BSPED Guideline: Testosterone Therapy in Infancy and Adolescence

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Scope

This guideline is intended for general paediatricians and paediatric endocrinologists who are regularly managing boys with absent/delayed puberty requiring exogenous testosterone therapy. This includes boys with hypogonadotrophic hypogonadism (HH) of various aetiology, androgen deficiency secondary to testicular failure (hypergonadotrophic hypogonadism) of various aetiology, and constitutional delay of growth and puberty (CDGP). The aim of testosterone replacement therapy is to mimic the normal pattern of puberty and mimic requirements at different stages of pubertal development[1]. This guideline aims to provide the clinician with testosterone dosing regimens for pubertal induction, progression and post-pubertal maintenance, as well as for penile growth in infants with micropenis. It also discusses the various preparations of testosterone delivery that are available, and which are preferred based on evidence, risk-benefit balance current practices and availability. Where good quality evidence is unavailable to guide practice, consensus positions are provided. The rationale and use of gonadotropin replacement for pubertal induction in males with HH is outside the scope of this guideline.

Licensing

There are no testosterone preparations licensed for children in the UK. However, the following are licensed in the UK for adults and are used in children off-label: Sustanon 250®, testosterone enantate, Nebido® and all testosterone gels. There are other testosterone preparations that are unlicensed in the UK for any age group or indication, including testosterone propionate and Andractim® gel.

Micropenis in infancy

In male infants with micropenis (due to hypogonadism), testosterone can be given during the 'mini-puberty' of infancy. The aims of treatment are to improve penile length, and to allow urination while standing up[2].

The two preferred modes of testosterone delivery in infants are intramuscular and topical[2,3] (regimes summarised in Table 1):

Table 1: Testosterone delivery in infants with micropenis

	Intramuscular	Topical
Preparation	Testosterone enantate, Sustanon 250®, testosterone propionate	Testosterone 1-5% cream
Dose	25mg	1 application
Frequency	Monthly (weekly for testosterone propionate)	Three times daily
Duration	3 months	3-6 weeks

See also notes within the text

Intramuscular

- Preferred preparation - Testosterone enantate or Sustanon 250® (for neonates <28 days, can only use testosterone propionate)
- Dose – 25mg
- Frequency – Monthly (weekly for testosterone propionate due to shorter half-life)
- Duration – 3 months

Testosterone propionate is preferred primarily only for neonates <28 days of age as it is not made up in any benzyl alcohol which may be toxic to infants. However, availability is a significant issue, and therefore Sustanon 250® or testosterone enantate is recommended for infants above 28 days of age. Sustanon 250® (containing a mixture of testosterone esters) contains benzyl alcohol and testosterone enantate contains benzyl benzoate which is partially hydrolysed to benzyl alcohol[4]. Benzyl alcohol carries the risk of a severe and potentially fatal toxic reaction (gasping syndrome)[5], although the risk is highest in the neonatal period, and therefore the European Medicine Agency recommends cautious use in infants >4 weeks of age, citing that previous recommendations were too strict[6]. Both preparations have also been used in infants in clinical practice without any adverse effects reported. Testosterone enantate also contains castor oil, which has been associated with severe anaphylactoid reactions[7] and the safety profile of benzyl benzoate in infants is not known.

Potential pitfall: Sustanon 250® contains arachis oil, and therefore should be used with caution in those with peanut allergy (and soya allergy, due to cross-reactivity)[4]. The arachis oil does not contain peanut protein and therefore most individuals with peanut allergy will tolerate the preparation, unless their sensitivity is very high. Nonetheless, parents should be counselled about this possible reaction.

Topical

- Preparation – Testosterone 1-5%* cream
- Dose – 1 pea-sized application, applied locally to the penis

- Frequency – Three times daily
- Duration – 3-6* weeks

*Significant variability exists between manufacturers in the concentration of testosterone cream (although 1% seems the most abundant) and duration of treatment (i.e. longer treatment suggested for lower concentrations), because testosterone cream is a non-standard preparation. This also makes assurances of excipients and advice on dosing regime difficult.

Potential pitfall: There is the risk for inter-person transfer of testosterone cream preparations, therefore a female carer should wear gloves when applying.

Potential pitfall: Care must be taken to specify cream rather than gel when prescribing topical testosterone preparations for micropenis in infancy, as the testosterone content of each per application varies significantly.

Dihydrotestosterone/androstanolone 2.5% gel (Andractim®) is not licensed in the UK, but has been shown to be of benefit in infants with 5-alpha reductase deficiency[2]. Dosing in studies have recommended 0.2-0.3mg/kg applied once daily for 3-4 months[2]. However, caution has to be applied as this gel contains 96% alcohol, which can be absorbed systemically and reach high levels in infants who have large surface area to mass ratios. Furthermore, high concentrations of alcohol can dehydrate and irritate the skin. Testosterone gels and patches are unsuitable for infants as they contain high alcohol contents and propylene glycol.

Practical tip: Liaison with a local pharmacist is often required to calculate an easy measure of volume of gel to be applied when using dihydrotestosterone 2.5% gel (Andractim®)

The following leaflet from Great Ormond Street Hospital provides useful practical information regarding Andractim®:
https://media.gosh.nhs.uk/documents/Andractim_F0390_A4_bw_FINAL_Jul17.pdf

Hypogonadism

For the purposes of this guideline, hypogonadism refers to both hypogonadotrophic hypogonadism and testicular failure, as the management of both from a testosterone initiation and maintenance perspective is similar. In hypogonadism, the goals of testosterone treatment in puberty are to induce the development of secondary sexual characteristics, promote linear growth, promote normal accrual of muscle mass and bone mineral density, improve sexual function (libido, frequency of erections, masturbation and penetrative intercourse), improve energy levels and sense of well-being, whilst avoiding mistimed epiphyseal closure[8-10]. Testosterone replacement therapy does not increase testicular volume or improve the chances of fertility - other agents are available for these purposes, which are outside the scope of this

guideline[10]. In children with suspected congenital HH, if there is evidence of testicular enlargement (suggesting gonadotrophin activity), the diagnosis of HH needs to be reviewed and a period off of testosterone treatment during induction is recommended. Similarly, a trial off testosterone treatment may be considered at some stage once full adult replacement doses have been reached, as 10% of cases show evidence of reversal of hypogonadism[10].

Timing

Unless a boy with hypogonadism also has growth hormone deficiency (multiple pituitary hormone deficiency), and therefore pubertal induction may be delayed to maximise height with growth hormone treatment, puberty is induced in boys with hypogonadism at 12-13 years of age[8,11]. In boys with hypergonadotrophic hypogonadism, some clinicians choose to start testosterone replacement when serum testosterone falls below the normal range and serum LH rises to >2.5 SD above the mean normal value[8].

Low doses are initiated and gradually increased to adult dosage over time. This is to mimic testosterone levels during the natural pubertal process and maximise growth, while allowing psychosexual development and minimising the risk of precocious sexual activity[10,12]. Intramuscular testosterone remains the most popular preparation for induction of puberty, however recent studies have suggested a possible role for transdermal preparations[13-15] (regimes summarised in Table 2).

Intramuscular

The mode of delivery most commonly utilised by clinicians to induce puberty is intramuscular[16]. This is due to much greater experience with these regimens over time, with a greater evidence-base and better known side-effect profile[11,16]. Furthermore, doses can be easily titrated to match the various stages and requirements through puberty[1,15].

Intramuscular testosterone regime[1,8,10,12,13]

- Preparation – Testosterone enantate, or mixture of esters (Sustanon 250®)
- Dose – 50-100mg, increasing by 50mg every 6 months until 200-250mg reached
- Frequency – Monthly, reducing in frequency to 2-3 weekly 6 months after 250mg is reached

Potential pitfall: Sustanon 250® contains arachis oil, and therefore should be used with caution in those with peanut allergy (and soya allergy, due to cross-reactivity)[4]. The arachis oil does not contain peanut protein and therefore most individuals with peanut allergy will tolerate the preparation, unless their sensitivity is very high.

Potential pitfall: Great care and clarity must be taken when prescribing volumes of Testosterone for intramuscular injections to avoid dosage errors – both testosterone enantate and Sustanon 250® come as 250mg per 1ml ampoules. For example: when

prescribing 50mg of testosterone enantate, wording should read "Testosterone enantate at a dose of 50mg (0.2ml of 250mg/1ml vial) IM monthly".

Post-pubertal maintenance intramuscular testosterone regime

After 2-3 years, adult doses can be used for post-pubertal maintenance - these vary in the adult literature from 100-250mg 2-4 weekly, though mostly 200-250mg 2-3 weekly in clinical practice[10,17-21]. Dosing for adult maintenance needs to be guided by monitoring of trough morning serum testosterone concentrations - aiming to maintain these at the lower end of the normal range[10,18].

Potential pitfall: Intramuscular testosterone undeconate (Nebido®) is a longer acting intramuscular testosterone preparation, but should only be used for post-pubertal maintenance rather than induction, and is only licensed in males over 18 years old[22].

Dosing for Nebido® is 1g every 10-14 weeks (with the second dose given after 6 weeks to achieve rapid steady state plasma testosterone levels). Again, dosing needs to be adjusted according to trough serum testosterone concentrations. Nebido® needs to be administered very slowly (over 1-2 minutes).

Transdermal

Transdermal testosterone gels, although popular amongst patients (due to lack of injections and ease of application), carry virtually no good-quality evidence of efficacy in the adolescent population, with dosing regimes also extrapolated from adult doses[1,8,10,15].

Transdermal testosterone gel regimes[1,10,13]

- Preparation – 2% metered-dose testosterone gel (Tostran®). Each metered-dose application contains 0.5g of gel, which contains 10mg of testosterone.
- Dose – 10-20mg (1-2 metered applications), increasing by 10mg every 6 months until adult doses achieved
- Frequency – Once daily
- Adult dosing – 60-80mg once daily; Once 60mg once daily is reached, serum testosterone concentration can be measured 2 hours after application of Tostran®, with the dose increased to 80mg once daily if the testosterone level is suboptimal

There are now other gel pump preparations available (Testavan® and Testogel®) that can be used in case of shortages with Tostran®, but where each actuation delivers 20mg of testosterone (i.e. double that of Tostran®), making dose titration slightly less refined for pubertal induction.

Potential pitfall: If gel pump alternatives to Tostran® are used (e.g. Testavan® and Testogel®), care has to be taken with dose prescription, as each metered-dose application delivers 20mg (equivalent to 100mg of intramuscular testosterone) rather than the 10mg of testosterone delivered with each metered-dose application of Tostran®.

The gel pump preparations are preferred to the sachet preparation, as they allow more accurate dose delivery and titration.

- Preparation – 1.6% testosterone gel sachets (Testogel®), containing 40.5mg of testosterone per 2.5g sachet (the previous 1% sachet preparation [50mg in 5g] has been discontinued).
- Dose – 10-20mg (approximately one-quarter to one-half of a sachet), increasing by one-quarter of a sachet every 6 months until 50mg daily achieved
- Frequency – Once daily
- Adult dosing – 50-100mg once daily

There is plenty of evidence supporting use of transdermal testosterone gels within the adult setting, with the key advantage of sustained drug plasma levels that most closely resemble the natural diurnal variation in serum testosterone concentrations [18,23]. Therefore, they may have more of a place in post-pubertal maintenance regimes, following induction through puberty with intramuscular testosterone, and switching to an equivalent adult dose of the gel preparation.

Potential pitfall: There are concerns and reports of inter-person transfer of testosterone gel preparations from contact to women and children, therefore care is needed in application, with female carers ensuring they wear gloves[18,23].

Potential pitfall: Care must be taken to specify gel rather than cream when prescribing topical testosterone preparations for pubertal induction and maintenance in hypogonadism, as the testosterone content of each per application varies significantly.

Potential pitfall: Testogel® is available both as gel sachets (40.5mg in 2.5g), and as a metered-dose pump dispenser (20mg per actuation). The desired preparation will need specifying on the prescription to ensure the correct formulation is provided.

Current advice is to apply the gel to areas of the skin which are not likely to come in contact with others, but also avoiding the genital and under-arm areas due to local irritation (shoulders and arms recommended). The gel should be allowed to dry before covering with clothing, and hands washed after application. Bathing and swimming should be avoided for at least 6 hours following application.

Transdermal testosterone patches (Andropatch® and Intrinsa®) have been discontinued and are no longer available.

Oral

Oral testosterone undecanoate is no longer available in the UK. There are preparations available in other countries (e.g. Kyzatrex®, with the previously used Restandol® no

longer available abroad either), but the dosing profile does not make it suitable for pubertal induction.

Table 2: Testosterone delivery for pubertal induction in boys with hypogonadism

	Intramuscular (preferred option)	Metered-dose gel (secondary option)	Gel sachet (secondary option)
Preparation	Testosterone enantate, Sustanon 250®	Tostran® (2%; 10mg testosterone per metered application)	Testogel®, (1.6%; 40.5mg testosterone per 2.5g sachet)
Initial dose	50-100mg	10-20mg (1-2 actuations)	Quarter to half of sachet
Initial frequency	Monthly	Once daily	Once daily/ alternate days
Titration	Increase by 50mg every 6-12 months, reducing frequency to 2-3 weekly once 250mg reached	Increase by 10mg (1 actuation) every 6 months	Increase by quarter of a sachet 6-monthly until full sachet daily achieved
Adult dosing	200-250mg 2-4 weekly (2-3 times a week for testosterone propionate)	60-80mg once daily	1-2 sachets daily

See also notes within the text
50mg intramuscular testosterone monthly = 10mg topical testosterone daily

Constitutional delay in growth and puberty (CDGP)

In boys with CDGP, testosterone therapy is initiated to induce pubertal development, with the body being able to progress itself through puberty (should the diagnosis be accurate) following a short course of testosterone. Although it is accepted that boys with CDGP will eventually induce themselves into puberty, testosterone is given to alleviate the distress boys often suffer because of their lack of growth and pubertal progression, which can affect school performance, social relationships and psychological well-being[8,12]. Testosterone treatment in boys with CDGP is usually initiated around 13-14 years of age. Low doses are used to avoid premature epiphyseal maturation and minimise suppression of the endogenous hypothalamic-pituitary-testicular axis. A one-off course of 3-6 months is usually given, with review 1-2 months after - if there has been no increase in testicular volume, a further 3-6 month course of testosterone can be given[8].

Potential pitfall: If there is no progress in testicular volumes and serum testosterone after two courses of testosterone treatment, then a diagnosis of HH must be considered and investigated[8].

Intramuscular testosterone remains the most popular preparation for induction of puberty, however recent studies have suggested a possible role for transdermal preparations[13-15] (regimes summarised in Table 3).

Intramuscular testosterone regime[3,8,12,13]

- Preparation – Testosterone enantate, or mixture of esters (Sustanon 250®)
- Dose – 50-100mg,
- Frequency – Monthly
- Duration – 3-6 months

Potential pitfall: Sustanon 250® contains arachis oil, and therefore should be used with caution in those with peanut allergy (and soya allergy, due to cross-reactivity)[4]. The arachis oil does not contain peanut protein and therefore most individuals with peanut allergy will tolerate the preparation, unless their sensitivity is very high.

Potential pitfall: Great care and clarity must be taken when prescribing volumes of Testosterone for intramuscular injections to avoid dosage errors – both testosterone enantate and Sustanon 250® come as 250mg per 1ml ampoules. For example: when prescribing 50mg of testosterone enantate, wording should read "Testosterone enantate at a dose of 50mg (0.2ml of 250mg/1ml vial) IM monthly".

Transdermal testosterone regime[13]

- Preparation – 2% metered-dose testosterone gel (Tostran®), containing approximately 10mg per metered application
- Dose – 10-20mg (1-2 metered applications)
- Frequency – Once daily
- Duration – 3-6 months

Potential pitfall: There are concerns and reports of inter-person transfer of testosterone gel preparations from contact to women and children, therefore care is needed in application, with female carers ensuring they wear gloves[18,23].

Potential pitfall: Care must be taken to specify gel rather than cream when prescribing topical testosterone preparations for induction of puberty in CDGP, as the testosterone content of each per application varies significantly.

Table 3: Testosterone delivery for pubertal induction in boys with constitutional delay in growth and puberty

	Intramuscular (preferred option)	Transdermal (secondary option)
Preparation	Testosterone enantate, Sustanon 250®	2% metered-dose testosterone gel (Tostran®; 10mg per metered application)
Dose	50-100g	10-20mg (1-2 actuations)
Frequency	Monthly	Once daily
Duration	3-6 months	3-6 months

See also notes within the text

50mg intramuscular testosterone monthly = 10mg topical testosterone daily

Advantages and disadvantages of preparations[12,17,21]

	Advantages	Disadvantages
Intramuscular	- Cheap - Known efficacy - Lots of experience of use - Long-acting - Easy dose titration - Can monitor compliance	- Fluctuating drug levels resulting in fluctuating symptoms (mood and libido –which may be an issue in boys with learning difficulties) - Local problems with injections (pain, inflammation, sterile abscess) - Attending to healthcare services - Priapism potentially if excess administered - Potential paroxysms of coughing and dyspnoea from lipid embolism (Nebido®)
Transdermal	- Pharmacokinetics most closely replicate natural diurnal variation - Convenient	- Evidence of efficacy lacking - Doses extrapolated from adults - More expensive - Transfer to other persons - Skin irritation

Side effects[3,18,22]

Possible issues in childhood

- Premature epiphyseal closure and stunting of final height (if high doses taken)
- Mood swings, acne, behavioural disturbance
- Worsening of sleep apnoea
- Polycythaemia
- Gynaecomastia
- Weight gain
- Hypertension

- Cholestatic jaundice
- Electrolyte disturbance

Future possible issues in adulthood

- Suppression of spermatogenesis - discontinue when seeking fertility
- Acceleration of male pattern balding
- Worsening of benign prostatic hypertrophy, possible prostate cancer
- Possible cardiovascular effects *not* substantiated on meta-analysis[24]

Reference list of currently available testosterone preparations

Name	Preparation	Notable excipients	Licensed status	Supplier
Testosterone esters (Sustanon 250®)	Injection ampoule 250mg in 1mL	**Arachis oil:** caution/avoid in peanut allergy **Benzyl alcohol:** avoid in neonates (risk of gasping syndrome)	Licensed in UK for adults Off-label use in children	Regular UK supply chain
Testosterone enantate	Injection ampoule 250mg in 1mL	**Benzyl benzoate:** avoid in neonates (risk of gasping syndrome); skin reactions in children under 3 years	Licensed in UK for adults Off-label use in children	Regular UK supply chain
Testosterone propionate (e.g., Testovis®)	Injection ampoule 100mg in 2mL	May vary depending on manufacturer	Unlicensed import	Clinigen (import) Lead time 1-2 months to order
Testosterone undecanoate (Nebido®)	Injection ampoule/vial 1g in 4mL	**Benzyl benzoate:** avoid in neonates (risk of gasping syndrome); skin reactions in children under 3 years	Licensed in UK for adults Not suitable for paediatric pubertal induction	Regular UK supply chain
Tostran® 2% gel	Gel pump 1 actuation = 10mg	**Butylhydroxytoluene :** local skin irritation **Propylene glycol:** local skin irritation; caution in neonates	Licensed in UK for adults Off-label use in children	Regular UK supply chain
Testavan® 20mg/g gel	Gel pump 1 actuation = 23mg	**Ethanol:** skin dryness; significant	Licensed in UK for adults	Regular UK supply chain

		systemic absorption in neonates **Propylene glycol:** local skin irritation; caution in neonates	Off-label use in children	
Testogel® 16.2mg/g gel	Gel pump 1 actuation = 20mg	**Ethanol:** skin dryness; significant systemic absorption in neonates	Licensed in UK for adults Off-label use in children	Regular UK supply chain
Testogel® 40.5mg sachets	Sachet 1 sachet = 40.5mg	**Ethanol:** skin dryness; significant systemic absorption in neonates	Licensed in UK for adults Off-label use in children	Regular UK supply chain
Andractim® 2.5% gel	80g Gel tube 1g gel = 25mg dihydrotestosterone (androstanolone)	**Ethanol:** skin dryness; significant systemic absorption in neonates	Unlicensed import (France)	Mawdsleys (import)
Testosterone 1% cream (e.g., Androfeme®)	50g Cream tube 1g gel = 10mg	Androfeme®: **benzoates** May vary depending on manufacturer	Unlicensed import (Australia) Unlicensed specials manufacturers (UK)	Clinigen or Mawdsleys (import) May be made by specials manufacturers (e.g., Nova or PCCA) in the UK on a named patient basis

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