COMPLICATIONS AFTER TRANSPLANTATION

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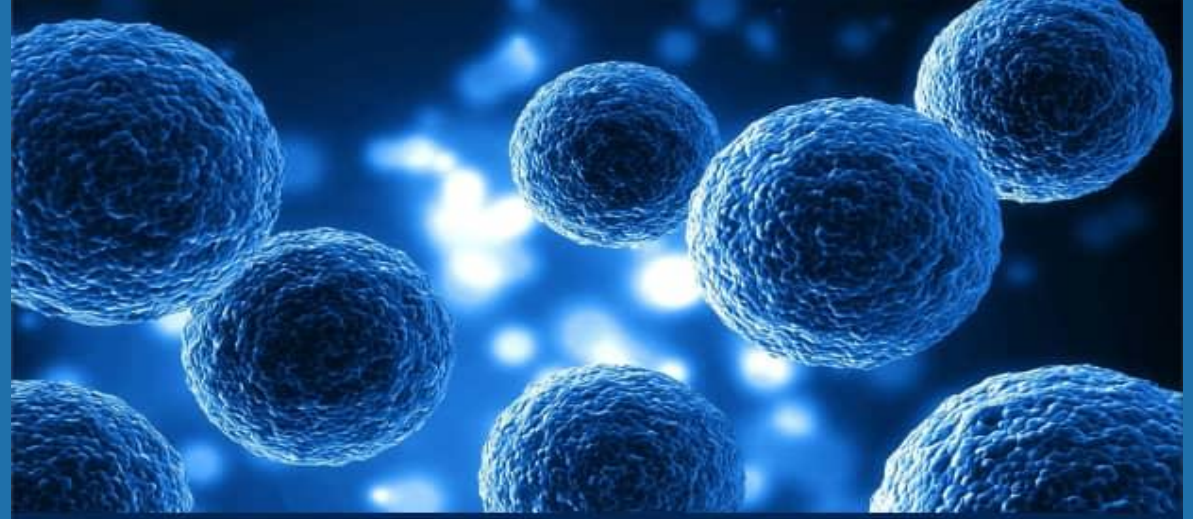

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چهاردهمین کنگره انجمن علمی پیوند سلولهای بنیادی خون‌ساز
و بیست و سومین کنگره سراسری هماتولوژی ایران (اولین کنگره مشترک)

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- عوارض پیوند به چه فاکتورهایی بستگی دارد؟

- Factors that affect the nature and severity of complications after HCT vary with the individual patient's circumstances. Factors that may contribute to early post-transplantation complications and the individual's reserves to tolerate them include:
- ●Prior cancer treatments (eg, chemotherapy, radiation therapy, immunotherapy)
- ●Status of the underlying cancer at the time of transplantation (eg, complete remission versus persistent disease)
- ●Comorbid medical conditions (eg, diabetes mellitus and hepatic, renal, cardiovascular, pulmonary conditions)
- ●Conditioning regimen (eg, myeloablative, reduced intensity, non-myeloablative)
- ●Donor source (eg matched sibling donor [MSD], matched unrelated donor [MUD], mismatched related or unrelated donor, haploidentical, and umbilical cord blood)
- ●Autologous versus allogeneic HCT
- ●Severity of graft-versus-host disease (GVHD), in patients who undergo allogeneic HCT
- ●Duration and degree of cytopenias and immunosuppression
- ●Organ dysfunction (eg, liver, kidneys, heart, lungs)

- عوارض early,intermediate and late پیوند چی هستند؟

HEMATOLOGIC

- **Cytopenias**
- **Bleeding**
- **Thrombotic microangiopathy**

- ORAL MUCOSITIS
- DIARRHEA
- LIVER DISEASE
- RENAL COMPLICATIONS
- PULMONARY COMPLICATIONS
- INFECTION
- NEURO-PSYCHIATRIC MORBIDITY

ORAL MUCOSITIS

- **Clinical presentation**
- Oral mucositis (OM) is a major source of morbidity in patients undergoing HCT
- OM is typically painful, impairs nutritional intake, adversely affects the quality of life, and may prolong hospitalization and increase hospital costs
- Severe OM has been associated with a greater risk of 100-day post-HCT mortality

- Oral cryotherapy
- Photobiomodulation (laser therapy)
- Palifermin (KGF)
- Other agents
- ●Other cytokines (eg, GM-CSF, G-CSF, IL-11)
- ●Glutamine
- ●Pentoxifylline

- اسهال بعد پیوند به چه علت هایی ایجاد میشود؟

DIARRHEA

- There are numerous causes of diarrhea in the setting of HCT, including non-oral mucositis, infections associated with cytopenias, graft-versus-host disease (GVHD), and others. Non-oral gastrointestinal (GI) mucositis may cause pain, nausea/vomiting, and diarrhea
- There are numerous possible causes of diarrhea in the post-transplantation setting, and management is informed by the severity and underlying cause
- Approximately 80 percent of patients will have at least one episode of acute diarrhea within the first 100 days following allogeneic HCT

Causes of diarrhea

- **Acute GVHD**
- **Infections**
- **Non-oral mucositis**
- **Cord colitis syndrome**
- **Other causes**

- علت عوارض کبدی بعد از پیوند؟

LIVER DISEASE

- Liver dysfunction is common after HCT (especially after myeloablative conditioning) and can range from asymptomatic elevations of serum bilirubin and hepatic enzymes to hepatic graft-versus-host disease, hepatic sinusoidal obstruction syndrome (SOS), and death from fulminant liver failure
- acute graft-versus-host disease
- chronic graft-versus-host disease
- Hepatotoxicity of chemotherapy and other cytotoxic agents
- Hepatic SOS (also referred to as veno-occlusive disease)

- علت وتشخیص ودرمان SOS

RISK FACTORS of SOS

- **Patient characteristics**
- The risk for hepatic SOS is increased in patients with pre-existent liver
- **Lung disease** Reduced diffusion capacity (eg, <70 percent of predicted)
- Increased age
- Performance status
- Underlying disease – Leukemias, including chronic myeloid leukemia

Aspects of transplantation of SOS

- ●**Preparative regimen**
- ●**Graft source**
- ●**GVHD prophylaxis**
- **Other causes of SOS** — Treatment with monoclonal antibodies conjugated with calicheamicin (eg, gemtuzumab ozogamicin, inotuzumab ozogamicin) are associated with a substantially increased risk (up to 20-fold) in patients who subsequently undergo HCT

EBMT diagnostic criteria for adults

- Following are the revised EBMT diagnostic criteria for adults; note that these criteria accommodate both classical SOS (ie, <21 days from HCT) and late-onset SOS (ie, ≥21 days after transplantation)
- **Classical SOS** – Diagnosis requires :
- ●Bilirubin (≥2 mg/dL; ≥34 micromol/L)
- **plus** two of the following:
- ●Painful hepatomegaly
- ●Weight gain >5 percent
- ●Ascites

Late-onset SOS

- Diagnosis of late-onset SOS (ie, ≥21 days after transplantation) requires :
- ●Classical SOS beyond day 21
- **or**
- ●Histologically-proven SOS
- **or**
- ●Two or more of the following:
- •Bilirubin ≥2 mg/dL
- •Painful hepatomegaly
- •Weight gain >5 percent
- •Ascites
- **plus**
- •Hemodynamic or ultrasound evidence of SOS

Prophylaxis

- For adults undergoing HCT, we suggest prophylaxis with ursodeoxycholic acid (UDCA) rather than no prophylaxis or prophylaxis using defibrotide or other agents, based on a meta-analysis of four randomized controlled trials that reported reduced incidence of SOS, decreased mortality attributable to SOS, no impact on overall survival (OS), but no increase in adverse effects with UDCA

Severe SOS

- For patients with severe/very severe hepatic SOS,
- suggest prompt treatment with defibrotide, rather than supportive care alone or other treatments
- Defibrotide treatment for severe SOS was associated with improved survival, according to a multicenter study of defibrotide treatment versus matched historical control patients and a systematic review of 17 studies

Options for management of refractory disease include

- ●High-dose methylprednisolone may be considered for treatment of SOS, but it should be used with caution due to the high risk of infection
- ●Insertion of a transjugular intrahepatic portosystemic stent-shunt (TIPS) has been performed in small numbers of patients with SOS; some had regression of hepatic and renal symptoms
- ●Orthotopic liver transplantation

چگونه می توان عوارض بعد پیوند را کاهش داد؟

(aGVHD)

GVHD

- **Classic acute GVHD**
- **●Persistent, recurrent, late-onset acute GVHD**
- **●Classic chronic GVHD**
- **●Overlap syndrome**

RISK FACTORS

- ●**Major**
- •Degree of human leukocyte antigen (HLA) disparity (HLA mismatch or unrelated donor)
- •GVHD prophylaxis regimen, especially the use of post-transplant cyclophosphamide (PTCy)
- ●**Minor**
- •Donor and recipient sex disparity (female donor to male recipient)
- •Intensity of the transplant conditioning regimen

RISK FACTORS

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- •Intensity of the transplant conditioning regimen

RISK FACTORS

- Unlike chronic GVHD, the graft source (ie, peripheral blood versus bone marrow) does not affect the incidence or severity of acute GVHD
- Less well-established risk factors include the increasing :
- age of the host
- the cytomegalovirus (CMV) status of the donor and host, donor
- Epstein-Barr virus (EBV) seropositivity
- peripheral blood stem cell versus bone marrow transplantation
- the presence of a sterile environment (including gut decontamination)
- particular HLA haplotype

Guidelines for GVHD prophylaxis have been proposed by the European Group for Blood and Marrow Transplantation (EBMT) and European LeukemiaNet

Consensus recommendations for the prophylaxis and treatment of GVHD in allogeneic transplantation

Prevention of GVHD

GVHD prophylaxis: myeloablative conditioning

- The standard prophylaxis is cyclosporine plus a short course of methotrexate. Tacrolimus plus methotrexate is regarded as equivalent, but experience in Europe is too limited to support recommendations. Institutions using tacrolimus plus methotrexate should establish institutional guidelines* and follow them.
- Antithymocyte globulin has been shown to reduce chronic GVHD and improve the quality of life in transplantations from an unrelated donor. Therefore, antithymocyte globulin can be included in the prophylaxis regimen for unrelated donor transplantations. Institutions using antithymocyte globulin should follow the EBMT/ELN recommendations or establish institutional guidelines and follow them.

Cyclosporine

- The initial dose is 3 mg/kg/day.
- The administration is initiated on the day preceding the infusion of the graft (day −1). In case of two or more graft products given on more than one day, the day of the first product is counted as day 0.
- The drug is given as short intravenous (IV) bolus infusion in two daily doses.
- The administration is changed to oral route when oral intake is possible.
- The first oral dose is twice the IV dose, administered in two daily doses.
- The dose is adapted according to whole blood cyclosporine concentration or toxicity (renal insufficiency, microangiopathy, neurological problems) necessitating change of dosage.
- The cyclosporine target concentration is 200 to 300 micrograms/L during the first three to four weeks, then 100 to 200 micrograms/L until three months after transplantation if there is no GVHD or toxicity.
- Cyclosporine concentrations are measured from whole blood at 12 hours after a dose (trough level before the next infusion/dose).
- The duration of cyclosporine prophylaxis is six months in the absence of GVHD.

Methotrexate

- The initial dose is 15 mg/m^2 given on day +1.
- Three additional doses of 10 mg/m^2 are given, on days +3, +6 and +11. The day +11 dose is omitted in case of any toxicity of WHO grade II or higher.
- The drug is given as bolus IV injection.
- No dose adaptation is made except for possible omission of day +11 dose (refer above).
- Leucovorin rescue is given to all patients.
- Leucovorin administration is started 24 hours after each methotrexate dose. The dosage is 15 mg × 3 given every six hours after methotrexate administration on day +1, the same dose × 4 given every six hours after methotrexate doses on days +3, +6 and +11.
- Leucovorin is administered orally, in case of severe mucositis IV route is used.

Antithymocyte globulin (rabbit)

- The brand of antithymocyte globulin is ATG-Fresenius (ATG-F) or Thymoglobulin.
- The dose of ATG-F is 10 mg/kg on three days (total 30 mg/kg) and that of Thymoglobulin is 2.5 mg/kg on three days (total 7.5 mg/kg).
- Antithymocyte globulin is administered on days -3, -2 and -1.

GVHD prophylaxis: reduced intensity conditioning

- The standard prophylaxis is cyclosporine plus mycophenolate mofetil.
- Antithymocyte globulin has been shown to reduce chronic GVHD and improve the quality of life in transplantations from an unrelated donor. Therefore, antithymocyte globulin can be included in the regimen for unrelated donor transplantations. Institutions using antithymocyte globulin should follow the EBMT/ELN recommendations or establish institutional guidelines and follow them.

Cyclosporine

- Depending on the intensity of conditioning, the prophylaxis can be given either IV or PO. If the IV route is used, the recommendation for the initial dosing of cyclosporine is the same as for transplantations with myeloablative conditioning.
- If the oral route is used, the initial dose is 12 mg/kg/day.
- The administration is started on day −1.
- The daily dose is given in two doses with a 12-hour interval.
- The doses are adapted according to whole blood cyclosporine concentrations, toxicity (renal insufficiency, microangiopathy, neurological problems) necessitating change of dosage or decreasing chimerism.
- The target concentrations are 200 to 300 micrograms/L during the first three to four weeks, then 100 to 200 micrograms/L until three months (if no GVHD, toxicity or decrease in chimerism).
- The cyclosporine concentrations are measured from whole blood at 12 hours after a cyclosporine dose (trough levels before next infusion/dose).
- The duration of prevention is six months, if there are no signs of GVHD. In case of persistent disease or relapse (sub-population chimerism or other sensitive method) prevention should be reduced earlier.
- The dose is tapered from three months onwards if there are no signs of GVHD. The dose is not tapered as long as there are signs of acute GVHD or signs of chronic GVHD exceeding mild skin disease.

Mycophenolate mofetil

- The dose is 30 mg/kg/day[¶], given orally in two doses.
- The administration is started on day +1.
- The dose is adapted according to toxicity.
- The duration of mycophenolate mofetil prophylaxis is one month in sibling transplantations, three months in transplantations from unrelated or mismatched donor.
- In case of persistent disease or relapse (sub-population chimerism or other sensitive method) prevention should be reduced earlier.

Antithymocyte globulin (rabbit)

- The brand is ATG-F or Thymoglobulin.
- The dose of ATG-F is 10 mg/kg on three days (total 30 mg/kg) and that of Thymoglobulin is 2.5 mg/kg on three days (total 7.5 mg/kg).
- Antithymocyte globulin is administered on days -3, -2 and -1.

Prophylaxis in cord blood transplantation

- The recommended prophylaxis is cyclosporine plus mycophenolate mofetil, with dosing and duration of administration as described above for transplantations with reduced intensity conditioning.

Selection of a GVHD prophylaxis regimen

- **Matched sibling donor (MSD)**
- suggest MTX plus either Tac or CsA
- This suggestion is based on similar survival with MTX plus either CNI, but Tac is generally associated with a lower incidence of aGVHD, according to randomized trials and retrospective studies

- **Addition of ATG to standard prophylaxis for MUD grafts**
- Addition of ATG to standard prophylaxis (ie, CNI plus an antimetabolite) does not affect OS, but it reduces cGVHD and enables more patients to discontinue immunosuppressive drugs
- There was more reactivation of CMV and Epstein-Barr virus (EBV) with ATG, but no difference in bacterial infections, rate of engraftment, or post-transplant lymphoproliferative disorder (PTLD)
- ATG was associated with modest delays in neutrophil and platelet engraftment (median of 2.7 and 7.5 days, respectively)

Haploidentical donor

- For haploidentical (haplo) HCT, suggest adding post-transplant cyclophosphamide (PTCy) to a CNI plus MMF, rather than other immunosuppressive regimens
- This suggestion is based on less GVHD, fewer relapses, less NRM, and a trend toward improved survival with PTCy

T CELL DEPLETION (TCD)

- TCD can be via in vivo or ex vivo methods

In vivo TCD

- **Antithymocyte globulin (ATG)**
- **Post-transplant cyclophosphamide (PTCy)**

Ex vivo TCD

- Eliminating T lymphocytes ex vivo could reduce the incidence of GVHD. Most such methods have been associated with no improvement in OS, but they may increase graft failure and disease relapse and delay immune reconstitution. There is no standard approach, and use of ex vivo TCD varies among institutions.

- ●**Methods** – Methods to deplete T lymphocytes from donor bone marrow include:
- •Ex-vivo treatment of the donor bone marrow with monoclonal antibodies with broad reactivity (eg, anti-CD52, anti-CD2, anti-CD3, and anti-CD5 antibodies) or more restricted reactivity (eg, anti-CD8 and anti-CD25)
- •Physical separation techniques include density gradients, selective depletion with lectins, treatment with cytotoxic drugs, and the use of anti-T cell sera or monoclonal antibodies

Outcomes

- In studies comparing TCD with pharmacologic therapy for the prevention of GVHD, TCD was associated with lower rates of severe aGVHD but higher rates of graft failure, relapse, infections, and other complications

- شانس جه عفونت هایی بعد پیوند بیشتر هست؟

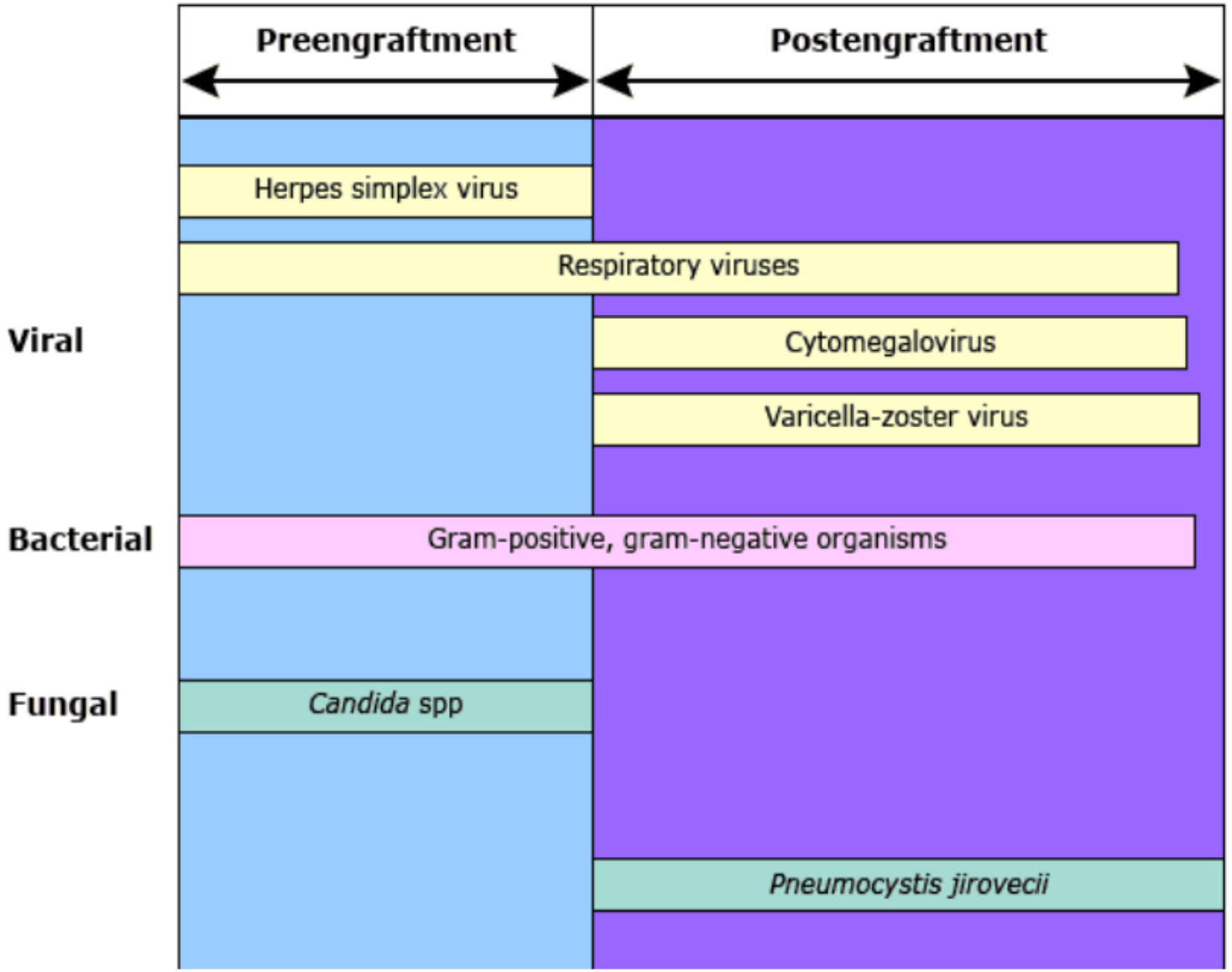
بازه زمانی هر نوع عفونت بعد از پیوند اتولوگ و الوژن چه زمانی هست؟

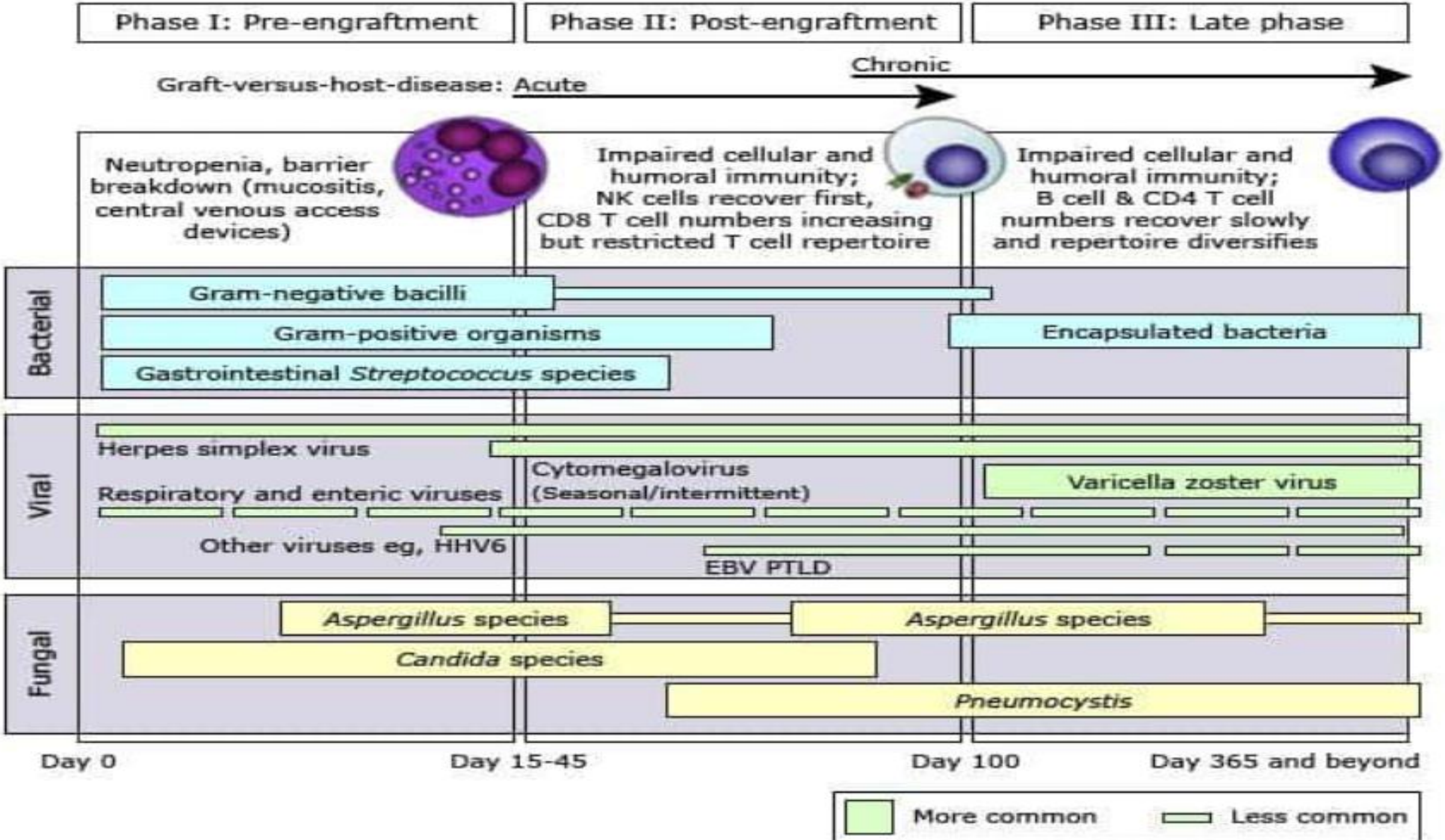
PREVENTION OF INFECTION

- Patients who undergo HCT are at risk for bacterial, viral, and fungal infections
- The types of infection vary with the time from transplantation, autologous HCT versus allogeneic HCT

  , and the degree of immune deficiency and cytopenias

Typical timing of infections among autologous hematopoietic cell recipients receiving antimicrobial prophylaxis




Phase I: Pre-engraftment
Phase II: Post-engraftment
Phase III: Late phase
Graft-versus-host-disease: Acute
Chronic
Neutropenia, barrier breakdown (mucositis, central venous access devices)
Impaired cellular and humoral immunity; NK cells recover first, CD8 T cell numbers increasing but restricted T cell repertoire
Impaired cellular and humoral immunity; B cell & CD4 T cell numbers recover slowly and repertoire diversifies
Bacterial
Gram-negative bacilli
Gram-positive organisms
Gastrointestinal Streptococcus species
Encapsulated bacteria
Viral
Herpes simplex virus
Respiratory and enteric viruses
Cytomegalovirus (Seasonal/intermittent)
Varicella zoster virus
Other viruses eg, HHV6
EBV PTLD
Fungal
Aspergillus species
Aspergillus species
Candida species
Pneumocystis
Day 0
Day 15-45
Day 100
Day 365 and beyond
More common
Less common

ANTIMICROBIAL PROPHYLAXIS OR PRE-EMPTIVE THERAPY

- **●Primary prophylaxis**
- **●Secondary prophylaxis**
- **●Pre-emptive therapy**

Antibacterial prophylaxis

- **Before engraftment**
- **●Myeloablative allogeneic HCT**
- **●Reduced-intensity and nonmyeloablative conditioning allogeneic HCT**
- **●Autologous HCT**
- **After engraftment**
- **Antifungal prophylaxis**
- **Pneumocystis prophylaxis**
- **Toxoplasma gondii prophylaxis**
- **Tuberculosis prophylaxis**
- **Antiviral prophylaxis or pre-emptive therapy**

- aGVHD درمان
- چگونه شروع می شود ؟
- ایا وابسته به ارگان درگیر هست؟
- خط دوم درمان کی شروع می شود؟

Treatment of GVHD

Treatment of acute GVHD

First-line treatment

- The first-line treatment of acute GVHD is methylprednisolone.
- Treatment is initiated for acute GVHD of grade II or higher.
- The initial methylprednisolone dose is 2 mg/kg/day.
- Methylprednisolone is given in two divided doses per day.
- The initial dose is continued for seven days. Treatment can be changed in case of clear progression after five days, but there is no evidence that change in treatment will affect the outcome.
- No reduction of the dose is done during the first seven days.
- Tapering of the dose is done slowly and depending on the response. No marked dose reductions are done in the early phase. Methylprednisolone is not discontinued before all signs of GVHD have disappeared.
- Failure of treatment (corticosteroid resistance) is defined as no response after seven days of treatment or clear progression after five days.
- Non-absorbable oral steroid (budesonide) is given, along with systemic corticosteroid, for GI GVHD in the dose of 9 mg/day in one daily dose orally.
- Topical steroids are used for skin GVHD according to center policy.
- The decision to initiate treatment is based on clinical signs. Skin biopsy before initiation of treatment is recommended, but the decision to treat should not depend on the biopsy result. The same recommendation applies to upper GI or sigmoid biopsy if GI manifestation is suspected.

Second-line treatment

- The indication for second-line treatment is failure of methylprednisolone treatment as defined above.

- There is no standard second-line treatment for acute GVHD. Widely used components are mycophenolate mofetil, anti-TNF-antibodies, other monoclonal antibodies, antithymocyte globulin, extracorporeal photopheresis, methotrexate and mesenchymal stem cells. Continuation of calcineurin inhibitors and corticosteroids with optimal supportive care is considered a valid option. Centers should have and follow their institutional guidelines, and the patients should be treated in trials as far as possible.

- Most treatments for aGVHD are based on suppression of donor T cells, which are primarily responsible for the syndrome
- the same cells also mediate the immunologic reaction against the tumor (graft-versus-tumor [GVT] effect)
- As such, treatment should aim to balance the benefit of reducing GVHD with the potential harm of decreasing the GVT effect

Grade ≥2 aGVHD

- For grade ≥2 aGVHD, we suggest treatment with a systemic glucocorticoid (GC; eg, methylprednisolone), rather than an alternative approach
- Systemic GCs have been widely adopted for treatment of grade ≥2 aGVHD and no other regimen has been proven superior for treatment of grade 2 to 4 aGVHD

STEROID-RESISTANT AGVHD

- **Ruxolitinib**
- **Mycophenolate mofetil (MMF)**
- **Etanercept**
- **Alpha-1 antitrypsin**
- **Sirolimus**
- **Extracorporeal photopheresis**
- **Anti-thymocyte globulin (ATG)**
- **Brentuximab vedotin**

- علایم Diagnostic and distinctive Cgvhd چه هستند؟
- تشخیص ودرمان Cgvhd

TREATMENT FOR CGVHD

- First-line therapy: corticosteroids The primary goals of treatment for cGVHD are to decrease activation of B- and T-cells, decrease inflammation, slow the development of fibrosis, and improve quality of life
- Corticosteroids have been used as front-line treatment for decades and possess potent anti-inflammatory and immunosuppressive properties
- The recommended starting dose for corticosteroids is 0.5–1 mg/kg/day of prednisone (or methylprednisone dose equivalent)
- Topical steroids can be used to enhance local treatment response for mild Cgvhd
- Consistent tapering protocols have yet to be established and are guided by the severity of GVHD and the response to treatment

Steroid refractory

- Steroid-refractory cGVHD is defined as having progression on prednisone 1 mg/kg/day for ≥7 days or having stable disease despite therapy with prednisone 0.5 mg/kg/day for ≥4 weeks
- Steroid-dependent disease is defined as the inability to taper prednisone below 0.25 mg/kg/day after ≥2 unsuccessful attempts separated by ≥8 weeks

Treatment of steroid-refractory cGVHD

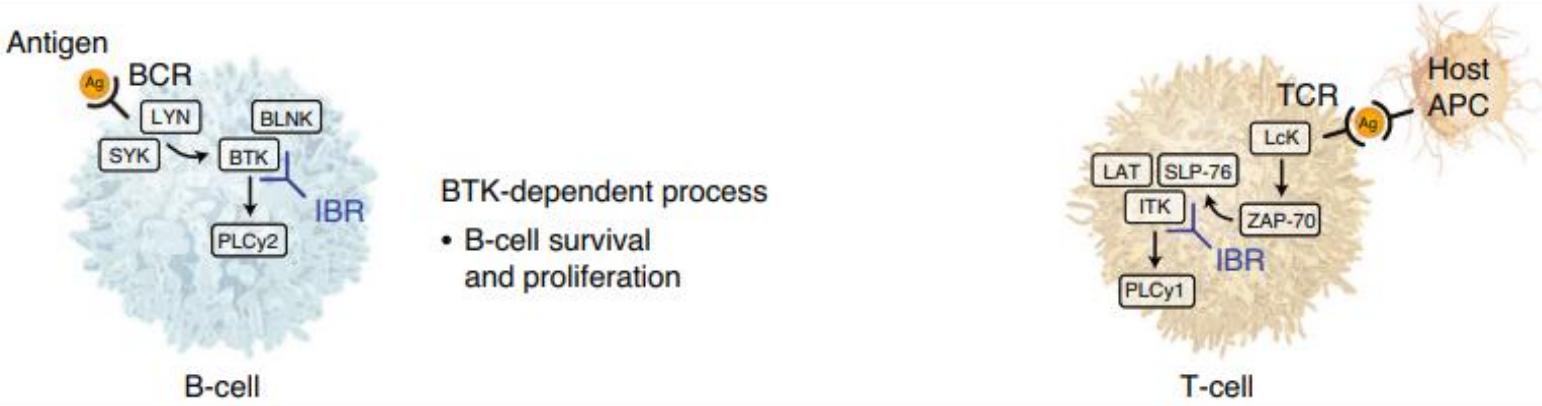
- (Federal Drug Administration [FDA] approved) Ibrutinib
- Ibrutinib is the first FDA-approved agent for steroid refractory cGVHD It is an irreversible dual inhibitor of both Tec family kinases, Bruton tyrosine kinase and IL-2–inducible T-cell kinase
- Antigen recognition by B-cell receptors results in activation of the Bruton tyrosine kinase signaling pathway, which leads to survival, proliferation, and migration of B-cells

Ruxolitinib

- Ruxolitinib is a potent and selective inhibitor of JAK 1 and 2
- In the early development of GVHD, activation of the intracellular JAK 1/2 pathway leads to transcription of proinflammatory cytokines, mediation of inflammatory neutrophil migration, and upregulation of MHC class II expression
- Alloreactive T-cell infiltration into target organs is mediated by IFN-γ and the chemokine receptor CXCR3
- By inhibition of the JAK/ STAT pathway, IFN-γ signaling is prevented
- Ruxolitinib is approved by the FDA for steroid-refractory cGVHD based on the results of REACH3, a phase III randomized controlled trial

Mechanism of action of FDA-approved cGVHD therapies

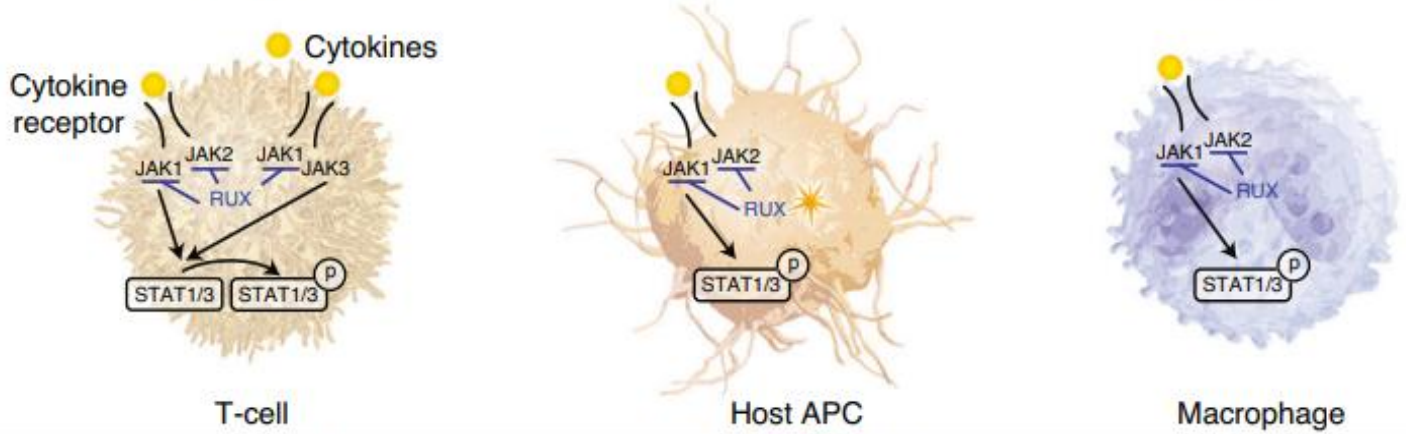
Ibrutinib



BTK-dependent process
- B-cell survival and proliferation

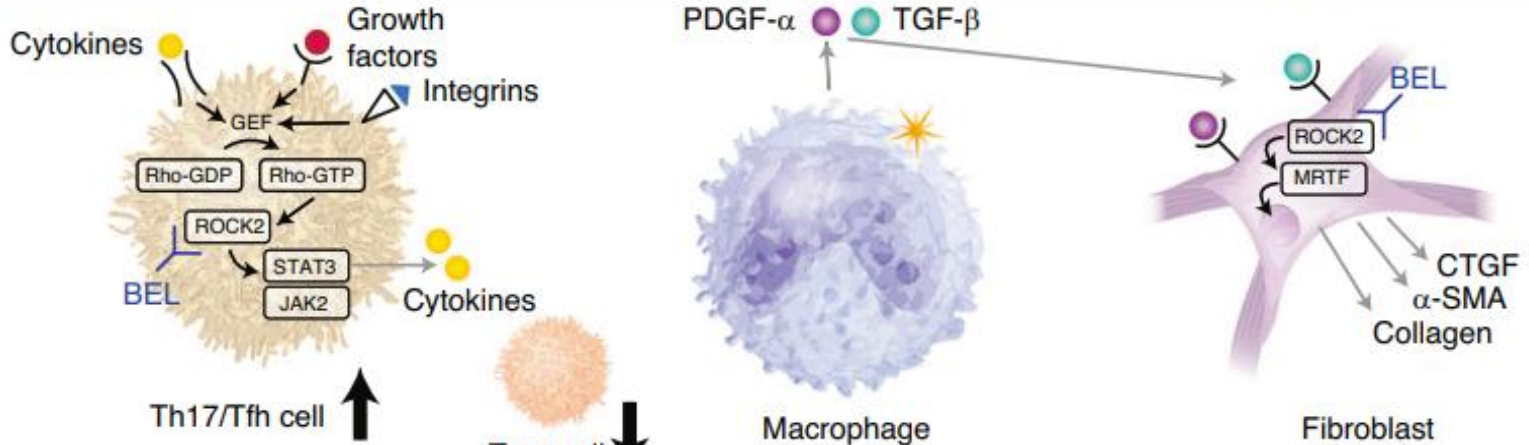
ITP-dependent process
- T-cell activation and proliferation
- Cytokine signaling

Ruxolitinib



JAK1/JAK2-dependent process
- Cytokine signaling
- T-cell activation
- Inflammation
- Target organ damage

Belumosudil



ⓟ =Phosphorylated
=Activated

ROCK2-dependent process
- Cytokine signaling
- Th17/Tfh cell upregulation
- Treg cell downregulation
- Fibrosis

Table 1. FDA-approved agents for steroid-refractory chronic graft-versus-host disease.

Drug	Mechanism of action	Study	Enrollment	Median time to response	Treatment response	Other outcomes	FDA indication	Dose	Drug/Drug Interactions	Toxicity
Ibrutinib (IMBRUVICA) [37, 39]	Bind to BTK active site, leading to inhibition of BTK enzymatic activity; results in downstream inhibition of B-cell antigen receptor and cytokine receptor pathways	Phase 1b/2	$N = 42$ After ≥1 line of therapy	12 weeks	ORR: 67% CR: 9% PR: 19%	FFS: 51% (18 months) Median duration of treatment: 1.8 months	After failure of ≥1 lines of therapy	420 mg daily Available in 140-mg, 280-mg, and 420-mg tablets Take with or without food	CYP3A4 inhibitors (fluconazole, posaconazole, voriconazole, isavuconazole) Anticoagulants	• Fatigue (57%) • Bruising (40%) • Diarrhea (36%) • Thrombocytopenia (33%) • Muscle spasms (29%) • Stomatitis (29%) • Nausea (26%) • Hemorrhage (26%) • Anemia (24%) • Pneumonia (21%)
		Retrospective single center	$N = 53$	NR	ORR: 12% CR: 4% PR: 8% SD: 64%	Median FFS: 4.5 months 2-year FFS: 9%				
Ruxolitinib (JAKAFI) [42, 44, 45]	Inhibit JAK1 and JAK2, inhibiting recruitment of STATs to cytokine receptors	REACH3 Phase III	$N = 329$ After ≥1 line of therapy	3 weeks	ORR: 49.7% CR: 6.7% PR: 43%	Median FFS: >18.6 months Median duration of treatment: 25.6 weeks	After failure of 1 or 2 lines of systemic therapy	10 mg twice daily Available in 5-mg and 10-mg tablets Take with or without food	CYP3A4 inhibitors (fluconazole, posaconazole, voriconazole, isavuconazole)	• Hypercholesterolemia (88%) • Anemia (82%) • Thrombocytopenia (58%) • Infection (45%) • Viral infection (28%) • Neutropenia (27%) • CMV (5%-8%)
		Retrospective single center	$N = 48$ After ≥1 line of therapy	2 months	ORR: 77% CR: 15%	Median duration of response: 11 months Median duration of treatment: 12 months				
Belumosudil (REZUROCK) [48, 51]	Inhibits ROCK2 and ROCK1, regulates STAT3/STAT5 pathways and shifting Th17/ Treg balance, inhibits aberrant profibrotic	ROCKstar Phase II	$N = 132$ After 2 to 5 lines of therapy	5 weeks	ORR: 74% (for belumosudil once daily) CR: 6% PR: 68%	FFS: 56% (12 months) Median duration of treatment: 10 months	After failure of ≥2 lines of systemic therapy	200 mg once daily Available in 200-mg tablets Take with food	CYP3A4 inducers Proton pump inhibitors Certain P-gp, OATP1B1, BCRP, and UGT1A1 substrates	• Fatigue (38%) • Diarrhea (33%) • Nausea (31%) • Cough (28%) • Upper respiratory tract infection (27%) • Dyspnea (25%) • Headache (24%) • Peripheral edema (23%) • Vomiting (21%)

Belumosudil

- Belumosudil is a selective ROCK2 inhibitor
- Inhibition of ROCK2 allows for the downregulation of proinflammatory cytokines including IL-17 and IL-21 in T-cells
- In pre-clinical models, the inhibition of ROCK2 by belumosudil interferes with this profibrotic process in cGVHD

Table 2. Future therapies for chronic graft-versus-host disease.

Agent	Mechanism/Target	Clinical trial identifier	Study phase	No. of patients	Line of therapy	Dosing schedule	Treatment response	Toxicity
Baricitinib [52, 55]	JAK 1/2 Inhibitor	NCT02759731	I/II	24	Refractory after ≥1 line of therapy	Initial: 2 mg once daily[a]	6-month ORR: 79.2% (PR: 66.7%; MR: 12.5%)	• Upper respiratory tract infection (33%) • Hypophosphatemia (21%) • Hypokalemia (17%) • Hypertriglyceridemia (13%) • Nausea (13%)
Abatacept [53]	Selective costimulation modulator inhibiting CD28	NCT01954979	II	36	Refractory after ≥1 line of therapy	10 mg/kg IV × 6 doses Doses 1–3: every 2 weeks Doses 4–6: every 4 weeks	5-month ORR: 58% (All PR)	• Fatigue (9%) • Neutropenia (6%) • Headache (4%) • Upper respiratory tract infection (3%)
Ixazomib [54]	20S proteasome inhibitor	NCT02513498	II	50	Refractory after ≥1 line of therapy	4 mg once weekly on days 1, 8, 15 of a 28-day cycle × 6 cycles	6-month ORR: 40% (All PR)	• Nausea • Fatigue • Thrombocytopenia
Axatilimab [56, 68]	CSF-1R inhibitor	NCT04710576	II	241	Refractory after ≥2 lines of therapy	Cohort 1: 0.3 mg/kg IV every 2 weeks (maximum 2 years)	6-month ORR: 74%	**Cohort 1** • Fatigue (23%) • Increased aspartate aminotransferase (14%) • Increased lactate dehydrogenase (14%) • Increased alanine aminotransferase (13%) • Increased creatine phosphokinase (11%) • Increased lipase (11%)
						Cohort 2: 1 mg/kg IV every 2 weeks (maximum 2 years)	6-month ORR: 67%	
						Cohort 3: 3 mg/kg IV every 2 weeks (maximum 2 years)	6-month ORR: 50%	

CSF-1R colony-stimulating factor–1 receptor, *IV* intravenous, *JAK* Janus-associated kinase, *MR* mixed response, *ORR* overall response rate, *PR* partial response, *1L* first line, *2L* second line.

[a]After 12 weeks, maintain at 2 mg once daily if the patient has a complete response or increase to 4 mg once daily if the patient has a partial response. If progression of disease occurs within 12 weeks, increase

- واکسیناسیون بعد از پیوند الوژن و اتولوگ کی وبرای چه بیماریهایی انجام می شود؟

Immunization

- **Active immunization**
- **Passive immunization**

Timing of vaccines for autologous hematopoietic cell transplant recipients

Vaccine	Recommendation	Number of doses	Comments
3 to 6 months post-transplant			
RZV[1]	Age 18 years or older	2 (2 to 6 months apart)	Antiviral prophylaxis (eg, acyclovir) is also used to prevent herpes zoster early after transplant.
COVID-19 (SARS-CoV-2) vaccine	All HCT recipients ≥6 months of age[2]	2 or 3 (depending on vaccine formulation)	We prefer the mRNA vaccine because there is more evidence on efficacy and safety.
Pneumococcal conjugate vaccine-21 (PCV-21)*	All HCT recipients	3 doses (1 month apart) 4th dose at 12 months	If PCV21 is not available, administer PCV20. If patients received PCV15 or lower valency conjugate vaccine for the first 3 doses: ▪ No GVHD: administer PPSV23 for the 4th dose. ▪ GVHD: administer PCV10, 13, or 15 for the 4th dose (the highest valency available).
6 to 12 months post-transplant			
Influenza vaccine (inactivated)	All HCT recipients ≥6 months of age	1 dose (annually)	Can be given as early as 4 months if community outbreak. If given early, a 2nd dose should be administered at least 4 weeks after initial dose to provide additional protection against influenza.
Tetanus, diphtheria, and pertussis vaccine	All HCT recipients	3 doses DTaP (1 to 3 months apart)	For patients ≥7 years of age, an alternative schedule includes 1 dose of Tdap followed by either 2 doses of DT or Td, with all doses spaced 1 to 3 months apart.
Haemophilus influenzae b conjugate vaccine	All HCT recipients	3 doses (1 month apart)	
Polio-inactivated (inactivated poliovirus vaccine)	All HCT recipients	3 doses (1 to 3 months apart)	

Haemophilus influenzae b conjugate vaccine	All HCT recipients	3 doses (1 month apart)	
Polio-inactivated (inactivated poliovirus vaccine)	All HCT recipients	3 doses (1 to 3 months apart)	
Meningococcal conjugate vaccine[¶]	Age 11 to 18 years or other risk factors present (eg, asplenia, residing or traveling to areas of hyperendemicity or epidemicity)	2 doses (4 to 5 years apart)	
MenB vaccine[¶]	Age 16 to 23 or other risk factors (eg, asplenia, residing or traveling to areas of hyperendemicity or epidemicity)	1 dose	
Human papillomavirus vaccine	Age 9 to 26 years	2 to 3 doses[Δ]	
Respiratory syncytial virus	Age 60 years or older	1 dose	In the absence of efficacy and safety data with this vaccine in HCT recipients, balancing risk of significant disease in this population, we engage in shared decision making with our patients when deciding whether to administer this vaccine.
Hepatitis A vaccine	If risk factors present (eg, chronic liver disease, travel to endemic areas)	2 doses (6 months apart)	
Mpox virus vaccine (non-replicating, modified vaccinia Ankara vaccine)	If risk factors present (eg, males who have sex with males and have multiple sex partners or a diagnosis of an STI in the past 6 months)	2 doses (1 month apart)	
1 year post-transplant			
Hepatitis B vaccine	All HCT recipients	3 doses (dosing intervals depend on the specific vaccine formulation used)	Can be administered as early as 6 months if necessary. We prefer to wait until 12 months when possible to optimize immunity from vaccine. Test serology ≥1 month following the 3rd dose to assess the response to vaccine.

1 year post-transplant			
Hepatitis B vaccine	All HCT recipients	3 doses (dosing intervals depend on the specific vaccine formulation used)	Can be administered as early as 6 months if necessary. We prefer to wait until 12 months when possible to optimize immunity from vaccine. Test serology ≥1 month following the 3rd dose to assess the response to vaccine.
≥2 years post-transplant			
Measles, mumps, and rubella vaccine	HCT recipients who meet **all** of the following criteria: ▪ Measles and/or rubella seronegative ▪ No active GVHD ▪ Not receiving any immunosuppression ▪ Last dose of IVIG and other blood products[3] was administered more than 8 to 11 months ago	2 doses (at least 4 weeks apart)	
Varicella	HCT recipients who meet **all** of the following criteria: ▪ Varicella seronegative ▪ No active GVHD ▪ Not receiving any immunosuppression ▪ Last dose of IVIG and other blood products[3] was administered more than 8 to 11 months ago	2 doses (4 to 8 weeks apart)	

Timing of vaccines for allogeneic hematopoietic cell transplant recipients

Vaccine	Recommendation	Number of doses	Comments
3 to 6 months post-transplant			
COVID-19 (SARS-CoV-2) vaccine	All HCT recipients ≥6 months of age[1]	2 or 3 (depending on vaccine formulation)	
Pneumococcal conjugate vaccine-21 (PCV21)*	All HCT recipients	3 doses (1 month apart) 4th dose at 12 months	If PCV21 is not available, administer PCV20. If patients received PCV15 or lower valency conjugate vaccine for the first 3 doses: ▪ No GVHD: administer PPSV23 for the 4th dose. ▪ GVHD: administer PCV10, 13, or 15 for the dose (the highest valency available).
6 to 12 months post-transplant			
Influenza vaccine (inactivated)	All HCT recipients ≥6 months of age	1 dose (annually)	Can be given as early as 4 months if community outbreak. If given early, a second dose should be administered at least 4 weeks after initial dose to provide additional protection against influenza.
Tetanus, diphtheria, and pertussis vaccine	All HCT recipients	3 doses DTaP (1 to 3 months apart)	For patients ≥7 years of age, an alternative schedule includes 1 dose of Tdap followed by either 2 doses of DT or Td, with all doses spaced 1 to 3 months apart.
Haemophilus influenzae b conjugate vaccine	All HCT recipients	3 doses (1 month apart)	
Polio-inactivated (inactivated poliovirus vaccine)	All HCT recipients	3 doses (1 to 3 months apart)	
Meningococcal conjugate vaccine¶	Age 11 to 18 years or other risk factors present (eg, asplenia, residing in or traveling to areas of hyperendemicity or epidemicity)	2 doses (4 to 5 years apart)	

	hyperendemicity or epidemicity)		
MenB vaccine[¶]	Age 16 to 23 or other risk factors (eg, asplenia, residing or traveling to areas of hyperendemicity or epidemicity)	1 dose	
Human papillomavirus vaccine	Age 9 to 26 years	2 to 3 doses[Δ]	
Respiratory syncytial virus	Age 60 years or older	1 dose	In the absence of efficacy and safety data with this vaccine in HCT recipients, balancing risk of significant disease in this population, we engage in shared decision making with our patients when deciding whether to administer this vaccine.
Hepatitis A vaccine	If risk factors present (eg, chronic liver disease, travel to endemic areas)	2 doses (6 months apart)	
Mpox virus vaccine (non-replicating, modified vaccinia Ankara vaccine)	If risk factors present (eg, males who have sex with males and have multiple sex partners or a diagnosis of an STI in the past 6 months)	2 doses (1 month apart)	
1 year post-transplant			
Hepatitis B vaccine	All HCT recipients	3 doses (dosing intervals depend on the specific vaccine formulation used)	Can be administered as early as 6 months if necessary. We prefer to wait until 12 months when possible to optimize immunity from vaccine. Test serology ≥1 month following the 3rd dose to assess the response to vaccine.
RZV	HCT recipients who meet the following criteria: ▪ At least 12 months has passed since HCT ▪ Off immunosuppressive therapy ▪ No GVHD flares	2 doses (2 to 6 months apart)	Antiviral prophylaxis (eg, acyclovir) is also used to prevent herpes zoster early after transplant

RSV	HCT recipients who meet the following criteria: ▪ At least 12 months has passed since HCT ▪ Off immunosuppressive therapy ▪ No GVHD flares	2 doses (2 to 6 months apart)	Antiviral prophylaxis (eg, acyclovir) is also used to prevent herpes zoster early after transplant
≥2 years post-transplant			
Measles, mumps, and rubella vaccine	HCT recipients who meet **all** of the following criteria: ▪ Measles and/or rubella seronegative ▪ No active GVHD ▪ Not receiving any immunosuppression ▪ Last dose of IVIG and other blood products[2] was administered more than 8 to 11 months ago	2 doses (at least 4 weeks apart)	
Varicella	HCT recipients who meet **all** of the following criteria: ▪ Varicella seronegative ▪ No active GVHD ▪ Not receiving any immunosuppression ▪ Last dose of IVIG and other blood products[2] was administered more than 8 to 11 months ago	2 doses (4 to 8 weeks apart)	

he table outlines the general timing of when to administer vaccines to allogeneic HCT recipients. Patients with GVHD or other complications may warrant a different timeline of vaccine administration.

THANK YOU FOR ATTENTION