Review Article

Narrative review of contemporary strategies in stem cell transplantation for chronic granulomatous disease

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Background and Objectives: Chronic granulomatous disease (CGD) is an inherited immunodeficiency characterized by recurrent, often life-threatening infections and a dysregulated immune response. Through early diagnosis, infection surveillance, and prophylactic antimicrobials, survival has improved with greater than 90% of patients living into early adulthood. Despite this improvement, nearly 50% of patients with CGD do not survive past 30 years of age. Furthermore, compounding morbidities from infections and inflammatory disease significantly compromise quality of life. Allogenic hematopoietic stem cell transplantation (HSCT) is curative for CGD and can reverse existing inflammatory lesions. We review approaches to HSCT for children with CGD, including impact of patient and donor characteristics on outcomes, conditioning regimens that have demonstrated success, and continued challenges of transplant-related morbidity and post-transplant autoimmunity.

Methods: An electronic search was performed on PubMed to identify relevant articles from 2000 to 2021.

Key Content and Findings: Children with CGD have excellent overall survival, disease-free survival, and event-free survival after HSCT. Best outcomes are in patients transplanted at early (prior to 5 years of age), prior to the onset of severe infection or inflammatory lesions, and with a matched family donor. Recent studies have demonstrated very good outcomes with alternative stem cell sources (unrelated, mismatched/haploidentical, and umbilical cord blood), especially when conditioning regimen and immunosuppression are customized. Reduced toxicity or intensity regimens can successfully promote durable donor engraftment and restore normal immune function. Graft versus host disease (GVHD) continues to be a concern.

Conclusions: Advances in stem cell transplant, including use of alternative donors and reduction in acute and late toxicities, have improved outcomes leading to expanded use of HSCT for CGD. Further research is required to determine optimal approaches for preparative regimens, mitigating GVHD, and reducing post-transplant complications unique to CGD.

Keywords: Chronic granulomatous disease (CGD); hematopoietic stem cell transplantation (HSCT); transplant outcomes; transplant toxicity

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Introduction

Chronic granulomatous disease (CGD) is a primary immunodeficiency characterized by recurrent infections, dysregulated inflammation, and autoimmunity. Mutation in one of the five structural subunits of the NADPH oxidase complex produces decreased or absent reactive oxygen species within granulocytes (1). The inability of innate immune cells (neutrophils, monocytes and macrophages) to efficiently generate reactive oxidative species predisposes patients to invasive, life-threatening infections by catalase positive organisms and impairs clearance of apoptotic debris resulting in immune dysregulation and autoinflammation (1). Through early detection and supportive care, including antimicrobial therapy, the life expectancy for patients with CGD has improved from early death in childhood to a median life expectancy between 28–40 years of age (2-4). However, as a consequence of the cumulative effects of recurrent infections and inflammatory dysregulation, patients develop severe morbidities that significantly impair quality of life (3-6).

Allogeneic hematopoietic stem cell transplantation (HSCT) is curative for CGD. HSCT halts disease progression and can reverse existing inflammatory processes (7-10). Compared to conventional therapy, patients treated with HSCT have superior clinical outcomes and improvement in quality of life (5,6). However, HSCT has significant risks, including organ toxicity from conditioning therapy, graft-versus-host disease (GVHD), infection and transplant-related mortality. Due to these risks, HSCT was historically reserved for individuals with severe disease (i.e., recurrent or refractory life-threatening infection, refractory granulomas, or organ dysfunction) (11). Furthermore, HSCT was primarily pursued in patients who could tolerate intensive conditioning and had an HLA-matched family donor (MFD). Evolution in the approach to transplant, such as earlier transplantation before severe disease, modifications in conditioning, and aggressive treatment of infections prior to transplantation have been paramount in increasing the utilization and availability of HSCT for CGD. With these advances, patients have been successfully transplanted with stem cell grafts from unrelated, haploidentical and cord blood donors. New reduced intensity and reduced toxicity conditioning (RTC) regimens have led to improved outcomes with less immediate and long-term side effects. Consequently, the indications and methods for transplant in CGD are expanding. However, while HSCT is increasingly used for patients with CGD, existing co-morbidities, such as refractory infection and inflammation, can adversely impact outcomes and toxicities. Here we review recent progress in HSCT for CGD, including patient-specific characteristics, donor selection, conditioning regimen, transplant-associated toxicities, and outcomes.

Methods

An electronic literature search via the PubMed database was performed by the authors. Peer-reviewed articles published in English (or translated to English by the publisher) between 2000-2021 were considered. Relevant sources were identified using search terms/phrases such as “chronic granulomatous disease”, “CGD”, “pediatric”, “hematopoietic stem cell transplant”, and “conditioning” individually or in combination. Primary research was used for data comparison. Additionally, review articles were used to manually identify some studies.

Patient characteristics

Several patient-specific variables can impact outcomes after HSCT for CGD, including patient age, active infection, and concomitant inflammatory disease (9). Outcomes for pediatric patients less than 14 years of age have been excellent with reported survival rates consistently over 90% (1). Lum *et al.* reported that patients transplanted earlier in childhood have superior outcomes with 100% overall survival (OS) in patients less than 5 years old compared to 81% OS in those older than 5 years of age (12). Younger age may confer better prognosis, at least in part, due to fewer comorbidities from the sequelae of recurrent infections and chronic inflammatory disease.

Historically, transplant-related mortality has been a major barrier in adolescents and young adults with CGD due to unacceptably high mortality rates ranging from 28–50% (1,10,13). However, a recent large retrospective, multicenter analysis of 712 patients with CGD highlighted that while children <10 years of age continue to have better OS, outcomes of patients ≥18 years of age have improved in comparison to historical outcomes with 3-year OS and event-free-survival (EFS) of 76% and 69%, respectively (14). In a smaller report of 7 adolescent patients transplanted using newer RTC regimens, all patients were alive and well at a median follow-up of 32 months with sustained donor engraftment in 6 patients (9). Post-transplant complications, though, were significant, including severe GVHD, viral reactivation, progression of ongoing

fungal infection, and new infection with *Pneumocystis jiroveci* pneumonia (9). While tools for predicting these complications do not currently exist, stringent supportive care, including antimicrobial and GVHD prophylaxis, in the post-transplant period is essential for minimizing their incidence and severity.

In addition to age, active infection and chronic inflammatory bowel disease (IBD) have been associated with a reduced survival after HSCT. In a cohort of patients receiving myeloablative conditioning (MAC) and MFD HSCT, Seger *et al.* reported that 4 of 9 patients with active fungal infection at the time of transplant died and patients with active inflammation, including IBD, had high rates of GVHD (15). Similarly, a retrospective report from the European Society for Blood and Marrow Transplantation (EBMT) Inborn Errors Working Party described a trend toward reduced survival in patients with colitis (HR =1.72; P=0.052) (14). In contrast, a retrospective review by Marsh *et al.* found no difference in engraftment, occurrence of GVHD, or OS between CGD patients transplanted with (n=49) or without (n=96) pre-existing IBD (16). A study by Soncini *et al.* also showed that patients with CGD and active colitis were successfully transplanted and had resolution of colitis post-HSCT (17). Risks of post-transplant complications, particularly GVHD, are higher in patients with pre-existing inflammatory disease, such as colitis (8,17,18). Furthermore, transplant outcomes are better in patients transplanted prior to development of organ dysfunction secondary to cumulative effects of infections and inflammation (8). However, delaying transplant for control of infection or inflammation does not necessarily translate to better survival (8). Overall, these studies support early HSCT for CGD patients prior to development of refractory infections, chronic inflammatory disease, and disease-related morbidity. However, advancements in transplant regimens and supportive care practices continue to lead to improvements in EFS and OS for adolescents and young adults with CGD and for patients with existing comorbidities.

Stem cell source

The first large report of successful transplantation for CGD utilized primarily MFD and MAC (10). Of the 23 patients receiving MAC, 22 had sustained donor engraftment with OS and EFS of 85% and 81%, respectively (10). In order to broaden availability of transplant to patients without HLA-identical familial donors, efforts have centered on utilizing stem cell grafts from alternative donors, including matched unrelated donors (MUD), mismatched unrelated donors (mMUD), haploidentical donors, and cord blood units. Several studies have shown that outcomes with MUD are comparable to those with MFD (7,12,17,19,20). However, a large retrospective study from the EBMT Inborn Errors Working Party found that use of grafts from MUD (HR, 1.89; P=0.006), 1-antigen mMUD (HR, 2.37; P=0.001), and >1-antigen-mismatched donor (HR, 3.69; P=0.001) all had decreased EFS when compared to MFD due to increased risk of graft failure (14). Furthermore, compared to transplants with MFDs or MUDs, patients who received mMUD had reduced OS due to late deaths, mostly from GVHD (14).

Successful transplant for CGD using haploidentical donors has been recently reported (*Table 1*). Hoenig *et al.* published the first case report of successful haploidentical HSCT in a patient with high-risk CGD using CD34-selected peripheral blood stem cells and reduced intensity conditioning (RIC) with sustained donor engraftment at 4 years post-HSCT and no GVHD (22). While there was delayed immune reconstitution with T cell recovery occurring after 1 year and immunoglobulin replacement therapy required for 9 months, the patient did not experience any serious infections (22). Parta *et al.* also reported successful donor engraftment using a haploidentical peripheral blood graft and post-transplant cyclophosphamide (23). However, in a follow up report of 7 patients the authors describe unacceptable toxicity from severe GVHD and infection resulting in death of 2 patients, despite successful engraftment in all patients (18). Similarly, Fernandes *et al.* recently published outcomes of patients with primary immune deficiencies transplanted using haploidentical bone marrow grafts and post-transplant cyclophosphamide (26). Of the 10 patients with CGD transplanted with this approach, 7 patients had graft loss requiring rescue transplant and only 4 of the 10 patients were alive and well 2 years post-HSCT (26). Based on these reports, haploidentical transplant with post-transplant cyclophosphamide should be pursued with caution in patients with CGD. An alternative approach to haploidentical HSCT utilizes TCRαβ$^+$/CD19$^+$-depletion of donor stem cell grafts. Lum *et al.* reported a 2-year 100% OS in 4 patients who received a TCRαβ$^+$/CD19$^+$ depleted haploidentical graft following conditioning with fludarabine, thiotepa, anti-thymocyte globulin, and rituximab (12). Shah *et al.* also reported successful engraftment in two patients with CGD utilizing this graft modification strategy and a

Table 1 Outcomes using UCB and haploidentical donors for HSCT in CGD

Reference	# Patients	Graft	Conditioning	GVHD prophylaxis	OS	EFS	Graft Failure	Donor chimerism	GVHD incidence
Tewari *et al*. 2012 (21)	7	UCB	MAC (busulfan, cyclophosphamide, fludarabine, ATG)	CSA + (MMF, or steroids)	100%	71%	1° failure: 29%	>92%	aGVHD: 100%; cGVHD: 43%
Hoenig *et al*. 2014 (22)	1	Haplo-HSCT PBSC, modified: CD34+ selection, T cell depletion	RIC (busulfan, fludarabine, thiotepa, alemtuzumab)	Not specified	100%	100%	0%	90%	aGVHD: 0%; cGVHD: 0%
Parta *et al*. 2015 (23)	1	Haplo-HSCT	RIC (busulfan, cyclophosphamide, fludarabine, TBI)	PTCy + Sirolimus	100%	100%	0%	100%	aGVHD: 100%; cGVHD: 0%
Shah *et al*. 2019 (24)	2	Haplo-HSCT PBSC, modified: TCRαβ/ CD19-depleted	RTC (treosulfan, fludarabine, thiotepa, serotherapy)	CSA ± MMF	100%	100%	0%:	100%	aGVHD: 100%; cGVHD: 0%
Lum *et al*. 2019 (12)	4	Haplo-HSCT PBSC, modified: TCRαβ/ CD19-depleted	RIC (treosulfan fludarabine, thiotepa, ATG, rituximab)	CSA+MMF: 1; None: 3	100%	NR	NR	NR	aGVHD: NR; cGVHD: 0%
Tang *et al*. 2020 (25)	28	Haplo-HSCT	MAC (busulfan, cyclophosphamide, fludarabine, ATG)	CSA + MMF + MTX	94%	85%	2° failure: 3.5%	100%	aGVHD: 59%; cGVHD: 4%
	10	UCB		CSA + MMF	80%	80%	0%	100%	aGVHD: 40%; cGVHD: 10%
Parta *et al*. 2020 (18)	7	Haplo-HSCT	RIC (busulfan, cyclophosphamide, fludarabine, TBI)	PTCy + Sirolimus	71%	71%	0%	>96% in all patients	aGVHD: 100%; cGVHD: 29%
Fernandes *et al*. 2020 (26)	10	Haplo-HSCT	MAC (n=3) (Busulfan, fludarabine, serotherapy) or RIC (n=7) (fludarabine, cyclo-phosphamide, TBI)	PTCy + MMF + calcineurin inhibitor	40%	40%	1° failure: 40%	NR	aGVHD: 10%; cGVHD: 30%

UCB, umbilical cord blood; HSCT, hematopoietic stem cell transplant; CGD, Chronic granulomatous disease; OS, overall survival; EFS, event free survival; PBSC, peripheral blood stem cells; RIC, reduced intensity conditioning; RTC, reduced toxicity conditioning; MAC, myeloablative conditioning; TBI, total body irradiation; CSA, cyclosporine; MTX, methotrexate; MMF, mycophenolate mofetil; PTCy, post-transplant cyclophosphamide; GVHD, graft-versus-host disease; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; NR, not reported.

RTC (comprised of treosulfan, fludarabine, and thiotepa). Both developed acute skin GVHD, but severity was limited to grade I–II. (24).

Umbilical cord blood (UCB) products have also been used as donor source (*Table 1*). In a retrospective review of 38 individuals who received either a UCB (n=10) or unmanipulated haploidentical donors (n=28) following MAC, Tang *et al.* reported 100% initial donor engraftment with only one patient experiencing graft failure at 120 days after haploidentical HSCT (25). At three years post-transplant, OS was 94% and 80% with EFS of 85% and 80% in the haploidentical and UCB recipients, respectively (25). Overall transplant-related mortality was 9.1% at 3 years, with no significant difference between the haploidentical and UCB HSCT groups (25). In a separate study, Tewari *et al.* reported 100% survival in seven patients who received a UCB transplants (6 unrelated, 1 sibling donor) following MAC (21). Two patients experienced primary graft loss, but were successfully re-transplanted using a second UCB product (21). Notably, all patients developed acute GVHD and 43% (3/7) developed extensive chronic GVHD (21). In follow-up of this study, Connelly *et al.* reported outcomes of the total cohort of 14 CGD patients transplanted with MAC and UCB grafts (8). Overall, 13 of 14 patients (93%) were alive and disease

free at a median follow-up of 7 years (8). Advancements in conditioning regimens, graft manipulation, and GVHD prophylaxis will be imperative in ongoing efforts to improve outcomes with use of alterative donor sources for HSCT in CGD patients.

Conditioning therapy

At present, there is no consensus on the best conditioning strategy for HSCT in patients with CGD. MAC has been successfully utilized but is associated with higher risk of toxicities and post-transplant complications (10,27). Consequently, recent efforts have centered on implementation of modified conditioning regimens with the goal of reducing toxicities while maintaining optimal donor engraftment. Horwitz *et al.* reported high rates of mixed chimerism in 10 patients transplanted using a non MAC regimen in combination with T cell depleted MFD peripheral blood grafts (13). Patients required post-HSCT donor lymphocyte infusions to aid in engraftment (13). Two patients had graft failure, three patients developed Grade II–IV acute GVHD, and three patients died (13). In contrast, HSCT utilizing myeloablative, reduced toxicity regimens have demonstrated excellent engraftment and survival. Güngör *et al.* published a large prospective, multicenter study of 56 patients transplanted using RTC with low dose busulfan, fludarabine, and serotherapy (ATG or alemtuzumab) (27). Despite the cohort having high-risk features, OS and EFS were excellent at 96% and 91%, respectively, at 2-years post-HSCT. The cumulative incidence of grade III–IV acute GVHD and chronic GVHD were both low at 4% and 7%, respectively (27). The majority of patients (93%) had stable donor myeloid chimerism (>90% donor) (27). Notably, a subsequent case series of three patients reported high rates of graft failure and mixed chimerism utilizing a similar regimen (28). Treosulfan-based RTC has also been successful in the pediatric patients with CGD (7). In a retrospective analysis of 70 patients transplanted using treosulfan conditioning, OS was 91.4% and EFS was 81.4% at a median follow-up of 34 months (7). Nearly all patients (80%) had full donor engraftment in myeloid cells (7). Secondary graft failure occurred in 12% of patients. Incidence of GVHD was relatively low with grade III-IV acute GVHD and chronic GVHD occurring in 12% and 13% of patients, respectively (7).

We and others have reported on the use of RIC regimens for transplant of patients with CGD. Parta *et al.* transplanted 40 patients using RIC with low dose busulfan and alemtuzumab (low dose TBI added for MUD recipients) utilizing sirolimus for GHVD prophylaxis (29). OS and EFS were 82.5% and 80%, respectively (29). Donor myeloid engraftment was greater than 70% in 93% of evaluable patients at a mean follow up of 3.4 years (29). Acute and chronic GVHD occurred in 45% and 12.5% of patients, respectively, with 6 patients developing severe GVHD (grades III-IV and/or steroid refractory disease) (29). Khandelwal *et al.* compared a cohort of 14 patients who received MAC with busulfan, cyclophosphamide, and ATG to 4 patients who received RIC with fludarabine, melphalan, and alemtuzumab (30). Secondary graft failure was a significant problem for patients receiving RIC with 3 of the 4 (75%) patients requiring withdrawal of immune suppression or additional stem cell infusion to achieve stable engraftment (30). In comparison, 13 of 14 patients (93%) in the MAC group achieved stable donor chimerism without further intervention. However, acute GVHD occurred in 64% of patients who received MAC while no patients in the RIC group developed GVHD (30). Our group reported outcomes using a similar RIC regimen with the addition of thiotepa to the combination of fludarabine, melphalan and alemtuzumab (31). Of the 4 patients treated, all patients engrafted at day 30; however, one patient had graft failure at day 100 in the setting of acute adenovirus infection (31). Two patients developed grade II-III acute skin GVHD and one patient developed grade II acute gastrointestinal GVHD in the setting of acute adenovirus infection that persisted as limited chronic GVHD (31). All three patients with sustained engraftment were alive and disease free at a median of 5 years post-HSCT (31). Mehta *et al.* reported transplant outcomes of 4 patients with CGD conditioned with alemtuzumab, fludarabine, and low dose TBI (200 cGy × 2) (32). The three patients receiving peripheral blood grafts had sustained donor engraftment at a median follow up of two years with one patients developing grade II acute GVHD that progressed to extensive chronic GVHD (32).

A recent report by the EBMT Inborn Errors Working Party concluded that patients with CGD transplanted with myeloablative busulfan and cyclophosphamide had a lower risk of graft failure but an increased risk of GVHD (14). Importantly, they reported no significant difference in EFS and OS for patients receiving myeloablative versus RTC (14). Thus, given the short-term and long-term toxicities expected with a MAC regimen, a reduced toxicity approach is the preferred treatment strategy for HSCT in patients with CGD. Further studies, though, are needed to define the optimal

reduced toxicity regimen for these patients.

Transplant outcomes relative to conservative management

An important consideration in HSCT for CGD has been the risk of transplant-associated toxicities/mortality relative to the overall clinical benefits, particularly in comparison to conservative management outcomes, which have significantly improved survival and quality of life in CGD patients. Using data from the United States Immunodeficiency Network, a retrospective analysis of 507 patients diagnosed with CGD between 1953-2016 with a median follow up time of 9.1 years found that OS did not significantly differ between transplanted and conservatively managed patients (11). However, patients who received HSCT had significantly decreased incidence of infections, decrease in existing granulomata, decreased prevalence of disability, and higher performance scores (11). Conversely, patients managed conservatively experienced higher frequency of pulmonary insufficiency and colitis (52% versus 11% in the transplanted cohort) (11).

In a separate study of 62 children with CGD (<16 years of age), patients who received HSCT (n=30) had fewer infections, admissions, and surgeries per CGD life year as well as better height for age compared to patients managed conservatively (n=32) (5). Both groups had similar OS with 90% of patients surviving to age 15 (5). In a similar study, Åhlin *et al.* found higher long-term survival in transplanted patients with 93% alive at median follow-up of 7 years compared to 37% mortality for patients managed with conservative therapy (6). Notably, mortality was significantly worse (53%) for patients with X-linked CGD treated conservatively (6). Overall, with recent advancements in transplant, HSCT leads to improved quality of life in CGD patients without adding significant morbidity or reducing OS.

Post-transplant autoimmune disease

As longitudinal data emerges, some concern has risen for an increased occurrence of post-transplant autoimmune diseases in CGD as compared with the expected incidence in patients transplanted for other indications. Yanir *et al.* prospectively evaluated 24 patients with CGD who had undergone HSCT with varied conditioning strategies and donor sources (33). Surprisingly, though transplant outcomes paralleled previous studies with excellent OS, 50% of patients developed autoimmune events, including immune thrombocytopenic purpura, autoimmune hemolytic anemia, Guillain-Barre syndrome, transverse myelitis, and autoimmune thyroid disease (33). In comparison, the predicted incidence of post-transplant autoimmune disease is 3–4% in patients transplant for other diseases (34). In a more recent study, Lum *et al.* observed a cumulative incidence of autoimmune disease of 12% at 5 years post-transplant (12). Despite being strikingly lower than results from Yanir *et al.*, this incidence is still significantly higher than that expected across other transplant indications. Patients with CGD may be at increased risk for the development of autoimmune disease post-transplant due to higher immune dysregulation and inflammation prior to transplant. Currently, it is not evident if reduction in CGD-associated immune dysregulation and inflammation prior to HSCT reduces risk of autoimmune disease post-HSCT or if other CGD-specific risk factors influence the incidence of this post-HSCT complication. Further research is necessary to delineate these risk factors, to quantify the incidence of autoimmune disease with newer transplant regimens, and to develop strategies to mitigate this complication.

Conclusions

While significant advancements in conservative medical management of CGD have improved survival, patients still experience recurrent invasive infections and inflammatory complications that negatively impact quality of life and lead to shortened lifespan. Allogeneic HSCT is curative for CGD but has inherent risks and toxicities that must be carefully considered in relation to standard conservative management approaches. Following HSCT, overall and event free survival (EFS) rates have significantly improved and are comparable or better than those achieved with standard medical management. Longitudinal studies have demonstrated sustained improvement in quality of life after HSCT with better growth and reduced incidence of inflammatory lesions and infections. HSCT early in childhood with MFDs has the best outcomes. In the absence of a matched related graft, transplantation with an unrelated or mismatched donor should be considered as outcomes have improved substantially in recent years. Even higher risk patients including adolescents and patients with refractory inflammation and infections have demonstrated improved OS and EFS after HSCT. Use of MAC regimens consistently support the best donor

engraftment but are plagued by a high incidence of post-transplant toxicity. In recent studies, reduced intensity and RTC regimens have emerged as preferred approaches due to excellent survival and donor engraftment with reduced post-transplant morbidities. While new approaches to transplant and GVHD prophylaxis have reduced its incidence and severity, GVHD continues to be a serious complication with potential for a deleterious impact on survival and quality of life, particularly with the use of alternative and mismatched donors. Risk of GVHD is impacted by transplant-associated factors (donor selection, conditioning regimen, graft processing and post-transplant immunosuppression) as well as CGD-specific influences, such as pre-existing infections, organ dysfunction and inflammation. Continued efforts to reduce GVHD risks with novel prophylaxis and graft modification techniques are needed to further expand the utilization of HSCT in the treatment of CGD patients. Additional studies are also required to determine the incidence and optimal management of CGD-specific post-HSCT complications, such as autoimmune diseases. In light of recent advances, stem cell transplant should be considered for all patients with CGD with continued research focused on optimizing approaches to support long term survival with reduced complications and toxicities.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://pm.amegroups.com/article/view/10.21037/pm-20-106/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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