UW Medicine

免疫系统

接受肺移植后的感染及排斥

本讲义为您解释了免疫系统的工作原理，以及为什么肺移植手术后必须抑制免疫系统。

什么是免疫系统？

免疫系统是一个由特殊细胞及器官组成的复杂网络。当它工作良好时，系统会保护身体免受病毒、细菌、真菌及其他"入侵者 "的侵害或感染。

要做到这一点，免疫系统必须区分人的自身细胞及任何入侵的 "非自身 "细胞。如免疫系统发现 ″非自身 ″细胞，就会攻击它们。这就是一种*免疫反应*。
当免疫系统在体内发现*抗原*时，就会引发免疫反应。抗原通常是 "非自身 " 细胞。它们可能是来自细菌、病毒或其他感染类型的细胞。

抗原也可能是来自他人的细胞，如输血时使用的血液或移植时使用的器官。免疫系统将所有这些物质视为 ″异物″，并试图将其从体内清除。当器官移植后发生这种情况时，即称为*排斥*。

免疫系统是如何工作的？

当免疫系统感觉到抗原时，它会激活白血球来对抗入侵者。白血球的 2 种主要类型是淋巴细胞；称为 *T 细胞*和 *B 细胞*。

- **T 细胞**直接攻击外来细胞。
- B **细胞**产生*抗体*，附着在外来细胞上。这些抗体是给其他免疫细胞攻击外来细胞的信号。

作为移植受赠者，您需服用抑制免疫系统的药物，以防止其排斥新肺。

什么能阻止免疫系统对移植器官的排斥？

移植接受者将以药物来抑制他们的免疫系统，以防止它排斥移植器官。这些药物被称为*免疫抑制剂*或*免疫抑制药物*。

接受肺移植者在进入手术室做移植手术时，甚至在将捐赠的肺放入体内之前、就开始接受这些药物。受移植者在手术后必须终生服用免疫抑制剂。

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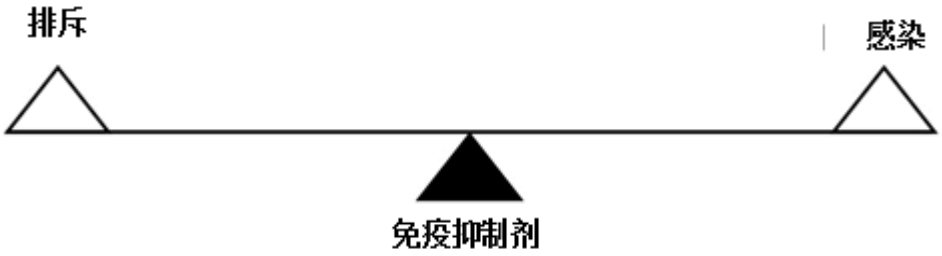
抑制免疫系统的挑战

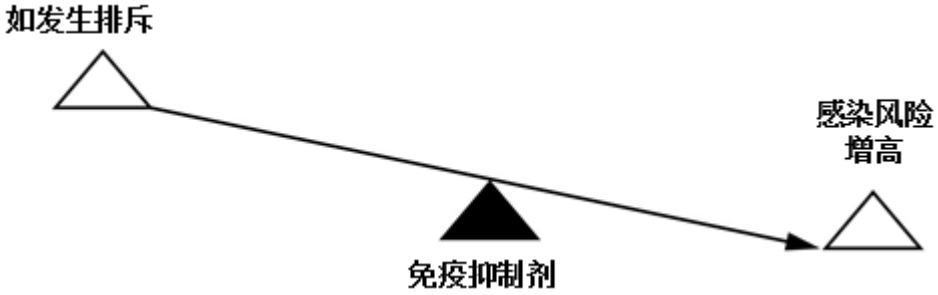
患者的免疫系统必须受到抑制以防止移植的肺被排斥。但是如免疫系统抑制过度，它将无法对抗感染。排斥和感染都会威胁到整体健康及移植器官的健康。

一旦移植了新的肺脏，我们既要防止患者自身体排斥新的肺脏，又要限制感染的风险。我们将尽最大努力调整免疫抑制剂的剂量，以找到合适的平衡点。这个过程需要时间。

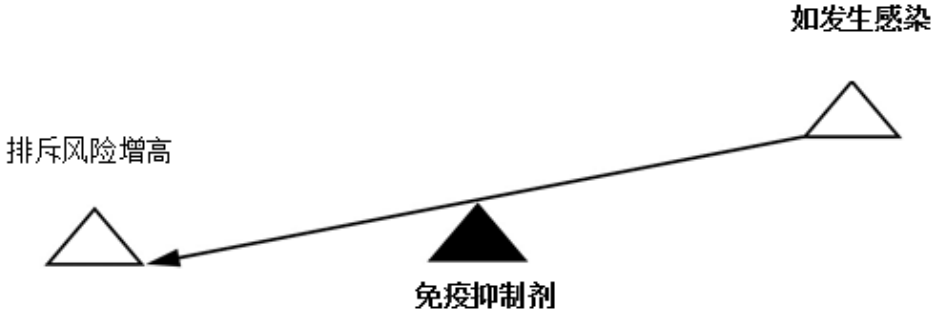
这些图片显示了免疫抑制剂、排斥和感染之间的关系。



该图显示了一种良好地平衡状态，其中免疫抑制剂药物可防止排斥、并最大程度地减少感染。



如发生排斥，我们将提高免疫抑制水平。 这增加了感染的风险。



如发生感染，我们可能会降低免疫抑制水平。 这增加了排斥的风险。

我们将密切监测患者的肺部及手术后的整体健康状况。如有需要，我们可能会在复诊时调整免疫抑制剂的剂量。这也是患者在移植手术后头几个月必须经常复诊的原因之一。

我需要服用多长时间的免疫抑制剂？

每位接受肺移植的患者都必须终生每天服用免疫抑制剂。这是因为患者的身体永远不会把移植的器官当作自己的器官。只要接受肺移植者活着，就永远存在排斥的风险。肺移植手术后，免疫抑制药物的用量根据每个肺移植受者的特殊情况而异。

排斥的风险会随着时间而改变吗？

大多数情况下排斥反应发生在肺移植手术后的前 12 个月。但它也可能发生在任何时候，甚至在移植手术后的许多年以后。

肺移植手术后，接受肺移植的患者会立即接受高剂量的免疫抑制剂。以防止免疫系统对新肺的排斥或破坏。随着时间，免疫系统可能会减少对新肺的排斥。如出现这种情况，我们可能会逐渐减少免疫抑制药物的剂量。

如在肺移植后的任何时候发生排斥反应，免疫抑制剂水平即需要增加。在治疗患者的排斥后，可能需要找到一种免疫抑制药物的新平衡量，以防止再次发生排斥反应。

有那些排斥反应的症状？

肺移植手术后不一定容易诊断出排斥反应。 排斥性的症状可能包括:

- *肺活量*（呼吸测试）下降，尤其在一秒钟内能从肺部排出的最大空气量（FEV1）下降
- 呼吸急促
- 发烧
- 胸部 X 光或计算机断层扫描（CT）图像起变化。
- *氧饱和度*的变化
- 发生新的疲乏

如在肺移植后有感染或其他问题，也会出现这些症状。如有这些*症状*我们可能会要求患者做*支气管镜*的检查，以帮助我们找到原因。

支气管镜检查是以一个前端有相机的软管从鼻子或口腔插入患者的肺部。如此即可以看到新的肺脏，并做活检以测试是否发生排斥、感染或其他问题。

如发生排斥反应如何处理？

排斥反应的治疗是基于急性排斥反应或是慢性排斥反应，慢性排斥也称为*慢性肺同种异体移植功能障碍*（CLAD）。

急性排斥

急性排斥主要有 2 种类型:

- *急性细胞排斥*，通常是由 T 细胞引发的。
- *抗体介导的排斥反应*，通常由 B 细胞引发。

如发现了排斥反应，或者我们强烈地认为症状是由排斥反应引起的，即会提高免疫抑制水平，直到排斥反应消退。治疗方法是根据最有可能引起排斥反应的免疫细胞类型而定。

急性排斥治疗后，患者的肺功能通常会恢复到以前的基线。但有时移植的肺部会因排斥反应而受损。这可能意着肺功能将永远无法像排斥前那样好。患者在排斥治疗后的情况将因肺部损伤的严重程度而异。

急性细胞排斥 是因为 T 细胞直接攻击新肺而发生。大多数情况下，对急性细胞排斥的第一种治疗是以大剂量类固醇药物（甲基强的松龙然后是强的松作"脉冲式"治疗（短期治疗）。

如这第一种治疗对排斥没有改进，我们将试用其他方法来消除引起排斥的 T 细胞。这些其他的治疗方法可以包括抗胸腺细胞球蛋白（ATG）及阿仑单抗（*alemtuzumab*）等药物，这两种药物都可以杀死 T 细胞。这些药物会在一段时间内强烈抑制免疫系统。有时，它们会造成免疫系统严重的、永久性的抑制。

抗体介导的排斥需要针对 B 细胞及引发攻击新肺的抗体来治疗。这些可能是组合治疗：

- *血浆置换术*（*Plasmapheresis*），从血液中去除抗体的过程， 就像肾衰竭患者通过透析去除毒素一样
- *利妥昔单抗*（*rituximab*），一种杀死未成熟 B 细胞的药物
- *硼替佐米（Bortezomib），*一种杀死可以产生抗体的成熟 B 细胞的药物
- *静脉免疫球蛋白*（IVIG），使循环抗体失活并减少产生新抗体的药物。

慢性肺同种异体移植功能障碍

慢性肺同种异体移植功能障碍（CLAD）*也称为闭塞性细支气管炎综合征*（BOS）或*慢性排斥反应*。慢性肺同种异体移植功能障碍（CLAD）的定义是：在没有其他导致原因的情况下，*肺活量持续下降*（一秒钟内能从肺部排出的最大空气量（FEV1）及/或强制呼吸流速（FEF）下降到 25％至 75%。

肺脏移植后大多数移植患者都会随着时间渐渐地发生慢性排斥（CLAD）。我们不知道它发生的原因。可能有许多因素起着作用，包括：

- 发生了急性排斥反应
- 感染，包括呼吸道病毒(感冒和流感)
- *胃食管胃酸反流* (GERD)

有时，似乎没能找到一个会导致肺移植患者发生慢性肺移植功能障碍的具体原因。即使我们控制并治疗了植患者发生慢性肺同种异体移植功能障碍（CLAD）的问题，我们也可能无法阻止患者发生慢性肺移植功能障碍。

诊断慢性肺移植功能障碍是非常困难的。我们没有一种测试可以明确指出慢性肺移植功能障碍是导致患者症状或肺活量永久性下降的原因。

研究表明，慢性肺移植功能障碍最后可能导致的结果是：支气管（肺部非常细小的呼吸道）的损伤和肺组织的疤痕。支气管发炎，导致支气管变形、变窄，并被疤痕组织堵塞。支气管被破坏后，患者会出现严重的*阻塞性气管疾病*（无法排出空气）。当大量的疤痕组织形成后，患者就会出现严重的*限制性肺病*（不能进气）。

支气管被破坏后，我们没有药物可以恢复肺功能。我们能做的最好的方法是通过治疗任何已知的潜在问题，如急性排斥、感染或胃食管反流来防止发生更多的损害。

对肺移植患者来说，预防慢性肺移植功能障碍的最佳方法是：

- **严格**遵照医嘱服药。
- 用家用肺活量仪密切监测呼吸。如一秒钟内能从肺部排出的最大空气量（FEV1）下降超过基线的 10%，请**立即**致电肺移植办公室。
- 与华大肺移植团队保持密切联系。如有任何新的症状，请立即致电肺移植办公室。

感染

移植后，患者会服用免疫抑制剂来防止排斥反应。但抑制免疫系统会降低身体对抗感染的能力。因而容易被细菌、病毒或真菌引起感染，而这些感染通常不会影响免疫系统正常的人。

我们吸入肺部的空气可能含有*传染性病原体*(导致感染的微生物) 。这对于免疫系统受到抑制的人来说是很危险的。

病毒

在接受移植者发生的感染中，约有 40%的感染是由病毒引起的（100 个感染中就有 40 个）。有些感染在移植手术后的早期比较常见，但也有一些在移植后的任何时候都可能发生。

疱疹病毒

疱疹病毒族群是移植患者最常见的病毒感染原因之一。在 25 岁之前，80% 以上的人（100 人中有 80 人）都被疱疹病毒（感冒疮、水痘等）感染过。

当一个人感染了疱疹病毒，病毒会在他们的身体里生活一辈子。这些 "潜伏 "的感染通常不会引起问题。但是，當免疫系統受到抑制時，疱疹病毒會重新活躍或 "苏醒"，而引起問題。

疱疹病毒有 4 种类型。：

单纯疱疹病毒(HSV)

单纯疱疹病毒 HSV I 型(HSV-1)发作时常引起唇疱疹。II 型(HSV-2)的发作通常会引起生殖器疱疹。

单纯疱疹病毒(HSV)在移植后的前 6 个月或排斥治疗后的 3 周内最常发作。在这些时期，患者要使用较高剂量的免疫抑制剂。渐渐地，随着免疫抑制剂的剂量降低，单纯疱疹病毒(HSV)发作的次数也会减少。

其他可能激活单纯疱疹病毒(HSV) 的因素有压力、焦虑、其他疾病、摩擦或擦伤。稀有的情况下，单纯疱疹病毒(HSV)感染可累及肺、肝、脑等内脏。对于单纯疱疹病毒(HSV）不断发作的患者，我们可能会给他们开出每天服用的抗病毒药物。

水痘带状疱疹病毒(VZV)

水痘带状疱疹病毒(VZV) 会引起水痘及带状疱疹。第一次接触水痘带状疱疹病毒(VZV) 的人首先会患上水痘（原发性疾病）。水痘带状疱疹病毒(VZV) 的再次激活称为带状疱疹（继发感染）。稀有的情况下，水痘带状疱疹病毒(VZV) 感染会影响其他器官，如肺部、眼睛或大脑。对于持续感染带状疱疹的患者，我们可能会给他们开出每日服用的抗病毒药物。

巨细胞病毒(CMV)

巨细胞病毒(CMV)是一种常见的疱疹病毒，出现在免疫被抑制的患者身上。肺移植后感染 CMV 的风险在于供体（D）和受体（R）的状态。

- 感染巨细胞病毒(CMV)的肺移植受者(R+)、可以从感染了巨细胞病毒(CMV)的器官捐赠者(D+)或从未被感染 CMV 的捐献者(D-)那里获得器官。
- 同样地，没有感染巨细胞病毒 CMV(R-)的肺移植接受者、可以从曾感染 CMV 的捐赠者(D+)那里获得器官，或从没有感染 CMV 的捐赠者(D-)那里获得器官。

任何移植患者都可能感染到巨细胞病毒(CMV)。但是，没有感染过巨细胞病毒 CMV 的肺移植患者(R-)，如从感染过巨细胞病毒 CMV 的捐献者(D+)那

里接受器官，则再激活的风险最高。这是因为他们的身体还没有产生对巨细胞病毒(CMV)的免疫力，而免疫抑制剂往往使这些患者无法产生对 CMV 的免疫力。这使得他们的免疫系统更难控制住巨细胞病毒(CMV)。

如肺移植受赠者或其捐赠者都有巨细胞病毒(CMV)感染史（R+或 D+），则受赠患者需接受预防性（*prophylaxisy 医学预防*）剂量的抗病毒药物，如缬更昔洛韦（*valganciclovir*）。患者接受这种预防性药物的时间的长短取决于捐赠者及受者的巨细胞病毒(CMV) 的情况、以及移植后是否发生巨细胞病毒(CMV)的感染。

患者在肺移植后的第一年，需经常测试血液以检查巨细胞病毒(CMV)。很多时候在患者出现任何症状之前、就能从血液中发现巨细胞病毒(CMV)。巨细胞病毒(CMV)也会引起发烧、严重疲劳、呼吸急促、腹痛、恶心、呕吐或腹泻等症状。

如发现巨细胞病毒(CMV)，我们会立即治疗。如患者有 CMV 的症状，我们可能会做一些测试，以观察巨细胞病毒(CMV)是否已在肺部或胃及胃肠道（消化道）引起问题。将持续治疗直到巨细胞病毒(CMV)消失。这可能需要 3 周到几个月的时间。

爱泼斯坦巴尔病毒(EBV)

*爱泼*斯坦巴尔病毒(EBV)导致单*核细胞增多症*。它还导致移*植后淋巴增生症*（PTLD），这是一种在服用免疫抑制剂的患者中发现的淋巴瘤（淋巴结癌）。移*植后淋巴增生症*（PTLD）是罕见的，但大多数情况下是可以治疗的。

呼吸道的病毒

肺移植术后可能会发生呼吸道感染（感冒）。感冒可能与没有服用免疫抑制药物的人一样。但是，肺移植患者可能会注意到他们的症状比其他人更严重，持续时间更长一些。

有时呼吸道病毒会对移植肺造成重大损害，甚至会引发急性排斥反应。如在移植手术后出现感冒或类似流感的症状：

- **即刻**电话联系华大肺移植团队
- 密切观察症状，并使用家庭肺功能仪监测仪、监测肺功能。

对大多数呼吸道病毒我们一般地没有治疗的方法，但还是要尽快告诉我们任何呼吸道症状。

细菌感染

在移植后发生的感染中，约有 40%（100 个感染中的 40 个）是由细菌引起的。这些感染可在肺移植后的任何时间发生，并可能影响身体的任何部位。需密切观察自己是否有任何感染的迹象或症状

如发现任何迹象，请**即刻**致电华大肺移植团队。我们可能会做一些测试，以帮助我们知道是什么细菌可能导致感染。一旦知道是细菌感染，就可以决定最佳的治疗方法。

真菌感染

在器官移植后发生的感染中，真菌引起的感染约占 10%至 20%（100 个感染中的 10 至 20 个）。通常在空气中都可发现真菌孢子（繁殖真菌的微粒）。通常在土壤被挖掘的地方，如建筑工地、耕作区和堆肥场，会有更多的孢子。

如移植者经常接触这些地方，又不戴口罩或其他保护措施，如手臂或腿部接触到土壤就会增加他们感染真菌的风险。

曲霉菌

肺移植后最常见的真菌感染是*曲霉菌*。*曲霉菌*是我们身边的一种霉菌。我们都会经常吸入一些*曲霉菌*孢子。一次性吸入大量的*曲霉菌*孢子（当空气中存在大量污垢时）是感染*曲霉菌*的危险因素。

曲霉菌 感染的症状包括发烧、呼吸急促或咳嗽。在症状出现之前，我们有时也可以在胸部 X 光或电脑断层断层扫描（CT）中发现它。*曲霉菌*感染的治疗包括服用抗真菌药物至少 3 到 6 个月。

预防感染

预防感染是保护健康的好方法。大多数有助于预防感染的措施都是有意义的。

洗手

简单的洗洗手、就是预防感染传播的最好方法! 大多数人都是通过接触门把手、水槽水龙头的把手和杂货店的推车等东西，然后又接触自己的*黏膜*（眼睛、鼻子和嘴巴）而感染呼吸道病毒的。随身带洗手消毒液，在到达公共场及别人接触过的物品周围，清洁双手是很容易做到的。

戴口罩

我们建议移植患者在某些情况戴口罩，以减少发生某些类型感染的风险。 这些包括:

- 每当您返回医院时。 医院里有很多病人可能会咳嗽或打喷嚏，所以要戴口罩！
- 在建筑工地或任何可以看到空气中灰尘或碎屑的地方需随时随地戴口罩。
- 在花园里挖土或做其他院子工作时

避免感染的提示

- 避免接触生病的人
- 经常洗手，尤其是在公共场所时。
- 如感觉不舒服，就请使用常识：给自己时间休息，吃健康的食物，多喝水。打电话给华大肺移植团队，告诉他们有何症状。他们可能会有其他的建议，可以照顾好自己。

疫苗

在您接受肺移植手术之前，我们会确保您补足了所有应该注射的疫苗。

可能包括预防下列疾病的疫苗:

- 肝炎疫苗
- 肺炎疫苗
- 流感疫苗
- 破伤风及百日咳 (Tdap) 疫苗
- 麻疹，腮腺炎和寻麻疹(MMR) 疫苗
- 带状疱疹疫苗

在肺移植手术后，我们建议每年注射一次流感疫苗。更新肺炎疫苗也很重要。请向华大肺移植团队询问多久需要注射一次疫苗。

关于活病毒疫苗的警告

有些疫苗含有活病毒。**移植后，患者绝对不可接受含有活病毒的疫苗接种**。患者在免疫系统受到抑制的情况下，可能会受到感染，而不是被免疫。下面是最常见的活疫苗:

- 带状疱疹
- 麻腮风疫苗（麻疹、腮腺炎、风疹）

其他活性疫苗:

- *鼻内 接种* (鼻腔喷雾)流感疫苗
- 天花疫苗
- 口服小儿麻痹症疫苗
- 黄热病疫苗

您有疑问吗?

我们很重视您的提问，您有疑问或顾虑时；请致电华大医学的肺脏移植组：

工作时间上午 8 点至下 4:30 : 请致电： 206.598.5668.

下班后及周末假日: 请致电：206.598.6190 接通后，请传呼当值的肺科移植医生。

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UW Medicine

The Immune System

Infection and rejection after a lung transplant

This handout explains how the immune system works, and why it must be suppressed after lung transplant surgery.

What is the immune system?

The *immune system* is a complex network of special cells and organs. When it is working well, it protects the body against "invaders" such as viruses, bacteria, fungi, and other infections.

To do this, the immune system must tell the difference between a person's own cells and any invading "non-self" cells. If the immune system finds "non-self" cells, it will attack them. This is a type of *immune response*.

An immune response can be triggered when the immune system finds *antigens* in the body. Antigens are often "non-self" cells. They might be cells from bacteria, viruses, or other types of infection.

Antigens can also be cells from another person, such as blood used in a transfusion or an organ used for a transplant. The immune system sees these substances as "foreign" and tries to remove them. When this happens after an organ transplant, it is called *rejection*.

How does the immune system work?

When the immune system senses antigens, it activates *white blood cells* to fight the invader. The 2 main types of white blood cells are *lymphocytes* called *T cells* and *B cells*:

- **T cells** attack the foreign cells directly.
- **B cells** produce *antibodies* that attach to the foreign cells. These antibodies signal other immune cells to attack the foreign cell.

As a transplant recipient, you will take medicines to suppress your immune system, to keep it from rejecting your new lung(s).

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What stops the immune system from rejecting a transplanted organ?

Transplant recipients are given medicines to suppress their immune system and keep it from rejecting the transplanted organ. These are called *immunosuppressants* or *immunosuppressive medicines*.

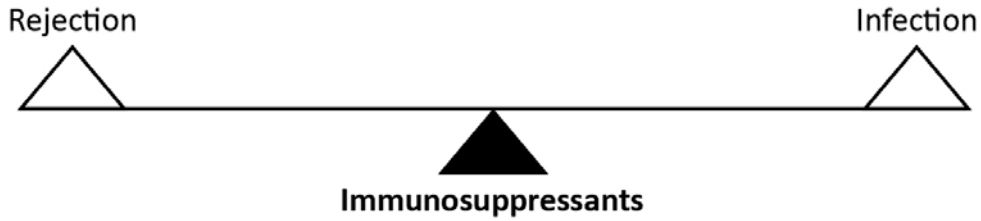
Lung transplant recipients start to receive these medicines when they go to the operating room for the transplant surgery, even before the donor lung(s) are placed in their body. After the transplant surgery, recipients must take immunosuppressants for the rest of their lives.

Challenges in Suppressing the Immune System

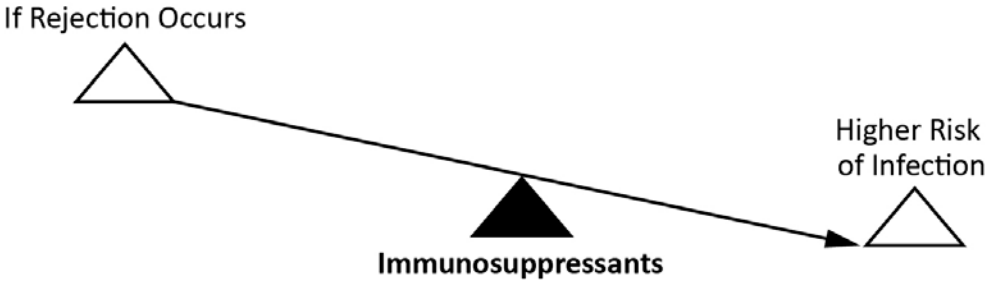
Your immune system must be suppressed to prevent rejection of the transplanted lung(s). But if your immune system is suppressed too much, it will not be able to fight infections. Both rejection and infections threaten your overall well-being and the health of your transplanted organ.

Once you have your new lung(s), we want to both keep your body from rejecting the new lung(s) and limit your risk of infection. We will do our best to adjust your immunosuppressant doses to find the right balance. This process takes time.

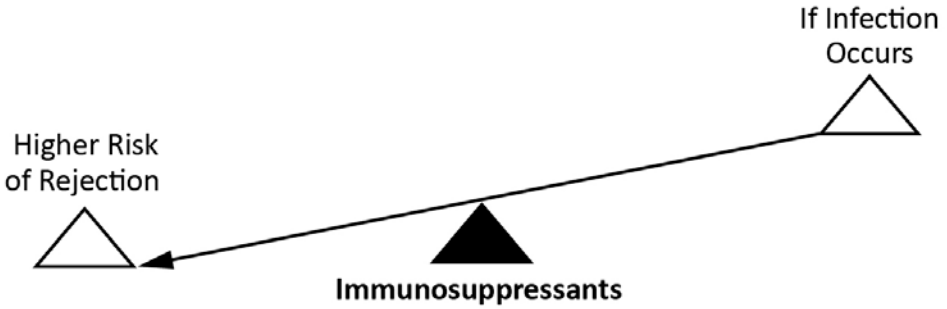
These drawings show the relationship between immunosuppressants, rejection, and infection:



When well balanced, immunosuppressant medicines prevent rejection and infections are minimized.



If rejection occurs, we will increase the level of immunosuppression. This increases the risk of infection.



If an infection occurs, we may decrease the level of immunosuppression. This increases the risk of rejection.

We will closely monitor your lungs and overall health after surgery. If needed, we may adjust your doses of immunosuppressants at your follow-up visits. This is one reason you must have follow-up visits very often in the first few months after transplant surgery.

How long will I need to take immunosuppressants?

Every lung transplant recipient must take immunosuppressive medicines every day for the rest of their life. This is because the recipient's body will never accept the transplanted organ as its own. As long as the recipient is alive, there is always a risk of rejection. The amount of immunosuppressive medicines varies, depending on each lung transplant recipient's unique situation after the lung transplant surgery.

Does the risk of rejection change over time?

Most times, rejection occurs during the first 12 months after a lung transplant. But it can occur at any time, even many years after the transplant surgery.

Right after a lung transplant, the recipient receives high doses of immunosuppressants. This high dose is needed right away to keep the immune system from rejecting or damaging the new lung(s). As time passes, the immune system may become less aggressive in its attempt to reject the new lung(s). If this happens, we may be able to reduce the level of immunosuppressive medicines over time.

If rejection occurs at any time after a lung transplant, your level of immunosuppression will need to be increased. After we treat you for rejection, we may need to find a new balance of immunosuppressive medicines to keep you from having another rejection episode.

What are the symptoms of rejection?

It is not always easy to diagnose rejection after a lung transplant. Symptoms of rejection might include:

- Decrease in *spirometry* (breathing tests), particularly FEV1
- Shortness of breath
- Fever
- Changes in chest X-ray or *computed tomography* (CT) images
- Change in oxygen saturation
- New fatigue

These symptoms can also occur if you have an infection or other problems after a lung transplant. If you have any of these symptoms, we may ask you to have a test called a *bronchoscopy* to help us find the cause.

During a bronchoscopy, a scope is inserted into your lung(s) through your nose or mouth. This allows us to look at the new lung(s) and take samples to test for rejection, infection, or other problems.

What happens if rejection occurs?

Treatment of rejection depends on whether it is *acute* rejection or *chronic* rejection, also called *chronic lung allograft dysfunction* (CLAD).

Acute Rejection

There are 2 main types of acute rejection:

- *Acute cellular rejection*, usually triggered by T-cells
- *Antibody-mediated rejection*, usually triggered by B-cells

If we find rejection or we feel strongly that your symptoms are being caused by rejection, your level of immunosuppression will be increased until the rejection subsides. Treatment depends on the type of immune cell most likely causing the rejection.

After acute rejection is treated, the patient's lung function often returns to their former baseline. But sometimes the transplanted lung(s) are damaged by the rejection episode. This can mean that the lungs will never work as well as they did before the rejection. The patient's symptoms after treatment of the rejection will depend on how severe the lung damage is.

Acute Cellular Rejection

Acute cellular rejection occurs when T-cells attack the new lung(s) directly. Most times, the first treatment given for acute cellular rejection is a "pulse" (short-term treatment) with high-dose steroid medicines (*methylprednisolone,* then *prednisone*).

If the rejection does not respond to this first treatment, we will try other ways to get rid of the T-cells that are causing the rejection. These other treatments can include medicines like *anti-thymocyte globulin* (ATG) and *alemtuzumab*, both of which kill T-cells. These drugs strongly suppress the immune system for a while. Sometimes, they can cause severe, permanent suppression of the immune system.

Antibody-mediated Rejection

Antibody-mediated rejection requires treatments directed at B-cells and the antibodies that are triggering an attack on the new lung(s). These treatments can involve some combination of:

- *Plasmapheresis*, a process that removes antibodies from the blood, much like dialysis removes toxins for patients with kidney failure
- *Rituximab*, a medicine that kills immature B-cells
- *Bortezomib*, a medicine that kills the mature B-cells that produce antibodies
- *Intravenous immunoglobulin* (IVIG), a medicine that inactivates circulating antibodies and decreases the production of new antibodies

Chronic Lung Allograft Dysfunction

Chronic lung allograft dysfunction (CLAD) is also called *bronchiolitis obliterans syndrome* (BOS) *or chronic rejection*. CLAD is defined as a *sustained* decline in spirometry (FEV1 and/or FEF 25% to 75%), without another cause.

CLAD occurs in most lung transplant recipients over time. We do not know why it occurs. There may be many factors that play a role, including:

- Episodes of acute rejection
- Episodes of infections, including respiratory viruses (colds and flu)
- Gastroesophageal reflux (GERD)

Sometimes, there does not seem to be a specific event that has caused CLAD to occur. And even when we manage and treat issues that could cause CLAD, we might not be able to keep it from occurring in lung transplant recipients.

It is very hard to diagnose CLAD. We do not have a test that clearly points to CLAD as the cause of a patient's symptoms or permanent decline in spirometry.

Studies show the most likely end-result of CLAD is damage to the *bronchioles* (very tiny airways in the lungs) and scarring of the lung tissue. The bronchioles become inflamed, causing them to be distorted, narrowed, and plugged with scar tissue. After the bronchioles are destroyed, the patient can develop severe *obstructive airway disease* (cannot get air out). When a lot of scar tissue forms, the patient can develop severe *restrictive lung disease* (cannot get air in).

We do not have medicines that can restore lung function after the bronchioles are destroyed. The best we can do is to try to keep more damage from occurring. We do this by treating any known underlying problems such as acute rejection, infection, or gastroesophageal reflux.

For lung transplant recipients, the best way to try to prevent CLAD is to:

- Take your medicines **exactly** as prescribed.
- Closely monitor your breathing with your home spirometry machine. Call the Lung Transplant office **right away** if you have a decline in FEV1 of more than 10% from your baseline.
- Keep in close contact with the UW Lung Transplant Team. Call the Lung Transplant office **right away** if you have any new symptoms.

Infections

After a transplant, the recipient takes immunosuppressants to prevent rejection. But suppressing the immune system lowers the body's ability to fight off infections. This means bacteria, viruses, or fungi can cause infections that don't often affect people with a normal immune system.

The air we take into our lungs may contain *infectious pathogens* (organisms that cause infection). This can be dangerous for someone whose immune system is suppressed.

Viruses

Viruses cause about 40% of infections (40 out of 100 infections) that occur in transplant recipients. Some infections are more common early after the transplant surgery, but others can occur at any time after a transplant.

Herpes Viruses

The *herpes virus* family is one of the most common causes of viral infections in transplant patients. By age 25, more than 80% of people (80 out of 100 people) have been infected by a herpes virus (cold sores, chicken pox, etc.).

When someone gets a herpes virus, the virus lives in their body for the rest of their life. These "latent" infections usually do not cause problems. But, when the immune system is suppressed, the herpes virus can reactivate or "wake up" and cause problems.

There are 4 types of herpes virus:

Herpes Simplex Virus (HSV)

HSV Type I (HSV-1) outbreaks often cause cold sores. Type II (HSV-2) outbreaks often cause genital herpes.

HSV outbreaks most often occur in the first 6 months after a transplant or up to 3 weeks after treatment for rejection. At these times, the patient is on higher doses of immunosuppressants. As the level of immunosuppression decreases over time, the number of HSV outbreaks also goes down.

Other factors which may reactivate HSV are stress, anxiety, other illness, friction, or chafing. Rarely, HSV infections can involve internal organs such as the lungs, liver, and brain. For patients who keep having HSV outbreaks, we may prescribe a daily anti-viral medicine.

Varicella Zoster Virus (VZV)

VZV causes both chicken pox and shingles. The first time you are exposed to VZV, you develop chicken pox (the *primary illness*). The reactivation of VZV is called shingles (the *secondary infection*).

Rarely, VZV infections can affect other organs such as the lungs, eyes, or brain. For patients who keep getting shingles, we may prescribe a daily anti-viral medicine.

Cytomegalovirus (CMV)

CMV is a common herpes virus that occurs in immunosuppressed patients. The risk of CMV infection after a lung transplant depends on the status of the donor (D) and recipient (R).

- A lung transplant recipient who has been infected with CMV (R+) can receive an organ from a donor who had also been infected with CMV (D+), or from a donor who had NOT been infected (D-).
- Likewise, a lung transplant recipient who has NOT been infected with CMV (R-) can receive an organ from a donor who had been infected with CMV (D+), or from a donor who had also not been infected (D-).

CMV infection can occur in any transplant patient. But, lung transplant recipients who have not had CMV infection (R-) who receive an organ from a donor who has been infected with CMV (D+) are at the highest risk of reactivation. This is because their bodies have not developed immunity to CMV, and the immunosuppressants often keep these patients from developing immunity to CMV. This makes it harder for their immune system to keep the CMV under control.

If either the lung transplant recipient or their donor has a history of CMV infection (R+ or D+), the recipient will receive a *prophylaxis* (preventive) dose of an anti-viral medicine such as *valganciclovir*. How long they receive this prophylactic medicine depends on the CMV status of the donor and recipient and whether a CMV infection occurs after transplant.

A blood test to check for CMV is done often during the first year after a lung transplant. Many times, we find CMV in the blood before the patient has any symptoms. CMV can also cause symptoms such as fever, severe fatigue, shortness of breath, abdominal pain, nausea or vomiting, or diarrhea.

If CMV is found, we will start treatment right away. If you have symptoms from CMV, we might do tests to see if the CMV is causing problems in your lung(s) or stomach and *gastrointestinal*

(digestive) tract. Treatment will continue until the CMV is gone. This can take 3 weeks to several months.

Epstein-Barr Virus (EBV)

EBV causes *mononucleosis*. It is also involved in *post-transplant lymphoproliferative disorder* (PTLD). This is a type of *lymphoma* (cancer of the lymph nodes) found in people who are taking immunosuppressants. PTLD is rare but most times can be treated.

Respiratory Viruses

Respiratory infections (colds) can occur after a lung transplant. Colds can be the same as they are for people who are not taking immunosuppressive medicines. But, lung transplant recipients might notice their symptoms are a little worse and last a little longer than in other people.

Sometimes respiratory viruses can cause major damage to the transplanted lung(s). They can even trigger acute rejection. If you get cold or flu-like symptoms after transplant surgery:

- Call the UW Lung Transplant Team **right away.**
- Watch your symptoms closely and use your home spirometry to monitor your lung function.

We do not have treatments for most respiratory viruses, but it is still important to tell us about any symptoms as soon as you can.

Bacterial Infections

About 40% of infections (40 out of 100 infections) that occur after a transplant are caused by bacteria. These infections can occur at any time after a lung transplant and may affect any part of the body. Watch yourself closely for any signs of infection.

If you notice any signs, call the UW Lung Transplant Team **right away**. We might do tests to help tell us what bacteria may be causing the infection. Once we know if bacteria are involved, we can decide the best treatment.

Fungal Infections

Fungi cause about 10% to 20% of the infections (10 to 20 out of 100 infections) that occur after an organ transplant. *Fungal spores* (pieces of the fungus) are normally found in the air. There are

usually more spores in areas where the soil has been disturbed, such as building sites, farming areas, and compost piles. If a transplant recipient is exposed to these areas often, and does not wear a mask or other protection, it can increase their risk of getting a fungal infection.

It is always a good idea to wear a mask and other gear to protect yourself when you are around areas where soil has been disturbed. This includes wearing long sleeves and long pants if your arms or legs might come in contact with the soil.

Aspergillus

The most common fungal infection after a lung transplant is *Aspergillus*. *Aspergillus* is a mold that is all around us. We all breathe in a few *Aspergillus* spores all the time. When there is a lot of dirt in the air, we may breathe in a large amount of *Aspergillus* spores at one time. This raises the risk of getting an *Aspergillus* infection.

Symptoms of *Aspergillus* infection can include fever, shortness of breath, or cough. We can also sometimes find it on a chest X-ray or *computed tomography* (CT) scan before symptoms appear.

Treatment for an *Aspergillus* infection can involve taking an anti-fungal medicine for at least 3 to 6 months.

Preventing Infections

Preventing infections is a good way to protect your health. Most of the things that help prevent infections make good sense.

Washing Your Hands

Simply washing your hands might be the very best way to prevent the spread of infection! Most people pick up respiratory viruses by touching things such as door handles, sink faucet handles, and grocery store carts and then touching their *mucus membranes* (eyes, nose, and mouth). It's easy to carry hand sanitizer and clean your hands when you are out in public and around objects that other people have touched.

Wearing a Mask

We advise transplant patients to wear masks at certain times to lower the risk of getting some types of infections. Remember to wear a mask:

- Whenever you return to the hospital or clinic. There are many sick people in the hospital who may cough or sneeze, so wear a mask!
- Anytime you are around building sites or any place where you can see dust or debris in the air.
- When you are digging soil in the garden or doing other yard work.

There may be other times we advise wearing a mask, such as during the outbreak of a disease such as COVID-19. Please talk with your transplant team to find out what to do during these times.

Tips to Prevent Infection

- Avoid being around anyone who is sick.
- Wash your hands often, especially when you are in public places.
- Use common sense if you do not feel well. Give yourself time to rest, eat healthy foods, and drink plenty of fluids. Call the UW Lung Transplant Team and tell them your symptoms. They could have other ideas of ways you can take care of yourself.

Vaccines

Before you receive a lung transplant, we will make sure you are up to-date on your vaccines.

Vaccines may include shots to prevent:

- Hepatitis
- Pneumonia
- Flu
- Tetanus and whooping cough (Tdap)
- Measles, mumps, and rubella (MMR)
- Shingles

After your lung transplant, we advise you to get a flu shot every year. It is also important to update your pneumonia vaccine. Ask the UW Lung Transplant Team how often you need to do this.

Warning About Live Virus Vaccines

Some vaccines contain live viruses. **After transplant, you must NEVER receive an immunization that contains a live virus.**

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With your suppressed immune system, you may get the infection instead of being protected against it.

The most common live vaccines are for:

- Shingles
- MMR (measles, mumps, and rubella)

Other live vaccines include:

- *Intranasal* (nasal spray) flu vaccine
- Smallpox vaccine
- Oral polio vaccine
- Yellow fever vaccine

Questions?

Your questions are important. Call the UW Medicine Lung Transplant Team if you have questions or concerns:

Weekdays from 8 am. to 4 p.m.: Call 206.598.5668.

After hours and on weekends and holidays: Call 206.598.6190 and ask to page the Pulmonary Transplant fellow on call.

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