# Iron chelation

DR.BAGHERSALIMI

1400

# Aims of iron chelation therapy

1. Prevention therapy
2. Rescue therapy
3. Emergency therapy
4. Dose adjustment of therapy
5. Adherence to therapy

# Aims of iron chelation therapy

1. Prevention therapy:

- The primary goal of chelation therapy is to maintain safe levels of body iron at all times, by balancing iron intake from blood transfusion with iron excretion by chelation (iron balance)

# Aims of iron chelation therapy

2. Rescue therapy:

- Once iron overload has occurred, the rate of iron excretion must exceed that accumulated from transfusion
- Removal of storage iron is slow , because only a small proportion of body iron is available for chelation at any moment
- Once iron has been deposited in some tissues, damage is often irreversible
- Prevention is therefore preferable to rescue

3. Emergency therapy:

- If heart failure develops, urgent action is required, which usually requires changing and/or intensifying the treatment

# Aims of iron chelation therapy

4. Dose adjustment of therapy:

- Dosing and treatment regimens require frequent adjustment
- Monitoring is important to avoid:

a) under-chelation with increased iron toxicity; or

b) over-chelation and increased chelator toxicity.

# Aims of iron chelation therapy

5. **Adherence to therapy:**

- Chelation must be taken regularly for it to work.
- Intermittent high dose chelation can induce negative iron balance but does not provide continuous protection and also increased toxicity from the iron chelator.
- Poor adherence can result from difficulty with deferoxamine infusions, intolerance of a particular chelator, psychological/ psychosocial issues or limited accessibility.
- A key role of the treating centre is the encouragement of adherence to chelation

# Sources of chelatable iron

- Only a small fraction of body iron is available for iron chelation at any moment.
- This is because iron chelators interact with low molecular weight ‘labile’ iron pools more rapidly than with iron stored as ferritin or haemosiderin.
- In iron overload, most of the storage iron in the body is in hepatocytes, and the ferritin in these cells is turned over less frequently than in the absence of iron overload .
- Other cells, such as cardiomyocytes, contain about one tenth of the storage iron concentration of hepatocytes
- iron from these cells is cleared mor slowly by chelators.

# DFO

Table 2. Decreasing complications in cohorts of Italian patients born after DFO became available. Reproduced with permission from (Borgna-Pignatti et al., 2004).

| | BIRTH 1970-74* | BIRTH 1980-84† |
|---|---|---|
| Death at 20 years | 5% | 1% |
| Hypogonadism | 64.5% | 14.3% |
| Diabetes | 15.5% | 0.8% |
| Hypothyroidism | 17.7% | 4.9% |

# DFO:Evidence of beneficial effects

**Deferoxamine monotherapy**

- DFO is licensed for the treatment of Iron overload above the age of 2 years
- DFO was reduced the complications of iron overload and, when taken sufficiently regularly and at sufficient doses, improved survival progressively.
- Only patients born after 1980 will have started treatment at an early age, a key factor affecting survival as well as co-morbidities such as hypogonadism and other endocrine disturbances, including diabetes mellitus .

# DFO:Evidence of beneficial effects

**Deferoxamine monotherapy**

- However, treatment is costly and inconvenient, requiring subcutaneous or intravenous infusion over at least 8 hours a day at least 5 days a week
- Adherence to therapy has been the main limiting factor to successful outcomes
- Over-chelation can also be a problem, particularly in children or when doses are not modified for age or level of iron overload
- Generally recommending that therapy not be started until serum ferritin levels reach 1000 μg/l,

# DFO: Effects on serum ferritin

- Long-term SF < 2500 μg/l has been linked to protection from heart disease and to improved survival
- With even better outcomes at levels <1000 μg/l
- Control of SF is dependent on dose, frequency of use and transfusional iron loading rate

# DFO: Effects on liver iron

- A dose of 37 mg/kg stabilized LIC for patients with baseline LIC values of between 3 and 7 mg/g dry weight (wt)
- In patients with LIC values >14 mg/g dry wt, a mean dose of 51 mg/kg resulted in LIC decreases of an average of 6.4 mg/g dry Wt .
- Thus, a dose of 50 mg/kg at least 5 days /wk is recommended, if a significant decrease to optimal LIC levels is required

# DFO: Effects on heart function

- SC DFO has been known to prevent or improve asymptomatic cardiac disease in TM
- After the introduction of DFO, the incidence of iron-induced heart disease fell progressively
- key factor is the age of starting treatment
- Continous IV doses of 50-60 mg/kg/day can normalize LVEF over three months, significantly earlier than normalization of liver or cardiac iron stores.
- However, if advanced heart failure has developed, the chances of successful rescue are reduced.

# DFO: Effects on cardiac iron (mT2*)

- Myocardial iron estimated by T2* can improve with either SC or IV DFO, if is given at adequate doses, frequency and duration
- Improvement in mild to moderate cardiac iron, even at low intermittent doses (5 days a week) has been confirmed

# Recommended treatment regimens for DFO monotherapy

**Standard therapy**

- *When to start DFO therapy?* Provided that treatment is :

1) begun within 2-3 years of beginning transfusion therapy,

(2) administered regularly (at least 5 times a week) and

3) administered in adequate doses,

- In TM, this should start before transfusions have deposited enough iron to cause tissue damage.
- Current practice is to start after the first 10-20 transfusions, or when the ferritin level rises above 1,000 μg/l
- If chelation therapy begins < 3 y/o, monitoring of growth is advised, along with reduced dosage

# Recommended treatment regimens for DFO monotherapy

***Standard dose regimen***

- The recommended method is slow subcutaneous infusion of a 10% DFO solution over 8-12 hours, a minimum of 5 days per week.
- Average doses should not exceed 40 mg/ kg/day until skeletal growth has been completed: 20-40 mg/kg for children and up to 50-60 mg/kg for adults
- To achieve negative iron balance, a dose of 50 mg/kg/day at least 5 days a week is required.

# Recommended treatment regimens for DFO monotherapy

***Use with vitamin C***

- Vitamin C increases iron excretion by increasing the availability of chelateable iron,
- But, if given in excessive doses, may increase the toxicity of iron
- It is recommended not to give more than 2-3 mg/kg/day as a supplement, taken at the time of the DFO infusion
- Should a patient have been started on DFO, the vitamin C supplement should not be given until after several weeks of treatment

# Recommended treatment regimens for DFO monotherapy

***Dose adjustment to avoid DFO toxicity***

- At ferritin levels <100 μg/l, the DFO dose needs to be reduced and toxicities monitored carefully
- keep Porter index (daily dose (mg/kg)/SF) < 0.025
- LIC may be a more reliable alternative to serum ferritin in monitoring response

***Rescue to achieve negative iron balance***

- Increased frequency, duration and dose

# Recommended treatment regimens for DFO monotherapy

***Rescue to remove cardiac iron***

- For patients with T2* 10-20, increasing to 50-60 mg/kg/day may be needed
- For patients with T2* 6-10 ms or less, other chelation regimes such as combination of DFP with DFO or DFX monotherapy
- For patients with abnormal LVEF, emergency therapy is recommended

***Intensive therapy for other reasons***

- Prior to pregnancy or BM transplantation, intensification of therapy may be helpful to minimize the degree of iron overload

# Recommended treatment regimens for DFO monotherapy

**Emergency therapy**

- In cases with decreased LVEF, continuous IV/SC infusion is better than periodic infusions
- And shown to normalize heart function, reverse heart failure, improve myocardial T2* and lead to long-term survival
- A 50 -60 mg/kg/day is recommended
- Addition of vitamin C is recommended only when acute heart dysfunction has settled (about 3 months of continuous treatment)
- Addition of DFP would appear a reasonable approach in these patients

# Deferiprone monotherapy

***Effects on serum ferritin***

- will maintain SF in transfused patients at desirable levels in about one third of patients.
- The effect on SF is generally greater when starting SF levels are high (>2500 μg)
- In DFP monotherapy a minimum 20% reduction in SF was met in only 50% of patients
- Comparing with DFO at various doses suggested no difference between the two drugs at 12 months

# Deferiprone monotherapy

***Effects on liver iron***

- Overall negative iron balance (decrease in LIC) is achieved in only about a third of patients receiving 75 mg/kg

***Effects on myocardial iron***

- In a study, the increase in mT2* was greater than that seen in the DFO

***Effects on heart function***

- Retrospective studies suggest that DFP monotherapy offers superior cardiac protection compared to DFO

# Deferiprone monotherapy

***Long-term benefits of DFP monotherapy***

- Retrospective studies have reported a survival advantage of DFP either alone or with DFO, over DFO alone.
- However, systematic analyses have not found clear evidence of survival advantages of any particular chelator regime

***Recommended treatment regimens with DFP***

- According to the FDA and European licensing Agency , is indicated when current therapy is inadequate
- DFP is licensed for use from the age of 6 years

# Deferiprone monotherapy

***Standard dosing and frequency***

- The dose of DFP is 75 -100mg/kg/day, given in three doses
- An oral solution is also available for pediatric use

***Dose escalation with DFP***

- The presumption is that higher doses will increase iron excretion and response rate
- Doses of 100 mg/kg/day have been given in at least one study, with no increase in side-effects reported
- Patients without iron overload may be more likely to develop agranulocytosis.

# Deferiprone monotherapy

***Age of commencement***

- There is less experience on the safety and efficacy of DFP in children under 6 years of age
- No specific tolerability issues were seen in patients aged >3 and even smaller
- DFP can be a treatment option in children

***Use of vitamin C***

- The effect of vitamin C on iron excretion is not clear and is thus not recommended

# Deferasirox (DFX)

- The drug is licensed as first-line monotherapy for thalassemia major in over 100 countries worldwide,

***Chemistry and Pharmacology***

- The original formulation, a tablet dispersible in water (DT) has been replaced by a film-coated tablet (FCT) formulation that is better absorbed, and preferred by patients
- Due to enhanced absorption, doses of the FCT formulation need to be decreased to 0.7 × of those previously recommended with DT

# Deferasirox (DFX)

**Evidence of effectiveness of DFX:**

***- On serum ferritin***

***- On iron balance***

***- On myocardial T2****

- ***On heart function and long term survival***
- ***On Convenience and impact on quality of life***

# Deferasirox (DFX)

***Recommended standard dosing***

- With high rates of iron loading a dose of 21 mg/kg day will be necessary
- For patients with severe iron overload, doses of 21-28 mg/kg /day
- Decreasing dose when ferritin values fall below 1000 µg/l is advisable
- The FCT to be swallowed before food or with a light meal

***Rescue therapy for mild to moderate myocardial iron (mT2* 5-20 ms)***

- Up to 40 mg/ kg have been used in patients with high levels of LIC or ferritin

***Rescue therapy for patients with severe myocardial iron (mT2* < 6 ms)***

- For patients with mT2* <6 ms, other alternative chelation regimes are recommended

***Emergency therapy for patients with reduced LVEF or symptomatic heart failure***

- DFX is not recommended

# Deferasirox (DFX)

***Other indications and contraindications***

- DFX is contraindicated in patients with renal failure or significant renal dysfunction.
- Caution for patients with advanced liver disease and hepatic decompensation
- Can be used in children as young as two years
- The safety and efficacy of the FCT in children below 2 yrs of age have not been studied

# Combination therapies

***Combination therapies***

- Is used to improve outcomes if monotherapy is inadequate
- Two chelators can be given simultaneously or sequentially
- If the drugs are given simultaneously, they may have 'shuttle' effect, which may lead to additional chelation of iron
- The most commonly used regimes is DFP plus DFO
- More recently, combinations of DFX with DFO or DFX with DFP have been used

# Which chelation regime, when and how much?

a. DFO monotherapy is effective for negative iron balance if it is given in sufficient doses and frequency, but adherence is often a problem

b. Dose escalation of DFX is effective at producing negative iron balance

- Doses >35 mg/kg and up to 40 mg/kg (up to 28 mg/kg of FCT) are effective in patients with high LIF or SF

c. DFP monotherapy achieves iron balance at 75 mg/kg in only one third of patients. It may be increased up to 100 mg/ kg. DFO is often added

d. Combination therapy can be useful when monotherapy is inadequate, either to control iron balance, particularly in the heart.

# Recommendations

1. Chelation therapy is an effective modality in improving survival, decreasing the risk of heart failure and other morbidities
2. Chelation therapy at the correct doses and frequency can balance iron excretion with iron accumulation
3. Absolute change in total body iron in response to chelation can be calculated from change in LIC
4. Direction of change in body iron can usually but not always be estimated from the trend in ferritin

# Recommendations

5. Prevention of iron accumulation using chelation therapy is preferable to rescue treatment because iron-mediated damage is often irreversible, and removal of storage iron by chelation is slow - particularly after it has escaped the liver
6. Response to chelation is dependent on the dose and duration
7. Response to chelation is affected by the rate of transfusion
8. Cardiac iron accumulates later than liver iron, and is rare before the age of 8 years
9. Chelation of storage iron from the liver tends to be faster than from myocardium

# Recommendations

10. Cardiac iron concentration is directly related to the risk of heart failure, which can be estimated by cardiac T2*
11. Chelation can reverse iron-mediated cardiac dysfunction rapidly (within weeks) if 24 h chelation cover is achieved
12. Chelation therapy removes myocardial storage iron slowly (months or years)
13. Over-chelation increases side effects , and doses should be decreased as serum ferritin or liver iron levels fall (specially with DFO)
14. Chelation therapy will not be effective if it is not taken regularly

| CATEGORY | DFO (DEFEROXAMINE) | DFP (DEFERIPRONE) | DFX (DEFERASIROX) |
|---|---|---|---|
| Children age 2-6 years | First line for TM | Insufficient information for licensing | First line in USA Second line when DFO contra- indicated or inadequate in Europe |
| Children age >6 years and adults | First line TM | If other chelation (FDA 2011) or DFO not tolerated or ineffective | First line TM<br>First line NTDT |
| Route | s.c./i.m. or i.v injection | Oral, tablet or liquid | Oral, dispersed tablet |
| Dosage and frequency | 20-60 mg/kg 5-7 x / week, 50 mg/kg in EU Children's dose up to 40 mg/kg | 75 -100 mg/kg/day in 3 divided doses daily | 14-28 mg/kg/day once daily for film coated tablet. Lower doses in NTDT |
| Contra-indications | - Pregnancy (but has been used in 3rd trimester)<br>- Hypersensitivity | - Pregnancy<br>- History of neutropenia or condition with under-lying risk of cytopenia<br>- Hypersensitivity including Henoch Schönlein purpura: urticaria and periorbital oedema with skin rash | - Pregnancy<br>- Hypersensitivity<br>- Estimated creatinine clearance <60 ml/min<br>- Hepatic impairment or renal failure |

| | | | |
|---|---|---|---|
| Precautions | – Monitor ferritin; if it falls to <1000 µg/l, reduce dose (so mean daily dose/ferritin remains <0.025)<br><br>- Monitor audiometry regularly, particularly as ferritin falls<br><br>- Monitor eyes regularly including electroretinography if on high doses<br><br>- Fever suggestive of septicaemia with organisms that used ferrioxamine (Yersinia, Klebsiella) | - Measure neutrophil count (ANC) before starting and monitor ANC weekly<br><br>- For neutropenia : ANC < $1.5 \times 10^9$ /l interrupt treatment<br><br>- For agranulocytosis (ANC < $1.5 \times 10^9$ /l), consider hospitalisation<br><br>- Advise patients to report immediately symptoms of infection; interrupt if fever develops<br><br>- Monitor for symptoms of arthropathy | - Monitor creatinine trends for 1st 4 weeks after starting or after dose escalation, then monthly<br><br>- If rapid fall in serum ferritin to <1000 µg/l, dose reduce. If ferritin 500 µg/l consider very low doses.<br><br>- Proteinuria may occur, occasionally with renal tubular acidosis. Monitor urine protein regularly |

| CATEGORY | DFO (DEFEROXAMINE) | DFP (DEFERIPRONE) | DFX (DEFERASIROX) |
|---|---|---|---|
| | - Renal failure or diminishing renal function with other comorbidities | - Monitor liver function regularly<br><br>- No guidance on dose adjustment at low ferritin | - Prescribing to the elderly; non-fatal gastrointestinal bleeding, ulceration, and irritation may occur; caution with drugs of known ulcerogenic or haemorrhagic potential, (e.g. NSAIDs, corticosteroids, oral bisphosphonates, and anticoagulants)<br><br>- Hypersensitivity reactions<br><br>- Monitor liver function regularly |
| Potential drug interactions | - Co-administration with prochlorperazine: may lead to temporary impairment of consciousness.<br><br>- Gallium-67: Imaging results may be distorted by rapid urinary excretion of deferoxamine-bound gallium-67. Discontinuation 48 hours prior to scintigraphy is advisable | - Theoretical interactions with UGT1A6 inhibitors (e.g. diclofenac, probenecid or silymarin (milk thistle))<br><br>- Avoid concomitant use with drugs associated with neutropenia<br><br>- Gallium-67 as with DFO<br><br>- Oral preparations containing polyvalent cations (e.g., aluminium containing antacids, and zinc) allow at least a 4-hour interval | - Theoretical interactions with drugs metabolized by CYP3A4 e.g. midazolam<br><br>-Theoretical interactions with drugs metabolized by CYP1A2: e.g. theophylline<br><br>- Gallium-67 as with DFO<br><br>- Oral preparations containing polyvalent cations as with DFP |

# Unwanted effects with deferoxamine

- The unwanted effects are seen mainly when doses are too high in relation to the level of iron overload:
- Hearing loss, tinnitus and deafness may occur when DFO is given in high doses, particularly to young children whose iron burden is low , and when the therapeutic index is >0.025 .Annual monitoring is particularly important in this patients
- Visual disturbances are rare , and may include retinal effects and cataracts, night-blindness, impaired colour vision, impaired visual fields and reduced visual acuity.The main risk factor appears to be high dosing and who have diabetes Treatment should be temporarily suspended in these patients

# Unwanted effects with deferoxamine

- Growth retardation
- Skeletal changes
- Rare complications:

-Renal impairment may occur at high doses and renal monitoring is therefore recommended.

-Interstitial pneumonitis has been reported

-Neurological complications have also been described

-Hypotension can also occur with rapid intravenous injection, and may occur during flushing of a line containing DFO, which should be avoided

# Unwanted effects with deferoxamine

**Use in pregnancy**

- DFO has been used in some higher risk pregnancies, particularly in the final trimester

***Unwanted effects not related to excessive chelation***

- Local skin reaction such as itching, erythema, induration and discomfort are common and may be due to inadequate dilution . Ulceration at the site of infusion results from an intradermal infusion. The % solution infused should not exceed 10%
- Infection with Yersinia enterocolitica
- Severe hypersensitivity is a rare event and can be treated by careful desensitisation. If unsuccessful, an alternative, such as DFP or DFX may be considered

# Unwanted effects with DFP and their management

General tolerability and frequency of adverse effects

- Adverse reactions based on pooled data collected from 642 patients showed nausea (13%), vomiting, abdominal pain (10%), elevations I alanine aminotransferase (8%), arthralgia (10%) and neutropenia (7%). Other unwanted effects >1% were back pain (2%), arthropathy (1%), agranulocytosis (1.7%) change in appetite (5%), diarrhoea (3%), dyspepsia (2%) and headache (3%)

Relationship to dose and levels of iron overload

- Most studies where tolerability has been reported have used 75 mg/kg in three divided doses. The drug is licensed up to 100 mg/kg/day but insufficient numbers have been reported to know whether the incidence of the most serious complication, namely
- agranulocytosis, is increased at these higher doses.

# Unwanted effects with DFP

**Agranulocytosis**

- Agranulocytosis is a serious and potentially fatal adverse event
- This is reported in approximately 1.7% of patients
- Each patient's absolute neutrophil count should be measured before starting DFP and every 1-2 weeks during treatment
- DFP should be interrupted and the patient's neutrophil count closely monitored if an infection develops
- It is not clear whether this effect is dose related
- If severe neutropenia or agranulocytosis develops, drug should be stopped and not reintroduced
- Use of G-CSF should be considered in the case of agranulocytosis

# Unwanted effects with DFP and their management

**Effects on liver**

- Fluctuation of liver enzymes more than twice the upper limit of normal should prompt investigation of the cause and consideration of interrupting DFP therapy.

**Arthropathy**

- Range from mild non-progressive arthropathy, typically in the knees and controllable with NSAID to severe erosive arthropathy

**Neurological effects**

- Are very rare and typically associated with overdosing

**Effects on ears and eyes**

- It may be advisable to monitor audiometric function and eye examination at least once yearly

# Unwanted effects with DFP

**Other effects**

- Zinc deficiency, especially in those with diabetes . Some clinicians routinely add zinc supplement (not given at the same time as the DFP)
- DFP is teratogenic in animals and must never be given to patients attempting to conceive. DFP should not be used in pregnant women

# Unwanted effects with DFX

- ***GI*** events are frequent but are mild to moderate and include diarrhea, abdominal pain, nausea and vomiting, occurring in 15-26% of patients . These symptoms rarely require dose adjustment or discontinuation, and decrease year on year .The film-coated tablet can be given with food and this seems to improve GI disturbances
- Skin rashes occurred in 7-11% of patients, and were typically pruritic, maculopapular and generalised,. Rash typically develops within two weeks of starting treatment. A minority of patients require permanent discontinuation of therapy

# Unwanted effects with DFX

Renal effects

- An increase in serum creatinine ≥30% was observed in 38% of patients
- Were more frequent in the population of patients having the most dramatic decrease in LIC and serum ferritin
- No evidence of progressive renal dysfunction
- If a patient becomes acutely unwell, it is wise to interrupt chelation therapy until the general condition stabilizes

# Unwanted effects with DFX

- **Proteinuria** may be present in about a quarter of patients, irrespective of the underlying chelation therapy
- It is recommended that urine is monitored regularly for protein
- If there is an upward trend, interruption or dose reduction should be considered.
- It is recommendded monthly urine testing for protein

**Hepatic effects**

- Increases in liver transaminases are occasionally seen, so checking ALT monthly is recommended.
- Abnormal liver function tests are more frequent in children
- In such instances chelation should be stopped and ALT levels carefully monitored to ensure they return to normal.

# Unwanted effects with DFX

**Eyes and ears**

- These are very rare and their significance is uncertain
- It is recommended yearly auditory and eye assessments

**Pregnancy and DFX**

- DFX has been shown to have teratogenic effects and its use is not recommended in pregnancy

# *Practical Issues with DFO Infusions*

**Strength of infusion**

- Each 500 mg vial of the drug is dissolved in at least 5 ml of water, giving a 10% solution. Concentrations in excess of this may increase the risk of local reactions at the site of infusion

**Site of infusion**

- The abdomen is generally the best place.
- Because of local reactions such as erythema, swelling and induration, it is often necessary to 'rotate' the sites used for injection
- The best needle to use will depend on the individual. Many patients are happy with butterfly needles of 25 gauge or smaller,
- Patient preference is highly variable and clinicians should explore the best type of needle for each patient, to help maximize compliance

# *Practical Issues with DFO Infusions*

**Local reactions**

- Persistent local reactions may be reduced by:
- varying injection sites,
- lowering the strength of infusion,
- or in severe cases, by adding 5-10 mg of hydrocortisone to the infusion mixture.
- Application of topical low potency corticosteroid cream after injection can reduce local reactions
- 10% solutions of DFO given to peripheral veins will damage the vein.
- Hence the solution must be diluted – for example in 200-500 ml of saline

**Intravenous DFO with blood transfusion**

- Its contribution to iron balance is very limited and not recommended as a standard procedure

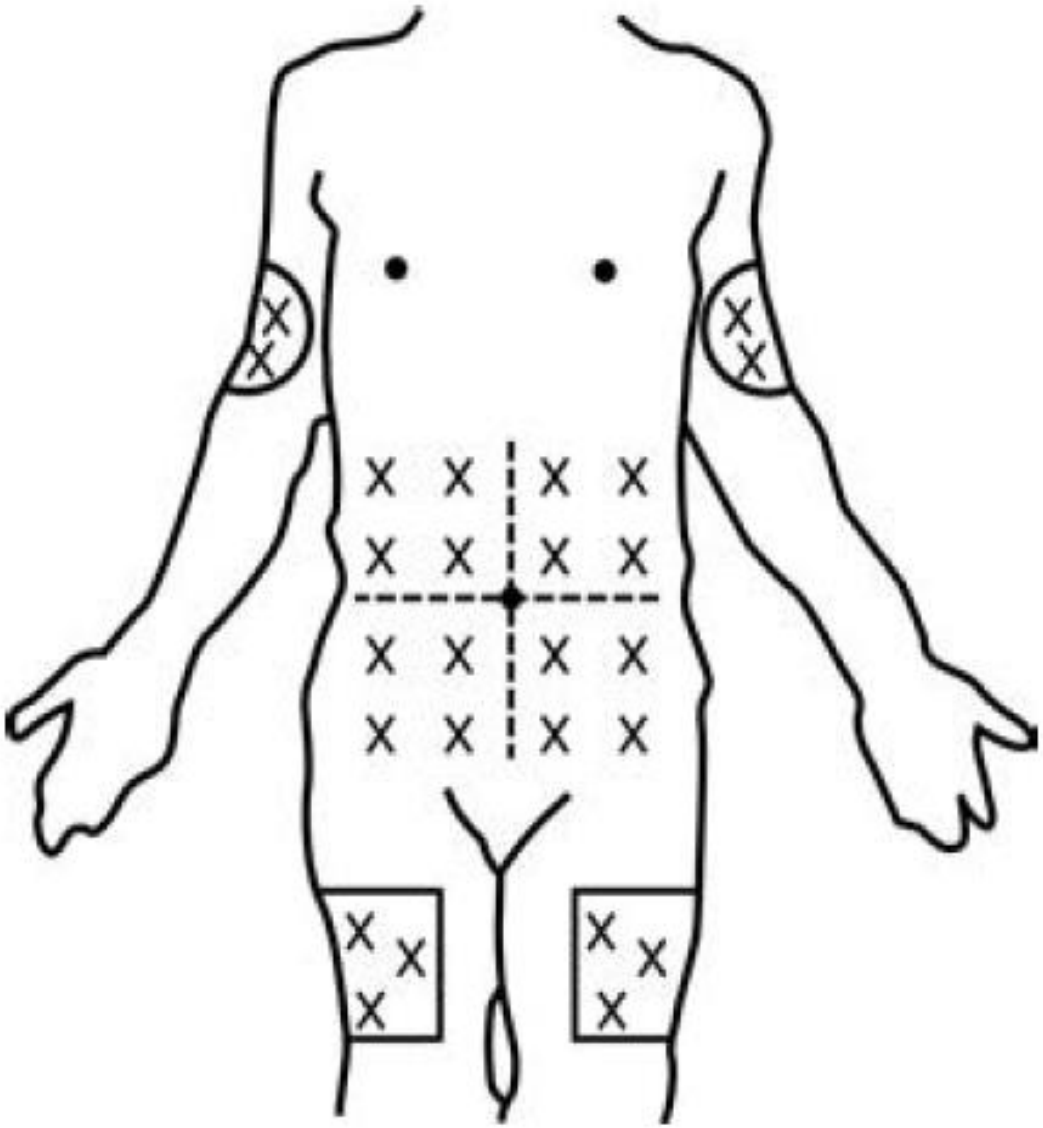

Figure 1. Rotation of infusion sites.

THANK YOU