GUIDELINES FOR THE MANAGEMENT OF TRANSFUSION DEPENDENT THALASSAEMIA (TDT)

3RD EDITION

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15 PSYCHOLOGICAL SUPPORT

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The need for continuity of care and psychological support for chronic disease is widely accepted (Falvo 2014, Lubkin 2014), as is the negative impact of psychological issues on chelation adherence in thalassaemia major (Porter 2011, Evangeli 2010, Panitz 1999, Beratis 1989). This chapter will (1) provide a comprehensive review of the published social and behavioral problems in thalassaemia, with a specific focus on any suggested interventions, and (2) articulate the social and psychological support interventions that have been successfully used for similar problems in other diseases.

However, there is a surprising lack of published evidence for psychological support interventions in thalassaemia. A 2001 Cochrane Review of psychological therapies for thalassaemia (Anie 2001), assessed as "up-to-date" in 2011, concludes that "no randomised controlled trials employing psychological therapies ... were identified" and "no trials, where quasi-randomization methods such as alteration are used, were found." This is particularly concerning since a standard observation in many clinical reviews of thalassaemia over the past 25 years is that patient behavior, primarily with adherence to iron chelation therapy (ICT), is a significant variable in long-term outcome (Efthimiadis 2006, Borgna-Pignatti, 2004, Porter 2002, Modell 2000, Olivieri, 1994).

The Challenge of Psychological Support: What Does the Literature Tell Us?

The challenge of "psychological support" in thalassaemia is not a simple construct. Psychological support encompasses a complex set of defined responses to a diverse set of problems that have become apparent in thalassaemia over the past 30 years. This is illustrated by a simple PubMed Title/Abstract search for thalassaemia and only "psychological support". The first of eleven reports (including the Cochrane review) appears in 1985 identified the need for psychological support in a child care centre in Italy (Colombino 1985), but it took over a decade before a second report described how psychosocial problems impacted chelation adherence, despite an expansion of clinical support services (Politis 1998). This was restated in 2003 with a characterization of adult patients (Galanello 2003) and a cross sectional patient survey (Vardaki 2004). A small cluster of subsequent articles looked at "psychological burdens" in different patient groups including children and caregivers (Prasosmuk 2007, Aydinok, 2005), adolescents (Roy 2007), and adults (Mednick, 2010, Gharaibeh 2009). A single, non-randomised interventional study in 2009 used cognitive behavioral family therapy to try and alter adherence to chelation therapy (Mazzone 2009). These results suggest a wide diversity in the application of psychological support in the clinical effort to manage the patient developmental pathway and their long-term survival associated with ICT adherence.

This finding suggests that "psychological support" is an undefined response to a clinical need that requires specification. In order to develop a more complete understanding of the component elements of psychological support in thalassaemia, we conducted a

comprehensive review of the 371 articles identified by a broad search of the "behavioral and social science research" (BSSR) literature (**Figure 1**). A full-text review determined that 9% (35) of the articles were either specific to BSSR or personal narratives. Another 11% (39) focused on clinical problems that happened to include a BSSR component (e.g. pregnancy in adult patients requires additional support services), and did not further an understanding of psychological support. The remaining articles are organised around the following clinical domains:

- Antenatal Screening (30% of articles): these articles show a well-organised response to the problem of introducing antenatal screening in an at-risk population. They illustrate the complexity of creating a comprehensive solution that includes governmental support, legislation, community education, and face-to-face interaction. These reports tend to be post hoc celebrations of an arduous ad hoc process (**TIF grade: D**). The efforts to replicate this success have yielded some articles that identify specific complications associated with community demographic diversity in migrant populations. These articles identify the challenges this presents for implementing interventional strategies (**TIF grade: C**). Experience from antenatal screening that led to successful implementation were in relatively small and homogenous environments. The challenges when implementing clinical intervention within complex heterogeneous populations have not been fully considered however. A few articles have addressed elements of this complex environment (Vichinsky 2005) by looking at the economics of ICT (Payne, 2007; Riewpaiboon 2010), clinical outreach to the communities of affected patients (Choy 2000), and addressing the needs of culturally different patients (Banerjee 2011) (**TIF grade: C**).
- Iron Chelation Therapy (10% of articles): most of these investigations either measure adherence (Matsui 1994), or assess patient experience with treatment (Porter 2012, Taher 2010, Payne 2007) (**TIF grade: B**). Over half of these articles appeared in the past 10 years with the introduction of new oral chelators and lay a scientific foundation to assess the patient reported health outcome as one step in understanding the patient's ICT practices (Porter 2012, Porter 2011, Sobota 2011, Evangeli 2010, Mednick 2010). These reports tend to have a very good scientific basis (**TIF grade: A**), because they are associated with other kinds of clinical investigations. They do not attempt to solve observed behavioral or social problems.
- Psychological problems (14% of articles): There appears to be a wide-ranging cross-national recognition that patients with thalassaemia are vulnerable to experiencing psychiatric problems (Cakaloz 2009, Saini 2007, Shaligram 2007a, Shaligram 2007b, Aydinok 2005, Pradhan 2003, Sadowski 2002). These articles look at the psychological problems within the context of patient adherence to therapy, with the implied connection that failure to adhere reflects a patient's psychological or cognitive makeup. The early reports tended to be at the level of clinical descriptive studies (**TIF grade: C**). More recent studies have shifted to identifying the neuropsychological investigation of cognitive deficits (Duman 2011, Zafeiriou, 2006, Armstrong 2005, Monastero 2000) (**TIF grade: B**). Angastinoitis points out that the problem of observed psychological problems in thalassaemia could actually be a function of the levels and kinds of support services that are available to patients (Angastiniotis 2002), and not simply a problem of patient's psychological makeup.
- Social Support (20% of articles): These studies address the range of needs of families and patients. The effort to scientifically specify these needs began with Ratip's work to develop disease specific standardised assessments of

these domains (Canastan, 2003, Ratip 1996, Ratip 1995) and has continued with other studies (Tsiantis 1996, Zani 1995). This domain appears to have the most interventional studies that include targeting changes in institutional organization practices (Marovic 2008), patient group sessions (Marovic 2008, Yamashita 1998), family therapy (Mazzone, 2009), and patient chelation camps (Treadwell 2001). While these reports suggest some success, they all lack a robust analytic assessment (**TIF grade: C**).

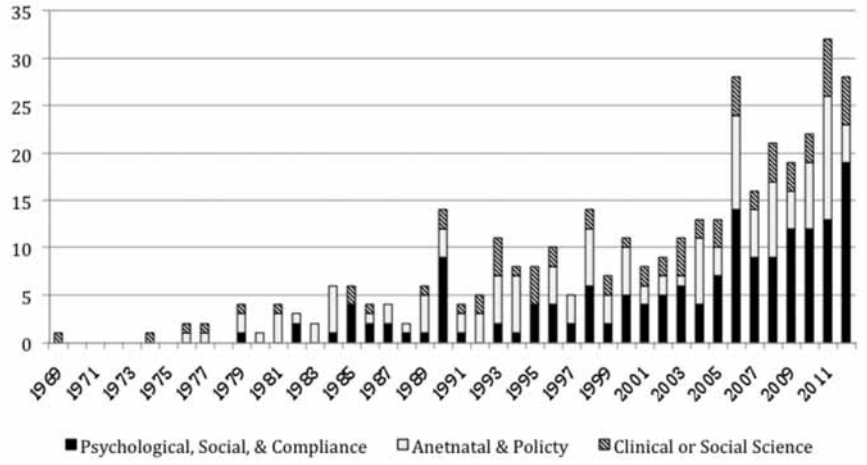

Figure 1. 1979-2012: BSSR articles on psychological aspects of thalassaemia by type. A comprehensive database of the available literature was constructed from title & abstract searches of thalassemia (thalassaemia) in a number of bibliographic databases: PubMed, biological abstracts, pscyINFO, CINHAL, sociological abstracts, social services, and JSTOR. This collection was then searched using a variety of truncated terms (e.g. psych*, soc*, quality of life), and relevant problems (e.g. counsel*, compl*, adher*, econ*, etc.). An abstract review for relevance was conducted since many clinical articles invoke BSSR terminology as a conclusion (e.g. the outcome improves patient quality of life), and do not substantively use it in the study.

As a whole this literature suggests that patients with thalassaemia and their caregivers are faced with many distinct psychological and social challenges which impact emotional functioning and may result in increased vulnerability for experiencing symptoms of psychiatric illnesses, such as depression and anxiety (Duman 2011, Gharaibeh 2009, Marovic 2008, Prasomsuk 2007, Roy 2007, Zafeiriou 2006, Aydinok 2005, Vardaki 2004, Galanello 2003, Angastiniotis 2002, Politis 1998, Ratip 1996, Ratip 1995). Psychological support appears to be loose reference to a broad mix of organizational responses to clinical needs, and not a coherent interventional strategy. Thus, there are no well-developed interventional trials aimed at providing psychological support to improve overall well-being of patients and their families (**TIF bold: F**). The few, small interventional studies are descriptive reports of clinic-level responses (**TIF bold: C**). They lack analytic rigor because standardised behavioral and social science research instruments were not used. Recent reports show an effort to develop the needed rigorous, scientific understanding of patient reported outcome within on-going studies of iron chelation therapy (Haines 2013, Porter 2012,Trachtenberg 2012a, Trachtenberg 2012b, Porter 2011, Sobota, 2011, Trachtenberg 2011, Evangeli 2010). Most are designed to inform a clinical response to underlying clinical problems. These efforts should establish the analytic foundation for future interventional studies in psychological support.

In the meantime, we can only offer recommendations for psychological support based on existing best practices and research done with other disease populations.

Practical Considerations

Recommendations for standards of care for psychological support require a practical organizational model. As the specific challenges associated with being a patient with thalassaemia differs throughout development, a clinical pathway model that starts with the functional landmarks that define the patient and family experience is helpful (diagnosis-treatment). There are two modifiers to the clinical experience. Firstly, because thalassaemia is a chronic disease presenting shortly after birth, the natural growth from infant to adult will shape how patients learn to live with their disease. In the early stages, patients are dependent on their family caregivers, and as they develop, the patient must learn to successfully manage their own care. The second is the institutional organization of clinical medicine. Pediatrics typically works with the patient and their family and adult medicine works with the individual patient. This situation complicates any psychological support recommendations. At each of the landmarks along the pathway (e.g. point of diagnosis, start of transfusion, initiation of chelation, transition into more self-care in adolescence, and transition to adult care), patients and families may be more vulnerable to experiencing psychological sequelae associated with the disease management and developmental challenges commonly experienced during that period of time. Our model of the "clinical pathway of thalassaemia" is illustrated in **Figure 2**.

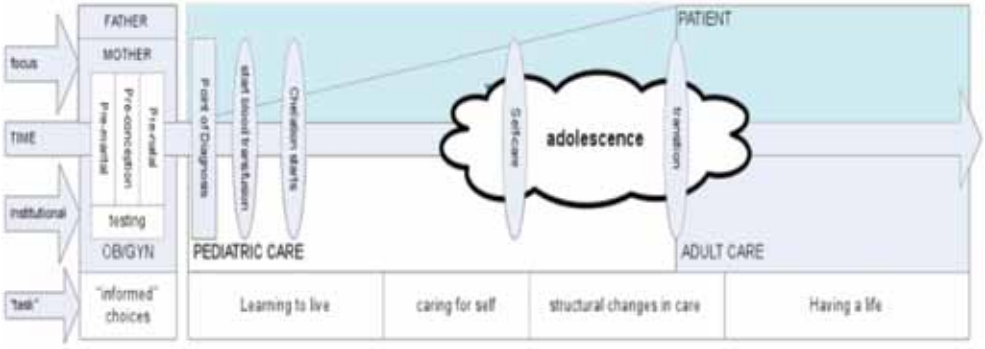

Figure 2. Clinical pathway diagram.

Systematic studies to examine different intervention modalities that may help patients and families effectively cope with the particular challenges inherent at each time point are needed. These should address how early "upstream" familial experiences impact "downstream" patient adherence adaptations and long term survival. As most of the existing literature consists of descriptive reports and cross-sectional studies, the following practical recommendations are largely based on what we know from our clinical work and/or research with other chronic illnesses.

Point of diagnosis

Parents will undergo a series of changes after their child is diagnosed with thalassaemia (shock, denial, sadness/anger, adaptation, reorganization) (Drotar, 1975). One of their most important immediate concerns is getting reliable information (Starke, 2002). Learning the additional tasks associated with caring for a child with thalassaemia

can be overwhelming to the parent and lead to psychological distress (Politis, 1998; Galanello, 2003; Yamashita, 1998). Importantly, if parents feel overwhelmed with caring for their child, effective management of the illness may become compromised (Otsuki, 2010). To minimize these feelings, effective psychological support of parents around the time of diagnosis should include:

- Providing necessary information about thalassaemia. This may need to be repeated several times for full comprehension.
- Opportunities to ask questions and share concerns.
- Occasions to meet parents of older children diagnosed with thalassaemia, as this can help increase social support and confidence, while decreasing feelings of helplessness and hopelessness.
- Access to psychosocial clinicians who can help them explore and manage their feelings of loss in a constructive manner.

It is especially important to help parents accept and learn to effectively cope with their child's chronic medical condition at this early stage. This is because parental behaviors and attitudes throughout development will lay the groundwork for how children will cope with their condition. Parents who demonstrate healthy coping and understand that a well-managed patient who adheres to his/her therapy can live a successful life (Pakbaz 2010) will help their children to learn to make thalassaemia a piece of who they are, rather than what defines them. Introducing the family to an appropriately experienced family with a child who has thalassaemia can be a helpful learning experience for parents of young children.

Start of blood transfusion

The best ways to provide psychological support aimed at helping children effectively cope with invasive medical procedures has been widely studied (Edwards 2010, Thompson 2009, Brown 2007, Hayman 2002, Brown, 1999, Hymovich, 1992). It is essential to help parents and children engage in effective coping strategies as soon as developmentally appropriate, as the experience of distress during a medical procedure has been found to be predictive of distress during future procedures (Frank 1995).

Starting at a very young age, children often look to their parents for signals on how they should react in anxiety-provoking, novel situations. In one study, parent behavior during an invasive medical procedure accounted for 53% of the variance in child distress behavior (Frank 1995). Providing information about the procedure prior to the actual procedure and giving the parent a job to do (e.g., distract the child), is likely to reduce parental anxiety, with positive indirect benefits for their children. However, if parents are not able to remain calm in front of their children during procedures such as blood transfusion, it is helpful for clinicians to give parents' "permission" to leave the room and instead consider including the presence of another supportive adult.

Specific coping strategies aimed directly at the child have been particularly useful in helping children cope effectively with invasive medical procedures. In a meta-analysis of psychological interventions for needle-related procedural distress in children and adolescents, distraction was found to be one of the most efficacious coping techniques (Uman 2008). In fact, a recent study conducted with patients with thalassaemia found that bubble blowing during an injection helped reduce anxiety (Bagherain 2012). Importantly, distraction techniques should be adapted to the child's interest and

age/developmental level. It is particularly useful to encourage parents who engage in excessive reassurance to instead focus on distracting their child, as reassurance often amplifies fear and distress (Manimala 2000), likely due to refocusing the child's attention onto the fearful and painful aspects of the situation.

As children get older, they may ask for more information about transfusions or other invasive medical procedures (e.g., MRI). Fostering trust, reducing uncertainty, correcting misconceptions, enhancing the belief in their ability to cope with a procedure, and minimizing distress are some of the potential benefits in providing advance information about a procedure to a child (Jaaniste 2007; Jipson 2007). Effective pre-procedural information should include:

- A developmentally appropriate verbal explanation of what the child will see, hear, feel, and smell during, before, and after the procedure.
- Minimally threatening, but accurate information, as children who are given information that turns out not to be true (e.g., "you will not feel a thing" when in fact the child is liable to experience some pain), are more likely to develop a distrustful relationship with their parents and/or the medical team, which may negatively affect future interactions.
- Use of visual aids (e.g., books, pictures, models, videos).
- Where possible, medical play can help young children understand their therapeutic regimen (Burns-Nader 2012, Bandstra 2008, Bolig 1991, McCue 1988).
- Time for the child to ask questions.

Initiation of chelation

Parents need to be provided with support and guidance about choosing which type of chelation is best for their child. For example, although oral chelators are associated with less distress and better quality of life in older patients, due to specific developmental characteristics of very young children (e.g., transient food preference, oppositional behavior, unpredictability), this may not be true for some children in this age group (Fiese 2005). Parents of very young children need to be encouraged to carefully consider their chelation options, and determine which option best fits with their own capacities and their child's personality characteristics.

When starting chelation therapy, parents should be encouraged to develop consistent routines around medication taking. Developing predictable routines around a child's medical regimen makes these tasks part of the typical daily schedule, thereby fostering good adherence by minimizing several of the problems often associated with adherence difficulties (e.g., forgetting, conflicts about when to take the medication) (Fiese 2005, Rand 2005).

Behavioral interventions which include increased monitoring and incentives for meeting goals have been shown to be successful at improving adherence in patients with thalassaemia (Koch 1993). The use of incentives may be particularly useful for pediatric patients who don't yet understand the intrinsic value of adhering to an undesirable medical regimen. These may include verbal praise, stickers, or small toys or other incentives earned either immediately or over time, for cooperating with daily chelation. By pairing a positive outcome (e.g., sticker, toy) with an aversive stimulus (chelation), the child develops a positive association with the aversive event, increasing the likelihood that the child will perform the behaviors again in the future.

At various times along the clinical pathway, patients may struggle with chelation adherence (Evangeli 2010). When this occurs, it is essential to identify why the patient is having difficulty following the prescribed plan. Interventions that do not consider the specific barrier to adherence will have limited success (see **Table 1** for common barriers and suggested interventions). In general, effective interventions aimed at improving adherence usually:

- Incorporate behavioral or multiple strategies.
- Include patients (and parents) in the development.
- Start from where the patient is at, gradually increasing goals, while working towards the ideal.
- Need revision over time.

Table 1. Common barriers to adherence and suggested interventions.

BARRIER	INTERVENTION
Lack of understanding concerning regimen implementation or importance	Provide age-appropriate education
Forgetfulness	Set alarms; use visual reminders
Inconvenience	Work with the medical team to change the regimen to fit better with the patient's lifestyle
Inconsistent schedule of medication	Implement a reminder system (e.g., alarms); use a self-monitoring chart to document completion of tasks
Side effects of treatment	Find ways to help minimize or cope with the side effects
Length of treatment	Help the patient find activities to do to during the treatment
Complicated regimen	Simplify regimen (with medical team); create a self-monitoring chart to document completion of each task
Social Stigma	Engage the patient in treatment aimed at improving self-esteem; encourage the patient to meet other individuals with similar medical conditions
Poor supervision	Increase adult involvement and monitoring
Cultural or religious beliefs	Work with family to understand their beliefs and when possible adapt treatments to fit within their values

BARRIER	INTERVENTION
Psychiatric illness	Treat underlying psychiatric illness
Family psychopathology	Work with caretakers to create an environment that is conducive to encouraging adherence (e.g., decreased conflict, increased communication)
Poor social support	Help the patient/family find resources within their community; encourage the patient to meet other individuals with similar medical conditions

Additional opportunities for psychological support during childhood

As children with thalassaemia frequently miss school for medical appointments and transfusions (Gharaibeh 2009), which can negatively impact school functioning (Thavorncharoensap 2010), parents should be encouraged to educate the school about their child's conditions and to set-up plans which support the child when he/she needs to miss school. Further, patients with thalassaemia may be vulnerable to experiencing cognitive deficits (Duman 2011, Nevruz 2007, Economou 2006, Zafeiriou 2006, Armstrong 2005, Lucke 2005, Zafeiriou 2004, Monastero 2000). If there are concerns from parents or the school, it may be valuable for patients to participate in neuropsychological testing to assess for any concerns and provide recommendations that could help support the patients learning potential.

Adolescence and transition to increased self-care

Adolescence is a time when adherence to daily medical regimens often declines (Trachtenberg 2011). Frequently the transition of responsibility from the parent to adolescent occurs before the patient is emotionally ready, resulting in poor adherence. Because adolescents are vulnerable to having their decision making being driven by their desire to be independent and to fit-in with peers, parents need to continue to play an active role in monitoring adolescents self-care. Shared responsibility between the patient and caregiver has been found to be associated with better adherence (Evangeli 2010, Treadwell 2001).

Also, to avoid the negative consequences of abrupt shifts in responsibility, the transition of responsibility needs to:

- Occur gradually over time, starting when children are young (e.g., help gathering supplies) and increasing their involvement as they mature.
- Teach older patients how to take over responsibility for often-overlooked tasks, such as ordering supplies and making medical appointments.

Transition to adult Care

One reason why adherence may be lowest in young adults (Trachtenberg 2011) is because of insufficient psychosocial support as patients transition from pediatric to adult medical providers. Often the transition to adult care providers happens in an abrupt manner, leaving the patient unprepared for the shift to adult medicine (Bryant 2009). Discussions about transitions should occur well in-advance of the actual transfer

in care and should include an exploration of the patients concerns and how they will prepare for and manage the changes inherent in moving from a pediatric to adult medicine clinic. Further, a well-coordinated transitional plan should be developed, which includes:

- Opportunities to orient the patient to an adult clinic and the adult care system.
- Overlapping visits with pediatric and adult hematologists.

An emerging concern that is common in adult patients with thalassaemia is the experience of pain (Haines 2013, Trachtenberg 2010). The presence of pain in the non-thalassaemia adults is associated with decreased social function and increased depression (Ozminkowski 2012, Garber 2010, Avlund 2007, Dunn 2004, Koenig, 1997, Burckhardt 1985). Clinicians should encourage patients with pain to engage in a variety of empirically validated (Shega 2012, Palermo 2010, Eccleston 2009) cognitive and behavioral coping strategies which have been shown to successfully help patients manage their pain and distress through learning how to regulate their emotional and physical responses to pain. Effective pain management includes a combination of pharmacologic and non pharmacologic approaches including and not limited to:

- Deep breathing
- Guided imagery
- Progressive muscle relaxation
- Hypnosis
- Biofeedback

Importance of social support throughout development

As social support has been found to play an important role in the psychological functioning of children and their families (Lewandowski 2007), starting from an early age, patients and their families would benefit from:

- Deciding how to present information about the patient's medical condition to friends and family.
- Learning about the harmful effects (e.g., feelings of shame) of keeping thalassaemia a secret.
- Relying on existing friend, family, religious, and community supports.
- Meeting other patients and families with chronic medical conditions through attending camps, events sponsored by specific illness foundations, or one-to-one meeting facilitated by a clinician.

Psychosocial support throughout the lifespan as part of standard care

As social and emotional concerns can occur anywhere along the clinical pathway and such concerns can impact the patient's quality of life, as well as physical health, opportunities for regular psychological support should be part of the treatment plan of all patients with thalassaemia. This is best accomplished through a multidisciplinary team approach, which include nurses, social workers and psychologists who meet with the patient and families on a regular basis as part of their standard care. These clinicians are best suited to assess for any social, emotional, or cognitive concerns and intervene with additional support when necessary. This could be especially useful for getting patients who experience significant symptoms of psychiatric disorders such as anxiety and depression, engaged in psychotherapy early on in an effort to prevent long-

term health consequences. Importantly, by including psychological support as part of standard care, some of the stigmatization associated with seeing a therapist may be removed.

Summary and Recommendations

Overall, despite a general lack of large scale, randomised, controlled trial evidence conducted with patients with thalassaemia, there are innumerable cohorts of case-controlled analytic studies to suggest that psychological well-being impacts on adherence to treatment for chronic disease in general **(B)**. In thalassaemia, the published reports to demonstrate this linkage are mainly descriptive studies **(C)**. A meta-analysis would suggest that more recent efforts are more towards "B" grade investigations (usually ancillary studies attached to robust controlled trials in other clinical areas). However, the lack of uniform instruments and standardised measurements weakens this assessment. The findings to date suggest that:

- Psychological well-being impacts on adherence to chelation treatment in Thalassaemia Major and hence on survival **(C)**.
- Patients with thalassaemia are vulnerable to experiencing psychological challenges **(C)**.
- Patient-reported health outcome shows that oral chelation therapy has a beneficial impact, relative to parenteral chelation **(B)**.
- Neuropsychological investigation of cognitive deficits show that there are clear intellectual and psychopathological problems in a very limited number of thalassaemia patients **(B)**.
- Benefits of psychological support have been suggested using a variety of approaches **(C)** which include:
  - targeting changes in institutional organization practices
  - patient group sessions
  - family therapy
  - patient chelation camps
- In all chronic illness, continuity of comprehensive care across the lifespan is essential for long-term, beneficial health outcome **(A)**. Institutional organizational support for multidisciplinary teams is essential **(A)**. There is a growing body of evidence that highlight the problems associated with transition from pediatric care to adult internal medicine in inherited chronic disease **(B)**. Rare and neglected diseases complicate resource allocation models and lead to notable health disparities **(A)**. In thalassaemia, these problems are known and reports from expert committees recommend addressing them, but there are no formal studies of the problems, much less any standardised evidence **(F)**.

While A and B grade evidence for psychological support in thalassaemia is scarce, experience in several large thalassaemia centres strongly suggests that psychological well-being is key to adherence and to outcome.

- Expert psychological support has to be available at all centres specializing in thalassaemia care **(C)**.
- Psychological support should be tailored to the patients age
  - Children (in general, **A**, thalassaemia **C**)
  - Adolescents – transition (in general, **B**, thalassaemia **C**)
  - Older adults –pain issues (in general, **A**, thalassaemia **C**)

Funding for clinical psychological support services could be more widely achieved if well-designed, multi-centre, interventional studies using common standardised instruments were undertaken to evaluate the benefit of psychological support to treatment adherence. The use of established behavioral and social science approaches in such studies need to identify the active components of "psychological support" that are most applicable to patients with thalassaemia.

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