primary bile acid synthesis defect. It usually presents in neonates, although onset can occur from 3 months to 14 years.  $\Delta^4$ -3-oxosteroid 5 $\beta$ -reductase deficiency can lead to rapid liver failure, with a 50% mortality rate in infants for whom diagnosis is delayed.
  - cerebrotendinous xanthomatosis, caused by a defect of sterol 27 hydroxylase. This may cause liver disease in infancy but it may also present with infantile onset diarrhoea, childhood onset cataract and developmental delay, and as a lipid storage disorder in adolescents and young adults with tendon xanthomata and progressive neurological dysfunction.
  - defects of peroxisomal enzymes and transporters, which can present with liver disease in infancy or childhood, or with developmental delay and, in some cases progressive neurological disease in childhood or adulthood.
  - oxysterol 7- $\alpha$ -hydroxylase deficiency, a disorder of the minor or “acidic” pathway of bile acid synthesis. This enzyme deficiency can result in severe liver damage in infancy

but can also present in childhood or adult life with hereditary spastic paraplegia.

- Secondary metabolic defects are disorders of assembly of peroxisomes or of cholesterol synthesis (Clayton 2006). They include
  - peroxisome biogenesis disorders (comprising Zellweger syndrome spectrum disorders with liver and neurological dysfunction). These often have prominent central nervous system involvement leading to developmental delay and regression with demyelination, resulting in neuro-disability and death. These patients present with liver disease of varying severity.
  - Smith-Lemli-Opitz syndrome, caused by a deficiency of  $\Delta^7$ -desaturase. This is a disorder of cholesterol synthesis with secondary defective bile acid synthesis. The usual presentation is as a dysmorphic developmental delay syndrome but severe liver disease in infancy can occur.

### **Standard treatment and pathway of care**

- Treatment includes supplementation with vitamins A, D, E, and K and nutrients for individuals with malabsorption (Clayton 2006).
- Standard treatment may include the oral administration of one of the two primary bile acids, cholic acid or chenodeoxycholic acid. Ursodeoxycholic acid may also be prescribed (Heubi 2007).
- Individuals who do not respond to other treatment options may require a liver transplant.

### **The intervention (and licensed indication)**

- Cholic acid and chenodeoxycholic acid are the only treatment options believed to improve liver disease and malabsorption in steroid nucleus modification disorders; chenodeoxycholic acid is also prescribed to improve neurological disease in cerebrotendinous xanthomatosis (NHS England Policy Working Group 2018). There are no other available licensed pharmaceutical therapies believed to have equivalent efficacy, though statins are sometimes prescribed for cerebrotendinous xanthomatosis (NHS England Policy Working Group 2018).
- Cholic acid is licensed for the treatment of inborn errors of primary bile acid synthesis due to sterol 27-hydroxylase deficiency presenting as cerebrotendinous xanthomatosis, 2- (or  $\alpha$ -) methylacyl-CoA racemase deficiency or cholesterol 7 $\alpha$ -hydroxylase deficiency (European Medicines Agency 2015). The British National Formulary (BNF) lists its indications as inborn errors of primary bile acid synthesis (BNF online).
- Chenodeoxycholic acid is licensed for the treatment of inborn errors of primary bile acid synthesis due to sterol 27-hydroxylase deficiency presenting as cerebrotendinous xanthomatosis (European Medicines Agency 2017). The BNF lists its indications as cerebrotendinous xanthomatosis, the defective synthesis of bile acids and Smith-Lemli-Opitz syndrome (BNF online).

### **Rationale for use**

- Cholic acid is thought to act by inhibiting the synthesis of toxic partial bile acid biosynthetic products that result from blockages in the normal bile acid synthetic pathway (European Medicines Agency 2015). Chenodeoxycholic acid is thought to act by inhibiting excessive synthesis of cholesterol and cholestanol (European Medicines Agency 2017).

## 2 Summary of results

- Six papers matching the PICO were included in this review. All were uncontrolled case studies or small case series, most reporting results in children.
- Three reported results of bile acid replacement in  $\Delta^4$ -3-oxosteroid 5 $\beta$ -reductase deficiency (Daugherty 1993 (two children), Clayton 1996 (one child) and Lemonde 2003 (one child)), one reported results in two children with Smith-Lemli-Opitz syndrome (Nwokoro 1997), one reported results in a child with Zellweger syndrome (Setchell 1992) and one reported results in an adult with 3 $\beta$ -hydroxy- $\Delta$ 5-C<sub>27</sub>-steroid dehydrogenase deficiency (Nittono 2010).
- All six studies reported results of liver function tests, and four also reported urinary bile acid concentrations. No other results were reported, nor any tests of statistical significance.
- For example, Nittono et al (2010) reported a reduction in their patient's serum alanine transaminase from 45 IU/l before treatment with cholic acid and chenodeoxycholic acid, to 10 IU/l on treatment (normal range 5 to 45 IU/l). Total bilirubin fell from 6.8 mg/dl before treatment to 0.94 mg/dl on treatment (normal range 0.2 to 1.1 mg/dl). Lemonde et al (2003) reported a reduction in one patient's serum bilirubin from 446 mmol/l before treatment with cholic acid and chenodeoxycholic acid, to 117 mmol/l on treatment (normal range not stated).
- Taken together, the studies are consistent with improvements in liver function after the introduction of combination treatment with cholic acid and chenodeoxycholic acid. However, the evidence is scanty, with no information about the effects of this treatment on symptoms, disease progression, liver transplant rates or survival.
- The available evidence does not allow any comparisons to be made between combination treatment with cholic acid and chenodeoxycholic acid and any other treatment.
- The literature search found no evidence comparing the safety or cost-effectiveness of combination treatment of cholic acid and chenodeoxycholic acid with that of any other treatment.
- There is no evidence to identify subgroups that may experience more or less benefit from second line combination treatment with cholic acid and chenodeoxycholic acid compared to others with inborn errors of bile acid synthesis.
- Studies are needed which compare the combination treatment of cholic acid and chenodeoxycholic acid with alternatives. These studies should be randomised if possible, should include symptoms, disease progression and survival among the outcomes which they report and should be of long enough duration to detect differences in rates of these outcomes.
- The lack of controlled studies makes it impossible to draw conclusions from this evidence about the clinical effectiveness of combination treatment with cholic acid and chenodeoxycholic acid. Although the studies' results are consistent with some improvement in liver function after combination treatment is started, this cannot be ascribed to the treatment without comparative studies. Fluctuations in the patients' clinical status or the play of chance are alternative explanations, particularly when so few patients are reported.

### 3 Methodology

- The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).
- An initial description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 9 for PICO).
- The PICO was used to search for relevant publications in Medline, Embase and Cochrane Library (see section 10 for search strategy).
- The search dates for publications were between 1 January 1990 and 20 March 2018.
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion.
- The initial search yielded no papers that fell within the PICO's scope. SPH consulted NHS England, who agreed to remove the requirement for papers to report controlled studies.
- Evidence from all papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using National Service Framework for Long term Conditions (NSF-LTC) evidence assessment framework (see section 7 below).
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8 below).

### 4 Results

Six papers matching the PICO were included in this review. All were uncontrolled case studies or small case series, most reporting results in children. Three reported results of bile acid replacement in  $\Delta^4$ -3-oxosteroid  $5\beta$ -reductase deficiency (Daugherty 1993 (two children), Clayton 1996 (one child) and Lemonde 2003 (one child)), one reported results in two children with Smith-Lemli-Opitz syndrome (Nwokoro 1997), one reported results in a child with Zellweger syndrome (Setchell 1992) and one reported results in an adult with  $3\beta$ -hydroxy- $\Delta^5$ -C<sub>27</sub>-steroid dehydrogenase deficiency (Nittono 2010).

All six studies reported results of liver function tests, and four also reported urinary bile acid concentrations. No other results were reported.

#### **Liver function tests**

Three studies reported changes in serum concentrations of alanine transaminase (ALT). Nittono et al (2010) reported a reduction in their patient's serum ALT from 45 IU/l before treatment with cholic acid and chenodeoxycholic acid, to 10 IU/l on treatment (normal range 5 to 45 IU/l). Lemonde et al (2003) reported a reduction in one patient's serum ALT from 1702 IU/l before treatment with cholic acid and chenodeoxycholic acid, to 184 IU/l on treatment (same normal range). Both patients reported by Daugherty et al 1993 had a normal ALT concentration before and after treatment.

Five studies reported changes in serum bilirubin concentrations. Nittono et al (2010) reported that total bilirubin fell from 6.8 mg/dl before treatment to 0.94 mg/dl on treatment (normal range 0.2 to 1.1 mg/dl). Lemonde et al (2003) reported a reduction in one patient's serum bilirubin from 446  $\mu$ mol/l before treatment with cholic acid and chenodeoxycholic acid, to 117  $\mu$ mol/l on treatment.

(normal range not stated). Clayton et al (1996) reported a reduction in their patient's serum bilirubin from 88  $\mu\text{mol/l}$  before treatment with cholic acid and chenodeoxycholic acid, to 5  $\mu\text{mol/l}$  on treatment (normal range not stated, results estimated from graphs and hence approximate). One twin in Daugherty et al's study had an unchanged bilirubin concentration of 20 mg/dl before and after treatment, while the other had values of 20mg/dl and 23mg/dl respectively (normal range 0 to 1.8mg/dl). Setchell et al (1992) reported that the infant in their study had a total bilirubin concentration before treatment of 3.2mg/dl, at three months of 1.1 mg/dl, at six months of 0.8 mg/dl and at eight months of 0.5 mg/dl (normal range not stated).

### **Urinary bile acid concentrations**

Two studies reported total urinary bile acid concentrations. Daugherty et al (1993) reported that one of the twins in their study had a concentration before treatment of 46 $\mu\text{mol/l}$ , and after treatment of 40 $\mu\text{mol/l}$ ; the other twin's results were 23 $\mu\text{mol/l}$  and 70 $\mu\text{mol/l}$  respectively (normal ranges not reported). The infant reported by Setchell et al (1992) had total urinary bile acids before treatment of 27.8  $\mu\text{mol/l}$ , on day 1 of 104  $\mu\text{mol/l}$ , on day 7 of 155  $\mu\text{mol/l}$  and on day 10 of 119  $\mu\text{mol/l}$  (normal ranges not reported).

None of the studies used tests of statistical significance to assess whether chance might explain their findings. Full details of the studies and their results are in the evidence tables in section 7.

Taken together, the studies are consistent with improvements in liver function after the introduction of combination treatment with cholic acid and chenodeoxycholic acid, compared with results before treatment. However, the evidence was scanty, with no information about the effects of this treatment on symptoms, disease progression, liver transplant rates or survival. The available evidence does not allow any comparisons to be made between combination treatment with cholic acid and chenodeoxycholic acid, and any other treatment.

### **What is the evidence for the clinical effectiveness of second line combination treatment of cholic acid and chenodeoxycholic acid compared to supportive care or single agent treatment in people with inborn errors of bile acid synthesis?**

The literature search found no evidence comparing the clinical effectiveness of combination treatment of cholic acid and chenodeoxycholic acid with that of any other treatment.

There are several studies which report the results of biochemical analyses of blood and in a few cases urine, before and after treatment. These are consistent with improvements in these measures, but no other outcomes were reported.

The absence of controlled studies severely limits the conclusions which can be drawn from this evidence.

### **What is the evidence for the safety of second line combination treatment with cholic acid and chenodeoxycholic acid compared with supportive care or single agent treatment for people with inborn errors of bile acid synthesis?**

The literature search found no evidence comparing the safety of combination treatment of cholic acid and chenodeoxycholic acid with that of any other treatment.



**What is the evidence for the cost effectiveness of second line combination treatment with cholic acid and chenodeoxycholic acid compared to supportive care or single agent treatment for people with inborn errors of bile acid synthesis?**

The literature search found no evidence comparing the cost effectiveness of combination treatment of cholic acid and chenodeoxycholic acid with that of any other treatment.

**Is there evidence to identify subgroups as defined in the PICO who may experience more or less benefit from second line combination treatment with cholic acid and chenodeoxycholic acid compared to others with inborn errors of bile acid synthesis?**

None was found. The number of participants with each diagnosis was too small for any conclusions specific to a subgroup to be possible.

## 5 Discussion

The available evidence on combination treatment with cholic acid and chenodeoxycholic acid is very limited. Only eight patients were reported in the studies included in this review, which covers four diagnoses. There appear to be no studies comparing this treatment with other treatments, and none reporting any outcomes other than liver function tests and urinary bile acid concentrations. There is no information on the effects of combination treatment on symptoms, disease progression, liver transplant rates or survival. Many of the studies were short-term.

This evidence is consistent with the hypothesis that combination treatment improves liver function tests and that urinary bile acid secretion is closer to normal during this treatment. However, this is not sufficient to demonstrate that the treatment is clinically effective or beneficial to patients. Fluctuations in the patients' clinical status or the play of chance are alternative explanations, particularly when so few patients are reported. In any case, the relationship of liver function tests to symptoms, activities of daily living, quality of life, prognosis, transplant rates and survival is unclear but unlikely to be simple; this severely limits the value of the evidence reviewed here.

Bile acids are part of several biochemically distinct pathways, and disorders of bile acid synthesis have variable effects. It is difficult to apply the findings more widely of a study of a particular enzyme deficiency, especially if it is confined to people with a specific gene defect.

The literature search found no information about the safety and the cost effectiveness of the combination treatment.

Studies are needed which compare the combination treatment of cholic acid and chenodeoxycholic acid with alternatives. These studies should be randomised if possible, should include symptoms, disease progression and survival among the outcomes which they report and should be of long enough duration to detect differences in rates of these outcomes.

## 6 Conclusion

The lack of controlled studies makes it impossible to draw conclusions from this evidence about the clinical effectiveness of combination treatment with cholic acid and chenodeoxycholic acid. Although the studies' results are consistent with some improvement in liver function after combination treatment is started, this cannot be ascribed to the treatment without comparative

studies. Fluctuations in the patients' clinical status or the play of chance are alternative explanations.

There is no available evidence about the safety of combination treatment with cholic acid and chenodeoxycholic acid.

There is no available evidence about the cost effectiveness of combination treatment with cholic acid and chenodeoxycholic acid.

There are no identifiable subgroups that may experience more or less benefit from this treatment.

## 7 Evidence Summary Table

Use of cholic acid and chenodeoxycholic acid to treat inborn errors of bile acid synthesis									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Nitto et al 2010	P1: Case report  Japan	An adult female with 3 $\beta$ -hydroxy- $\Delta^5$ -C <sub>27</sub> -steroid dehydrogenase deficiency. Age not reported	<p>In February 1999, treatment was started with CA (120mg/day) and CDCA (400mg/day, as Regalan).</p> <p>In April 2004, Regalan was replaced with the same dose of Chenocol, another preparation of CDCA.</p> <p>In July 2004, CDCA was reduced to 375mg/day.</p>	Primary outcome  Clinical effectiveness	Liver function	<p>ALT (normal range 5 to 45 IU/l): before CA and CDCA treatment (April 1997) 45 IU/L, most recent results on this treatment (January 2009) 10 IU/L</p> <p>Total bilirubin (normal range 0.2 to 1.1 mg/dl): before CA and CDCA treatment (April 1997) 6.8 mg/dl, most recent results on this treatment (January 2009) 0.94 mg/dl</p> <p>Direct bilirubin (normal range 0 to 0.4 mg/dl): before CA and CDCA treatment (April 1997) 4.5 mg/dl, most recent results on this treatment (January 2009) 0.3 mg/dl</p> <p>Serum total bile acid (normal range 0 to 10 <math>\mu</math>mol/l): before CA and CDCA treatment (April 1997) 4.1 <math>\mu</math>mol/l, most recent results on this treatment (January 2009) 11.3 <math>\mu</math>mol/l.</p>	4	Direct	<p>The patient had a new mutation with a seven-base deletion. It is not clear how prevalent this is among people with 3<math>\beta</math>-hydroxy-<math>\Delta^5</math>-C<sub>27</sub>-steroid dehydrogenase deficiency.</p> <p>The results indicate an improvement in liver function followed the introduction of CA and CDCA. However, the authors report no tests of statistical significance.</p> <p>The levels of <math>\Delta^5</math>-urinary biliary acids are described as "suppressed to significantly low values", suggesting the changes are beneficial.</p> <p>The study provides no information on the treatment's impact on symptoms, quality of life or survival.</p>
				Primary outcome  Clinical effectiveness	Urinary bile acid concentrations	CA (normal ranges not reported): before CA and CDCA treatment 0 $\mu$ mol/mmol creatine (0%), most recent			

Use of cholic acid and chenodeoxycholic acid to treat inborn errors of bile acid synthesis									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
						<p>results on this treatment (January 2009) 0.68 <math>\mu\text{mol}/\text{mmol}</math> creatine (43.9%)</p> <p>CDCA (normal ranges not reported): before CA and CDCA treatment 0.32 <math>\mu\text{mol}/\text{mmol}</math> creatine (0.8%), most recent results on this treatment (January 2009) 0.15 <math>\mu\text{mol}/\text{mmol}</math> creatine (9.5%)</p> <p><math>\Delta^5\text{-}3\beta,7\alpha\text{-dihydroxy-5-cholenoic acid}</math> (normal ranges not reported): before CA and CDCA treatment 5.68 <math>\mu\text{mol}/\text{mmol}</math> creatine (14.6%), most recent results on this treatment (January 2009) 0 <math>\mu\text{mol}/\text{mmol}</math> creatine (0%)</p> <p><math>\Delta^5\text{-}3\beta,7\alpha,12\alpha\text{-trihydroxy-5-cholenoic acid}</math> (normal ranges not reported): before CA and CDCA treatment 32.7 <math>\mu\text{mol}/\text{mmol}</math> creatine (83.8%), most recent results on this treatment (January 2009) 0.14 <math>\mu\text{mol}/\text{mmol}</math> creatine (9.4%).</p>			
Lemond e et al 2003	P1: Case series	Three children with $\Delta^4\text{-}3\text{-}$	MS presented at 3 weeks with bilirubin	Primary outcome	Liver function	<i>MS at 8 months, probably before the introduction of CA plus</i>	9	Direct	One of the children reported here is also reported in Clayton et al 1996.

# Use of cholic acid and chenodeoxycholic acid to treat inborn errors of bile acid synthesis

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
	UK	oxosteroid 5 $\beta$ -reductase deficiency and a <i>SRD5B1</i> gene mutation. Two received CA and CDCA: MS (a girl of 9 years) and BH (a boy of 34 months). The third child, RM, a girl of 19 weeks, received CDCA but not CA.	316 $\mu$ mol/l (conjugated 145), AST 2279 U/l, ALT 1123 U/l and prothrombin time 15.4 seconds (control 12) (normal ranges not stated). MS was treated at 3 months of age with ursodeoxycholic acid and continued to have steatorrhoea, failure to thrive and fat soluble vitamin malabsorption. At an unspecified time at or after 8 months of age, treatment was changed to CA (8mg/kg/day) and CDCA (8mg/kg/day).  BH was treated from 8 weeks of age with CA (8mg/kg/day) and CDCA	Clinical effectiveness		<i>CDCA, though the authors do not state this</i>  Bilirubin 88 $\mu$ mol/l, AST 511 U/l, ALT 252 U/l, $\gamma$ -GT 36 U/l, normal ranges not stated but the authors indicate that the first three results were elevated but the $\gamma$ -GT was normal. CDCA (normal range 0.2 to 12.7 $\mu$ mol/l) <0.05 $\mu$ mol/l; CA (normal range 0.4 to 6.7 $\mu$ mol/l) <0.05 $\mu$ mol/l; 7 $\alpha$ -hydroxy-3-oxo-4-cholenoic acid (normal range <0.05 $\mu$ mol/l) 1.9 $\mu$ mol/l; 7 $\alpha$ ,12 $\alpha$ -dihydroxy-3-oxo-4-cholenoic acid (normal range <0.05 $\mu$ mol/l) 2.1 $\mu$ mol/l.  <i>BH</i> <i>Before treatment:</i> bilirubin 446 $\mu$ mol/l (normal range not reported); albumin 31 g/l (normal range not reported); ALT (normal range 5 to 45 U/l) 1702 U/l; $\gamma$ -GT (normal range 20 to 155 U/l) 103 U/l; prothrombin time (after parenteral vitamin K, normal range 12 to 16 seconds) 19 seconds.			The main focus of this study is genetic, and the timing and impact of medication changes are not reported clearly. There are no reported results for MS after treatment, though it "led to normalisation of liver function within three months and she remains well with normal liver function tests at the age of nine years (on bile acid replacement therapy)."  The results are consistent with an improvement in liver function following the introduction of CA and CDCA in BH. However, the authors report no tests of statistical significance.  The study provides no information on the treatment's impact on quality of life or survival.

# Use of cholic acid and chenodeoxycholic acid to treat inborn errors of bile acid synthesis

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
			<p>(8mg/kg/day). At 12 weeks, CDCA was stopped because of pruritus. Liver function deteriorated, CDCA was restarted, cytomegalovirus infection was diagnosed and BH had a successful liver transplant.</p> <p>RM was treated at 6 weeks with ursodeoxycholic acid (30mg twice daily) and at 10 weeks CDCA was added (10mg three times daily). Liver failure led to transplantation at 19 weeks, but the patient died the next day.</p>			<p><i>After two weeks of treatment:</i> CDCA &lt;0.05 µmol/l; CA 0.026 µmol/l; 7α-hydroxy-3-oxo-4-cholenoic acid 6.7 µmol/l; 7α,12α-dihydroxy-3-oxo-4-cholenoic acid 7.6 µmol/l.</p> <p><i>After six weeks of treatment:</i> bilirubin 117 µmol/l; albumin 37 g/l; ALT 184 U/l; γ-GT 243 U/l; prothrombin time 13 seconds.</p> <p><i>RM</i> <i>Before treatment</i> Bilirubin 195 mmol/l; AST 680 U/l; ALT 559 U/l; ALP 818 U/l; γ-GT 29 U/l ("normal"); lactate dehydrogenase 1496 U/l; cholesterol 6 mM (normal range 1.2 to 4.6).</p> <p><i>At 10 weeks</i> Bilirubin 207 µmol/l.</p>			
Nwokoro et al 1997	P1: Case series USA	Six children with Smith-Lemli-Opitz syndrome.	AM was treated at 17 months of age CA "base" (15 mg/kg/day)	Primary outcome  Clinical effectiveness	Liver function	Results estimated from graphs and hence approximate. No normal ranges stated.	8	Direct	<p>The authors report no tests of statistical significance.</p> <p>It is unclear from the reported result what effect treatment had on liver function. The authors do not claim that there was a correlation between the blood</p>

# Use of cholic acid and chenodeoxycholic acid to treat inborn errors of bile acid synthesis

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
		<p>Two received CA and CDCA: AM (a girl of 44 months) and HS (also a girl of 44 months).</p> <p>KE (a girl of five years) received no bile acid replacement. She was on cholesterol treatment (increasing to 85mg/kg/day ) for the last eight months reported.</p> <p>The other 3 children, do not appear to have had significant liver disease; no blood analyses are reported for them.</p>	<p>and CDCA (7 mg/kg/day). CA was stopped at 32 months because of severe diarrhoea and, for reasons the authors do not specify, the CDCA was stopped at 43 months.</p> <p>HS was treated from 18 months with CA and CDCA (doses not reported). After 12 months, CDCA was stopped because of a rise in transaminase levels, and for reasons the authors do not specify CA was stopped at 40 months.</p>			<p><i>AM</i></p> <p>At start of treatment: cholesterol 40 mg/dl, 7-dehydrocholate 470 µmol/l.</p> <p>After 12 months of treatment: cholesterol 135 mg/dl, 7-dehydrocholate 110 µmol/l.</p> <p>After 24 months of treatment cholesterol 120 mg/dl, 7-dehydrocholate 100 µmol/l.</p> <p><i>HS</i></p> <p>At start of treatment: cholesterol 5 mg/dl, 7-dehydrocholate 210 µmol/l.</p> <p>After 12 months of treatment cholesterol 80 mg/dl, 7-dehydrocholate 250 µmol/l.</p> <p>After 24 months of treatment cholesterol 50 mg/dl, 7-dehydrocholate 220 µmol/l.</p> <p><i>KE</i></p> <p>At start of treatment: cholesterol 30 mg/dl, 7-dehydrocholate 250 µmol/l.</p> <p>No results reported after 12 or 24 months of treatment.</p>			<p>results that they report and the patients' clinical status. They provide no quantitative information on the treatment's impact on symptoms, quality of life or survival.</p>
Clayton et al	P1: Case	A child aged 1.4 years	The patient was treated	Primary outcome	Liver function	Results estimated from graphs and	8	Direct	The child reported here is also reported in Lemonde et al 2003.

# Use of cholic acid and chenodeoxycholic acid to treat inborn errors of bile acid synthesis

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
1996	report UK	with $\Delta^4$ -3-oxosteroid 5 $\beta$ -reductase deficiency.	from 0.2 to 0.7 years with ursodeoxycholic acid, and from 0.7 years with CA (8mg/kg/day) and CDCA (8mg/kg/day).	Clinical effectiveness		<p>hence approximate.</p> <p>At start of treatment: bilirubin 88 <math>\mu</math>mol/l, AST (normal range 20 to 60 IU/l) 511 IU/l. After 0.4 years of treatment bilirubin 5 <math>\mu</math>mol/l, AST 100 IU/l.</p> <p>Results tabulated in the paper:</p> <p>Plasma concentrations: 7<math>\alpha</math>-hydroxy-3-oxo-4-cholenoic acid (normally not detectable): on no treatment 1.94 <math>\mu</math>mol/l, on ursodeoxycholic acid 2.74 <math>\mu</math>mol/l, on CA and CDCA not detected.</p> <p>7<math>\alpha</math>,12<math>\alpha</math>-dihydroxy-3-oxo-4-cholenoic acid (normally not detectable): on no treatment 2.07 <math>\mu</math>mol/l, on ursodeoxycholic acid 3.05 <math>\mu</math>mol/l, on CA and CDCA not detected.</p> <p>Allocholic acid (normal range 0 to 0.15 <math>\mu</math>mol/l): on no treatment 0.76 <math>\mu</math>mol/l,</p>			<p>The results are consistent with an improvement in liver function following the introduction of CA and CDCA. However, the authors report no tests of statistical significance.</p> <p>The study provides no information on the treatment's impact on symptoms, quality of life or survival.</p> <p>The authors note that "The plasma bile acid profile of the patient was unique", limiting the generalisability of this study.</p> <p>Bilirubin concentrations are normally expressed in mmol/l, not <math>\mu</math>mol/l, raising the possibility of mis-reporting.</p>



# Use of cholic acid and chenodeoxycholic acid to treat inborn errors of bile acid synthesis

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
						on ursodeoxycholic acid 0.43 µmol/l, on CA and CDCA not detected.			
				Primary outcome	Urinary bile acid concentrations	Normal ranges not reported.			
				Clinical effectiveness		Urinary excretion: 7α-hydroxy-3-oxo-4-cholenoic acid: on no treatment 22 µmol/mmol creatinine, on ursodeoxycholic acid 9.1 µmol/mmol creatinine, on CA and CDCA 1 µmol/mmol creatinine.  7α,12α-dihydroxy-3-oxo-4-cholenoic acid: on no treatment 94 µmol/mmol creatinine, on ursodeoxycholic acid 82 µmol/mmol creatinine, on CA and CDCA 22 µmol/mmol creatinine.			
Daugherty et al 1993	P1: Case series  USA	Two male twins aged 5 years with Δ <sup>4</sup> -3-oxosteroid 5β-reductase deficiency.	The patients were started on CA and CDCA (doses not reported) on day 33 of life. After 16 days, CDCA was stopped for unreported reasons, and ursodeoxycholic acid was started.	Primary outcome  Clinical effectiveness	Liver function	<i>Twin A</i> Total bilirubin (normal range 0 to 1.8mg/dl): at day 28 20mg/dl, at day 49 20mg/dl;  Direct bilirubin (normal range 0 to 0.4mg/dl): at day 28 14mg/dl, at day 49 11mg/dl  AST (normal range 24 to 47 IU/l): at day 28 106IU/l, at day 49 167IU/l	7	Direct	There was no clear improvement in liver function test during the short period when CA and CDCA were both being prescribed. The authors report no tests of statistical significance. The paper was mainly concerned with liver histopathology and provides no information on the treatment's impact on symptoms, quality of life or survival.

Use of cholic acid and chenodeoxycholic acid to treat inborn errors of bile acid synthesis									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
						<p>ALT (normal range 7 to 56 IU/l): at day 28 "normal", at day 49 "normal"</p> <p>ALP (normal range 140 to 325 IU/l): at day 28 "normal", at day 49 "normal"</p> <p>Serum bile acids (normal range not reported): at day 28 52 µmol/l, at day 49 191 µmol/l</p> <p><i>Twin B</i> Total bilirubin: at day 28 20mg/dl, at day 49 23mg/dl</p> <p>Direct bilirubin: at day 28 14mg/dl, at day 49 18mg/dl</p> <p>AST: at day 28 92IU/l, at day 49 201IU/l;</p> <p>ALT: at day 28 "normal", at day 49 "normal"</p> <p>ALP: at day 28 "normal", at day 49 "normal"</p> <p>Serum bile acids: at day 28 12 µmol/l, at day 49 127 µmol/l.</p>			

# Use of cholic acid and chenodeoxycholic acid to treat inborn errors of bile acid synthesis

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
				Primary outcome  Clinical effectiveness	Urinary bile acid concentrations	<i>Twin A</i> Normal ranges not reported. At day 28 46µmol/l, at day 49 40µmol/l.  <i>Twin B</i> At day 28 23µmol/l, at day 49 70µmol/l.			
Setchell et al 1992	P1: Case report  Italy	A male child with Zellweger syndrome who died at one year of age	The patient was started on CA (100mg/day) and CDCA (100mg/day) at 28 weeks. This continued until the patient died at the age of one year from respiratory failure.	Primary outcome  Clinical effectiveness	Liver function	Normal ranges not reported for bilirubin.  Total bilirubin: before treatment 3.2mg/dl, at 3 months 1.1 mg/dl, at 6 months 0.8 mg/dl, at 8 months 0.5 mg/dl;  Direct bilirubin: before treatment 1.7 mg/dl, at 3 months 0.2 mg/dl, at 6 months 0.2 mg/dl, at 8 months 0.2 mg/dl.  Results estimated from graphs and hence approximate. Normal ranges shown on graph as 0 to 40 mU/ml for all the following liver function tests:  AST: before treatment 325mU/ml, at 3 months 350mU/ml, at 6 months 140mU/ml, at 8 months 140mU/ml  ALP:	7	Direct	The results indicate an improvement in liver function followed the introduction of CA and CDCA. However, the authors report no tests of statistical significance. They provide no quantitative information on the treatment's impact on symptoms, quality of life or survival.

Use of cholic acid and chenodeoxycholic acid to treat inborn errors of bile acid synthesis									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
						before treatment 110 mU/ml, at 3 months 90 mU/ml, at 6 months 60 mU/ml, at 8 months 50 mU/ml  γ-GT: before treatment 510 mU/ml, at 3 months 100 mU/ml, at 6 months 20 mU/ml, at 8 months 20 mU/ml.			
				Primary outcome	Urinary bile acids	Normal ranges not reported.			
				Clinical effectiveness		Total urinary bile acids: before treatment 27.8 μmol/l, day 1 104 μmol/l, day 7 155 μmol/l, day 10 119 μmol/l, day 27 92.9 μmol/l;  Total C <sub>27</sub> bile acids: before treatment 13.7 μmol/l, day 1 20.5 μmol/l, day 7 9.3 μmol/l, day 10 10.4 μmol/l, day 27 6.6 μmol/l.			

ALT = alanine aminotransferase, ALP = alkaline phosphatase, AST = aspartate aminotransferase, CA = cholic acid, CDCA = chenodeoxycholic acid, γ-GT = gamma-glutamyl transaminase.

## 8 Grade of Evidence Table

Use of cholic acid and chenodeoxycholic acid to treat inborn errors of bile acid synthesis					
Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
Liver function	Lemonde 2003	9	Direct	B	<p>Liver function tests are blood tests which indicate how well the liver is performing some of its functions.</p> <p>Lemonde et al (2003)'s reported results following the introduction of cholic acid and chenodeoxycholic acid in two infants with <math>\Delta^4</math>-3-oxosteroid 5<math>\beta</math>-reductase deficiency and a <i>SRD5B1</i> gene mutation.</p> <p>The first infant presented at 3 weeks with bilirubin 316 <math>\mu\text{mol/l}</math> (conjugated 145), AST 2279 U/l, ALT 1123 U/l and prothrombin time 15.4 seconds (control 12) (normal ranges were not stated). This infant was treated at 3 months of age with ursodeoxycholic acid and continued to have steatorrhea, failure to thrive and fat soluble vitamin malabsorption. At an unspecified time at or after 8 months of age, treatment was changed to CA (8mg/kg/day) and CDCA (8mg/kg/day). Results probably before the introduction of CA plus CDCA (though the authors do not state this), were bilirubin 88 <math>\mu\text{mol/l}</math>, AST 511 U/l, ALT 252 U/l, <math>\gamma</math>-GT 36 U/l. The authors do not state normal ranges but indicate that the first three results were elevated while the <math>\gamma</math>-GT was normal. Other results for this infant were CDCA (normal range 0.2 to 12.7 <math>\mu\text{mol/l}</math>) &lt;0.05 <math>\mu\text{mol/l}</math>; CA (normal range 0.4 to 6.7 <math>\mu\text{mol/l}</math>) &lt;0.05 <math>\mu\text{mol/l}</math>; 7<math>\alpha</math>-hydroxy-3-oxo-4-cholenoic acid (normal range &lt;0.05 <math>\mu\text{mol/l}</math>) 1.9 <math>\mu\text{mol/l}</math>; 7<math>\alpha</math>,12<math>\alpha</math>-dihydroxy-3-oxo-4-cholenoic acid (normal range &lt;0.05 <math>\mu\text{mol/l}</math>) 2.1 <math>\mu\text{mol/l}</math>.</p> <p>There are no reported results for this infant after treatment, though it "led to normalisation of liver function within three months and she remains well with</p>

### Use of cholic acid and chenodeoxycholic acid to treat inborn errors of bile acid synthesis

Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
					<p>normal liver function tests at the age of nine years (on bile acid replacement therapy)."</p> <p>The second infant was treated from eight weeks of age with CA plus CDCA. Pre-treatment results included bilirubin 446 µmol/l (normal range not reported), alanine transaminase (normal range 5 to 45 U/l) 1702 U/l and γ-glutamyl transaminase (normal range 20 to 155 U/l) 103 U/l. After 6 weeks of treatment, results were bilirubin 117 µmol/l, alanine transaminase 184 U/l and γ-glutamyl transaminase 243 U/l. However, the authors report no tests of statistical significance. The infant had a successful liver transplant.</p> <p>These results are consistent with an improvement in liver function. However, the impact of improvements in liver function tests of these magnitudes cannot be assessed, as such results are not directly related to improvements in patients' symptoms, ability to carry out activities, quality of life, disease progression and survival.</p> <p>The clinical benefit to patients from the use of cholic acid and chenodeoxycholic acid cannot be estimated from this study. Fluctuations in the patients' clinical status or the play of chance are alternative explanations, particularly when so few patients are reported. Furthermore, bile acids are part of several biochemically distinct pathways and disorders of bile acid synthesis have variable effects. It is difficult to apply the findings more widely of one study of a specific gene defect.</p>
Urinary bile acid concentrations	Clayton 1996	8	Direct	B	Urinary bile acid concentrations reflect the presence in the urine and blood of bile acids given as treatment or potentially influenced by treatment, and may indicate how well the liver is

### Use of cholic acid and chenodeoxycholic acid to treat inborn errors of bile acid synthesis

Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
					<p>performing some of its functions. A reduction in concentrations of abnormal urinary bile acids is consistent with improvements in liver function.</p> <p>Clayton et al 2003 reported results following the introduction of cholic acid and chenodeoxycholic acid in a child with <math>\Delta^4</math>-3-oxosteroid 5<math>\beta</math>-reductase deficiency. Urinary excretion of 7<math>\alpha</math>-hydroxy-3-oxo-4-cholenoic acid on no treatment was 22 <math>\mu</math>mol/mmol creatinine, on ursodeoxycholic acid it was 9.1 <math>\mu</math>mol/mmol creatinine, and on cholic acid and chenodeoxycholic acid it was 1 <math>\mu</math>mol/mmol creatinine (normal ranges not reported). Urinary excretion of 7<math>\alpha</math>, 12<math>\alpha</math>-dihydroxy-3-oxo-4-cholenoic acid on no treatment was 94 <math>\mu</math>mol/mmol creatinine, on ursodeoxycholic acid it was 82 <math>\mu</math>mol/mmol creatinine, and on cholic acid and chenodeoxycholic acid it was 22 <math>\mu</math>mol/mmol creatinine (normal ranges not reported). However, the authors report no tests of statistical significance.</p> <p>These results are consistent with an improvement in liver function. However, the impact of improvements in bile acid excretion of these magnitudes cannot be assessed, as such results are not directly related to improvements in patients' symptoms, ability to carry out activities, quality of life, disease progression and survival.</p> <p>The clinical benefit to patients from the use of cholic acid and chenodeoxycholic acid cannot be estimated from this study. Fluctuations in the patients' clinical status or the play of chance are alternative explanations, particularly when so few patients are reported. Furthermore, bile acids are part of several biochemically distinct pathways and disorders of bile acid synthesis have</p>

Use of cholic acid and chenodeoxycholic acid to treat inborn errors of bile acid synthesis					
Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
					variable effects. It is difficult to apply the findings more widely of one study of a specific biochemical defect in one child, especially one in which the authors note that "The plasma bile acid profile of the patient was unique", limiting the generalisability of this study.



## 9 Literature Search Terms

Search strategy	
<p><b>P – Patients / Population</b> Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?</p>	<p>Children and adults with the following inborn errors of bile acid synthesis:</p> <ol style="list-style-type: none"> <li>1. 3-beta-hydroxy-delta5-C27-steroid oxidoreductase deficiency (BAS defect type 1);</li> <li>2. delta4-3-oxosteroid 5-beta reductase deficiency (BAS defect type 2)</li> <li>3. Sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis or CTX),</li> <li>4. Oxysterol 7alpha-hydroxylase deficiency (<i>CYP7B1</i>)</li> <li>5. Defects of peroxisomal enzymes (ACOX2 deficiency and ABCD3 deficiency)</li> <li>6. Peroxisomal biogenesis defects (including Zellweger syndrome)</li> <li>7. Smith-Lemli-Opitz syndrome caused by a deficiency of D7-desaturase</li> <li>8. AMACR deficiency;</li> <li>9. cholesterol 7alpha-hydroxylase (<i>CYP7A1</i>) deficiency</li> </ol>
<p><b>I – Intervention</b> Which intervention, treatment or approach should be used?</p>	<p>Second line treatment of cholic acid in combination with chenodeoxycholic acid</p>
<p><b>C – Comparison</b> What is/are the main alternative/s to compare with the intervention being considered?</p>	<ol style="list-style-type: none"> <li>1. Supportive care (including vitamin supplements, dietary management, statins. For peroxisomal disorders phytanate restriction and docosahexaenoic acid and nutraceutical supplements)</li> <li>2. Single treatment with either cholic acid or chenodeoxycholic acid</li> <li>3. Liver transplant</li> <li>4. No comparison</li> </ol>
<p><b>O – Outcomes</b> What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.</p>	<p><u>Critical to decision-making:</u> Halt disease progression and maintain good quality of life measured through;</p> <ul style="list-style-type: none"> <li>• restoration of the normal liver function</li> <li>• prevention of the need for a liver transplant</li> <li>• prevention of progression of neurological disease in CTX and peroxisomal disorders</li> <li>• reduction in mortality/increase in life expectancy</li> <li>• weight/height gain</li> </ul> <p><u>Important to decision-making:</u></p> <ul style="list-style-type: none"> <li>• Suppression of abnormal bile acids production</li> <li>• quality of life</li> <li>• long term outcomes</li> <li>• adverse effects</li> <li>• cost effectiveness</li> <li>•</li> </ul>

### **Assumptions / limits applied to search**

*Inclusion and exclusion criteria e.g. study design, date limits, patients, intervention, language, setting, country etc.*

#### **Inclusion Criteria**

*Peer reviewed publications*

*English language*

#### **Exclusion Criteria**

*Abstracts*

*Letters*

*Commentaries*

*Conference papers*

*Studies without comparators [deleted after consultation with NHS England]*

*Papers published before 1990*

## **10 Search Strategy**

We searched PubMed, Embase and Cochrane Library limiting the search to papers published in England from 1 January 1990 and 20 March 2018. We excluded conference abstracts, commentaries, letters, editorials and case reports.

Search date: 20 March 2018

Embase search:

# Search 1



- 1 (bile acid? adj3 (therap\* or treat\*)).ti,ab.
- 2 (bile acid? adj3 (therap\* or treat\*)).ti.
- 3 1 or 2
- 4 exp Cholic Acid/
- 5 (cholic acid? or cholicacid? or cholalic acid? or cholate? or cholalin or colalin or cholsaeure or cholbam or c24h4005).ti,ab.
- 6 exp Chenodeoxycholic Acid/
- 7 (Chenodeoxycholic acid? or chenocholic acid? or chenodeoxycholate? or chenodiol or chenic acid? or chenodal).ti,ab.
- 8 4 or 5
- 9 6 or 7
- 10 8 and 9
- 11 3 or 10
- 12 exp "inborn error of metabolism"/
- 13 bile acid?.ti,ab.
- 14 ((gene\* or inborn) adj5 (error? or deficien\* or defect? or abnormal\* or malform\*)).ti,ab.
- 15 13 and 14
- 16 ((steroid\* or oxosteroid\* or oxysteroid\* or oxysterol\* or cholesteryl\* or sterol\* or oxyreductase or oxidoreductase or bas) adj5 deficienc\*).ti,ab.
- 17 (cerebrotendinous xanthomatosis or CTX).ti,ab.

18 (cyp7b1 or cyp7a1).ti,ab.  
 19 ((peroxisomal or acox2 or abcd3 or amacr) adj5 (defect\* or deficien\*)).ti,ab.  
 20 Zellweger Syndrome/  
 21 Smith-Lemli-Opitz Syndrome/  
 22 ((zellweger or smith lemli opitz) adj2 (syndrome? or disease?)).ti,ab.  
 23 12 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22  
 24 11 and 23  
 25 limit 24 to (english language and yr="1990 -Current")  
 26 (exp animals/ or nonhuman/) not human/  
 27 25 not 26  
 28 conference\*.pt.  
 29 27 not 28

# Search 2



1 \*Cholic Acid/  
 2 (cholic acid? or cholicacid? or cholalic acid? or cholate? or cholalin or colalin or cholsaeure or  
 cholbam or c24h4005).ti.  
 3 1 or 2  
 4 \*Chenodeoxycholic Acid/  
 5 (Chenodeoxycholic acid? or chenocholic acid? or chenodeoxycholate? or chenodiol or chenic  
 acid? or chenodal).ti.  
 6 4 or 5

## 11 Evidence Selection

- Total number of publications reviewed: 15
- Total number of publications considered potentially relevant: 7
- Total number of publications selected for inclusion in this briefing: 6

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