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成人对乙酰氨基酚(扑热息痛)中毒的病理生理学、临床表现和评估

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There is a newer version of this topic available in English. 该主题有一个新的英文版本。

引言

自1955年临床上开始使用对乙酰氨基酚[N-乙酰-对-氨基苯酚(N-acetyl-p-aminophenol, APAP)，扑热息痛]，该药已成为美国应用最广泛的解热镇痛药[1]。世界各地使用的数百种非处方药和处方药中都含有对乙酰氨基酚。

虽然人们认为使用常规治疗剂量(高达每24小时4000mg)时该药安全，但1966年发现该药过量会导致致命性和非致命性肝坏死[2,3]。人们怀疑，对于易感个体(如酗酒者)，重复给予治疗剂量或剂量轻微过度都可能有肝毒性[4-9]。对乙酰氨基酚是最常报道引起药物性肝损伤的药品之一[1,3,10,11]，在美国是急性肝衰竭的最常见原因，在所有报道病例中占50%，在肝移植病例中约占20%[12-16]。

本文将总结对乙酰氨基酚中毒的病理生理学、临床表现和诊断。对乙酰氨基酚中毒的治疗、在儿童中的临床表现和诊断详见其他专题。(参见 “成人对乙酰氨基酚(扑热息痛)中毒的治疗”和 “儿童和青少年对乙酰氨基酚(扑热息痛)中毒的治疗”和 “儿童和青少年对乙酰氨基酚(扑热息痛)中毒的临床表现和诊断”)

流行病学

对乙酰氨基酚应用广泛，多种药品都含该成分，人们常常低估其毒性[10]。此外，有相当部分患者会误解给药指导或没有发现其使用的多种药物中都含有对乙酰氨基酚，从而摄入过量[17]。阅读能力有限或使用大量对乙酰氨基酚的患者最常犯此类错误。

在美国及许多其他国家，对乙酰氨基酚仍然是药物过量以及过量相关肝衰竭和死亡的主要原因，这一点不足为奇[12,18]。如果尽早发现过量，死亡率非常低。然而，一旦发生急性肝衰竭，死亡率约为28%，1/3的患者需要肝移植[19]。美国在1998年建立了追踪急性肝衰竭病例的国家网络，发现近一半的急性肝衰竭病例由对乙酰氨基酚引起[13,20]。该组织的数据表明，在对乙酰氨基酚相关性肝衰竭病例中，故意(自杀性)和非故意(慢性)中毒各占一半[13,20]。

一项回顾性研究纳入加拿大卡尔加里地区10年间对乙酰氨基酚过量的所有病例，有以下发现[21]：

- 在1543例患者中，70例(4.5%)发生了肝毒性，15例在首次住院期间死亡。
- 肝毒性的危险因素包括：非故意过量(OR 5.18；95%CI 3.00-8.95)、酗酒(OR 2.21；95%CI 1.30-3.76)，以及基础肝脏疾病(OR 3.50；95%CI 1.57-7.77)。

患者使用含对乙酰氨基酚和阿片类物质的复方处方药时，也有发生肝毒性的风险。2010年，超过1.3亿处方开具了此类药品[3]。此外，至少6%的此类处方中，对乙酰氨基酚超过了4000mg的每日最大剂量[3,19,22]。在对乙酰氨基酚意外过量的患者中，63%使用了对乙酰氨基酚/阿片类物质复方制剂[20]。因此，现今美国FDA和很多其他机构要求降低复方制剂中的对乙酰氨基酚剂量，已有一些厂商这样做[11]。

药代动力学

对乙酰氨基酚有速释和缓释制剂(　表 1)。治疗剂量为儿童一次10-15mg/kg，成人一次325-1000mg，每4-6小时1次，每日最大推荐剂量儿童为80mg/kg，成人为4g。个体间的中毒剂量可能有差异，取决于谷胱甘肽基线水平和其他因素(参见下文‘可能影响毒性的临床因素’)。

- 儿童单次剂量小于150mg/kg或成人单次剂量小于7.5-10g时，不太可能导致中毒[23]。
- 单次摄入超过250mg/kg或24小时内摄入超过12g时，可能发生中毒[24,25]。
- 若不适当治疗，摄入剂量超过350mg/kg的患者几乎都会发生严重肝毒性，定义为AST或ALT峰水平超过1000U/L[24]。

对乙酰氨基酚经胃肠道(十二指肠)迅速完全吸收[26]。口服治疗剂量后，血清浓度在0.5-2小时达到峰值[27]。与食物同服可能使吸收延迟[26]。摄入过量速释制剂后通常4小时内会达到血清峰浓度，但如果同时摄入延迟胃排空的药物(如阿片类物质、抗胆碱能药物)或在摄入过量缓释制剂后，达峰时间可能延迟到4小时以后[28-30]。血清治疗浓度范围为10-20μg/mL(65-130μmol/L)。

所有对乙酰氨基酚制剂的清除半衰期都为2-4小时，但对于缓释制剂，药片的溶解和吸收时间都延长，清除相的开始时间可能延迟[29,31]。现已发现，出现肝毒性的患者中半衰期超过4小时[32]。

生化毒性

对乙酰氨基酚在肝微粒体中代谢。使用治疗剂量时，90%的对乙酰氨基酚在肝脏经磺基转移酶(sulfotransferase, SULT)和UDP葡萄糖醛酸基转移酶(UDP-glucuronosyl transferases, UGT)的作用，代谢为硫酸盐和葡萄糖醛酸结合物[26]。这些结合代谢物之后随尿液排泄[26,27,33,34]。大约2%的药物以原型随尿液排泄。通过肝细胞色素P450(CYP2E1、CYP1A2和CYP3A4)混合功能氧化酶途径的氧化作用，其余的对乙酰氨基酚被代谢为有毒的高反应性亲电子中间体，即N-乙酰-对-苯醌亚胺(N-acetyl-p-benzoquinoneimine, NAPQI)(图 1)[7,34-39]。

适量对乙酰氨基酚会产生少量NAPQI，这些NAPQI迅速与肝脏的谷胱甘肽结合，形成无毒的半胱氨酸和硫醇化合物，之后随尿液排泄[26,33,40]。然而，摄入中毒剂量的对乙酰氨基酚时，其硫酸化和葡萄糖醛酸化途径逐渐饱和，更多的对乙酰氨基酚会通过细胞色素P450酶途径而被代谢为NAPQI[41]。当肝脏的谷胱甘肽储备量被消耗70%-80%时，NAPQI开始与细胞蛋白反应，随即发生损伤[24,33,42,43]。血清蛋白加合物为中毒的标志，在对乙酰氨基酚治疗后最早1小时即可检出[26]。

NAPQI与肝脏大分子(尤其是线粒体蛋白)中的半胱氨酸基团共价结合并使其芳化，形成NAPQI-蛋白加合物[44-46]。该过程不可逆。形成这些加合物可导致肝细胞氧化损伤、线粒体ATP合酶α亚基改变，以及小叶中央型肝细胞坏死[47-49]。毒性自由基(如过氧亚硝基)会在线粒体内形成硝基酪氨酸加合物[11,36,38]。线粒体DNA和ATP合酶受损会导致ATP合成停止[11]。脂质过氧化反应和细胞膜损伤可能在肝细胞损伤的进展中发挥作用[36,50]。此外，受损线粒体释放的细胞因子、凋亡诱导因子(apoptosis-inducing factor, AIF)、核酸内切酶G(EndoG)以及活性氮和活性氧也在肝损伤扩散中发挥作用。肝细胞释放的细胞因子和细胞成份可能使库普弗细胞和其他炎症细胞激活并引发继发性炎症反应，从而使肝损伤范围扩大[51-55]。损伤相关的分子模式(damage-associated molecular pattern, DAMP)产物(例如，核碎片和线粒体DNA)会通过固有免疫系统募集炎症细胞[37,56]。这种继发性损伤出现在临床毒性的第 II 阶段。(参见下文‘临床表现’)

现已进一步阐明对乙酰氨基酚毒性的机制[11,57]，包括趋化因子的作用，尤其是C-C趋化因子受体2(C-C chemokine receptor type 2, CCR_2)阳性单核细胞[58]；炎症复合体的激活[59]；以及肝星状细胞[60]和肝脏修复[61]的促发作用。研究该药毒性的新模型包括类器官[62]和离体灌注人类肝脏[63]。

可能影响毒性的临床因素

在以下情况中，摄入对乙酰氨基酚会引发肝损害：

- 过量摄入对乙酰氨基酚(最重要)
- 摄入对乙酰氨基酚后延迟N-乙酰半胱氨酸(N-acetylcysteine, NAC)治疗
- 细胞色素P450活性过强
- 葡萄糖醛酸化或硫酸化的能力减弱
- 谷胱甘肽储备出现损耗

很多因素会通过这些机制影响对乙酰氨基酚引起肝毒性的倾向，包括在使用该药时饮酒或使用其他药物、共存疾病、高龄、基因组成以及营养状态[49]。

一项回顾性研究纳入了急性肝损伤的全国登记数据，发现对乙酰氨基酚诱导的急性肝衰竭在女性中更常见且更严重[64]。然而，先前研究并未一致发现这种趋势，现有数据还不足以证实女性更易发生对乙酰氨基酚诱导的肝衰竭。

急性酒精摄入 — 酒精是CYP2E1酶的底物。一个研究组在急性对乙酰氨基酚过量患者中发现，同时饮酒者的肝毒性发生率低于未饮酒者(5.1% vs 15.2%)[65]。急性酒精摄入似乎并不是肝毒性的危险因素，甚至可能通过与对乙酰氨基酚竞争CYP2E1而减少NAPQI的生成量，因此具有保护作用[65-70]。

长期饮酒 — 关于长期饮酒对该药诱发肝毒性的作用，目前仍有争议。长期饮酒[≥18标准杯(250mg/dL)]会使CYP2E1的生成及活性增至2倍，并消耗谷胱甘肽的储备和生成[5,22,26,65,71,72]。目前似乎没有证据表明长期酗酒者使用治疗剂量对乙酰氨基酚的肝毒性增加[65]。

单次过量 — 相比非酗酒者，长期酗酒者在**单次**摄入过量对乙酰氨基酚后发生肝毒性的风险似乎**并未**升高，因此不需要调整治疗[25,73]。

一项纳入2540例对乙酰氨基酚过量患者的多中心研究发现，长期饮酒并未增加低风险患者的肝毒性发生率；低风险是指在摄入对乙酰氨基酚后8小时内接受NAC治疗，或对乙酰氨基酚浓度低于原始版Rumack-Matthew列线图中“可能有肝毒性”的分界线(图 2)[74]。

另一篇报告纳入560例对乙酰氨基酚引起的严重肝毒性患者，发现过量饮酒史与预后显著恶化无关[25]。个案病例报告显示，尽管改良版Rumack-Matthew列线图预测一名长期饮酒者发生肝毒性的风险较低，但其发生了肝毒性[75]。

多次过量 — 与长期酗酒者单次摄入对乙酰氨基酚不同，长期酗酒者反复摄入超治疗剂量对乙酰氨基酚后发生肝毒性的风险似乎会升高[4-9,76,77]。该患者群中的很多病例极可能都是由中毒识别延迟以及持续使用该药引起的[9,11]。酒精至少起部分作用，通过诱导CYP2E1导致更多对乙酰氨基酚通过CYP2E1途径代谢，并增加NAPQI的生成量[71,72]。净效应为对乙酰氨基酚的清除率增加[78]及肝毒性风险升高。(参见 “酒精性肝病的发病机制”)

除了CYP2E1途径的活性增强，一些其他因素可能使酗酒者更容易发生严重的对乙酰氨基酚诱导肝毒性。与非酗酒者相比，长期酗酒者更常出现营养不良、更可能有近期禁食期且肝脏谷胱甘肽的储备更可能被耗损，这些因素都会使患者更容易发生肝损伤[7,77,79-81]。长期酗酒者合成线粒体谷胱甘肽转运蛋白的能力也可能降低，因此使线粒体对NAPQI的易感性增加[79,82]。

关于长期饮酒同时反复摄入治疗剂量(最多4g/d)对乙酰氨基酚的作用，目前尚存争议。一篇报告纳入161例经常饮酒者，其在因治疗目的摄入对乙酰氨基酚后发生了肝毒性，该报告提出了此类患者风险升高的问题[5]。虽然患者报告表明54%的患者摄入剂量小于等于6g/d，30%的患者摄入剂量小于4g/d，但总体死亡率达到20%[5]。

尽管该现象令人担忧，但前瞻性对照试验尚未证明长期饮酒者使用治疗剂量对乙酰氨基酚会引起肝毒性[9,73,81-85]。一项前瞻性双盲随机试验纳入201例酗酒者，持续2日给予最大治疗剂量对乙酰氨基酚(总计4g/d)或安慰剂，发现两组的AST和ALT浓度差异无统计学意义[85]。与之相似，一项较小型的前瞻性对照研究纳入20例慢性肝病(包括酒精性肝硬化)患者，持续2周给予对乙酰氨基酚(4g/d)并未使患者出现肝毒性[84]。

慢性肝病 — 未经常饮酒的慢性肝病患者发生对乙酰氨基酚诱导性肝损伤的风险似乎**并未**升高，但肝硬化患者的对乙酰氨基酚代谢减少[9,65,70,79,84,86]。该患者群中，对乙酰氨基酚的消除半衰期平均延长了2-2.5小时(最长者超过4小时)，但重复给药时并未发生药物蓄积[11,84]。更重要的是，该患者群的细胞色素P450酶活性较低且不能被诱导，这在药物过量后具有保肝作用[87]。对于肝硬化患者，尤其是失代偿性肝硬化患者，通常推荐对乙酰氨基酚的剂量不超过2000mg/d[65]。

药物和草药制品 — 即使没有明显的对乙酰氨基酚过量，同时使用可诱导CYP2E1酶的药物或草药制品也会使患者更易出现肝毒性，且可能使故意过量用药的结局恶化[88]。可改变CYP2E1活性的药物包括某些抗癫痫药(如卡马西平、苯巴比妥和苯妥英)、抗结核药(如异烟肼、利福平)等[86,89,90]。

复方磺胺甲噁唑、阿片类和齐多夫定等药物可能通过竞争葡萄糖醛酸化途径，导致对乙酰氨基酚的CYP2E1依赖性代谢增加，从而增强该药的肝毒性[91]。草药补充剂可能加重该药导致的损伤[92]。可能增强CYP450活性的草药产品包括圣约翰草、大蒜和石蚕属植物[1,11]。鉴于草药补充剂应用广泛，但常规就诊时患者通常不会提及，应特别询问患者使用草药补充剂的情况。五味子属(*Schisandra*)植物可能具有抗对乙酰氨基酚相关肝毒性的保护作用[11,93]。

营养状况 — 营养不良和一段禁食期会使患者更容易发生对乙酰氨基酚肝毒性[7,11,82,94,95]。正常情况下，肝脏葡萄糖醛酸化依赖于肝脏的碳水化合物储备。在禁食或营养不良状态下，对乙酰氨基酚的葡萄糖醛酸化减少，导致微粒体代谢增强和NAPQI生成增加[7,96,97]。谷胱甘肽储备损耗也与禁食和营养不良状态有关，这种损耗会损坏机体对NAPQI的解毒作用且更容易发生肝损伤[98]。在一项研究中，近期禁食似乎可增加对乙酰氨基酚中度过量(24小时内摄入4-10g)患者的肝毒性[7]。风险最高的患者似乎为反复过量摄入者，而非单次过量摄入者。

遗传学 — 细胞色素同工酶的多态性可使对乙酰氨基酚的氧化代谢减弱或增强[99,100]。尚不明确这些多态性的临床意义。继发于Gibert综合征的葡萄糖醛酸化受损似乎可增强毒性[101]。现已确定参与对乙酰氨基酚代谢的其他酶也会发生变化，包括UGT、SULT、谷胱甘肽S-转移酶(glutathione S-transferase, GST)、N-脱乙酰酶、N-乙酰转移酶2(N-acetyltransferase-2, NAT2)及脂肪酰胺水解酶[102]。

年龄 — 对乙酰氨基酚代谢似乎具有年龄依赖性，年龄较大者在急性过量后似乎更易发生肝毒性，而5岁以下儿童似乎不易发生[20,103-105]。40岁以上成人出现以下情况的风险更高：急性肝衰竭、肝移植以及过量后死亡[22]。幼儿很可能通过体内谷胱甘肽的供应和再生增加以及结合酶活性更高而受到保护[106,107]。然而，对乙酰氨基酚反复过量后，幼儿发生肝损伤的易感性不再较低[108]。

烟草 — 烟草烟雾含有CYP1A2诱导剂，会增加氧化代谢[109,110]。一项回顾性研究发现，吸烟是对乙酰氨基酚过量后死亡的独立危险因素，与吸烟量无关[111]。饮酒且吸烟者中死亡率最高。

用药方式 — 评估随后出现毒性的风险时，需着重考虑该药的剂量和使用方式。

反复摄入超治疗剂量 — 如果患者反复摄入超治疗剂量对乙酰氨基酚以减轻疼痛或发热，就可能意外发生有临床意义的中毒。这些患者更可能已经存在明确的肝毒性危险因素(如禁食、长期饮酒)，并且更可能在对乙酰氨基酚毒性已经发作时才就诊。一项研究纳入71例因对乙酰氨基酚中毒而入院的患者，发现意外过量组的严重肝毒性、肝昏迷和死亡发生率高于企图自杀组，即使摄入量比后者更少也如此[8]。

反复摄入治疗剂量 — 反复使用治疗剂量对乙酰氨基酚后可能发生亚临床毒性，即无临床意义的轻度自限性转氨酶升高。一项随机对照试验纳入145例持续10日摄入最大治疗剂量对乙酰氨基酚(4g/d)的健康成人，结果发现治疗组有31%-44%的受试者最高ALT大于3倍正常上限(>120U/L)，而对照组这一发生率为0[112]。一项观察性研究纳入24例持续10日摄入对乙酰氨基酚4g/d的健康成人自愿者，其中58%出现了ALT亚临床升高[113]。

磷酸盐浓度 — 低血清磷酸盐浓度似乎与对乙酰氨基酚过量后临床结局较好相关[11,114,115]。据推测，最可能的原因为肝细胞吸收磷酸盐使ATP再生而增加了细胞再生。

鉴别诊断

与大多数其他原因引起的肝炎不同，对乙酰氨基酚引起的肝炎起病急、进展迅速，特征为血浆氨基转移酶明显升高(通常>3000U/L)，伴有凝血酶原时间(prothrombin time, PT)延长/国际标准化比值(international normalized ratio, INR)升高。饮酒者发生慢性对乙酰氨基酚中毒的特征也包括氨基转移酶明显升高(>3000U/L)，伴低血容量、黄疸、凝血病、低血糖，50%以上的患者还会出现急性肾衰竭[4,5,38,116]。

如果证据提示急性肝功能障碍，应考虑的其他诊断包括：酒精性肝炎、其他药物或毒物引起的肝炎、病毒性肝炎、肝胆疾病、Reye综合征及缺血性肝炎(“休克肝”，常见于长期重度低血压后)。(参见 “肝生化和肝功能检查异常患者的评估”)

血清总胆红素水平显著升高(>1mg/dL；>17μmol/L)在对乙酰氨基酚过量后不常见，但在急性病毒性肝炎患者中可造成对乙酰氨基酚血清检测呈**假阳性**，从而可能延误对基础问题的识别[117]。(参见 “成人甲型肝炎病毒感染的流行病学、临床表现和诊断”和 “乙型肝炎病毒感染的筛查与诊断”)

与急性对乙酰氨基酚中毒不同，饮酒者发生急性酒精性肝炎和慢性对乙酰氨基酚中毒时，AST/ALT比值大于2[4,5]。酒精性肝炎患者的氨基转移酶水平也显著更低，极少超过500U/L。(参见 “酒精性脂肪性肝病和酒精性肝硬化的临床表现和诊断”和 “肝生化和肝功能检查异常患者的评估”，关于‘实验室检查’一节)

临床表现

对乙酰氨基酚中毒的初始表现通常轻微且无特异性，不能可靠预测随后的肝毒性[73,118]。然而，医生必须迅速识别对乙酰氨基酚中毒，以尽量减少随后的并发症和死亡。中毒的临床病程通常分为4个连续阶段。

阶段 I (0.5-24小时) — 在过量后24小时内，患者常出现恶心、呕吐、出汗、面色苍白、嗜睡和不适。一些患者仍无症状。实验室检查结果通常正常。对乙酰氨基酚大量过量后，可能出现中枢神经系统抑制和阴离子间隙增高型代谢性酸中毒，但很罕见[119,120]。这些中毒症状通常是由于同时摄入了其他物质，例如苯海拉明、阿片类或阿司匹林。血清氨基转移酶浓度一般正常，但该值可能在严重中毒者摄入后最早8-12小时就会升高[121]。

阶段 II (24-72小时) — 在摄入后24-72小时，实验室检查可以证实发生肝毒性及偶尔发生的肾毒性。(参见下文‘急性肾损伤(急性肾衰竭)’)

刚开始，阶段 I 的症状缓解，临床表现似乎有所改善，而肝脏氨基转移酶(AST和ALT)的亚临床性升高愈发严重。

在发生肝脏损伤的患者中，半数以上会在24小时内出现氨基转移酶升高，到36小时所有患者的氨基转移酶都会升高[121]。随着阶段 II 进展，患者会出现右上腹痛，伴肝脏肿大和压痛。PT延长、总胆红素水平升高、少尿和肾功能异常可能变得明显[122]。

病例报告显示有患者出现急性胰腺炎[123,124]。一些患者因同时饮酒而促发肝毒性和胰腺炎[125]。

阶段 III (72-96小时) — 肝功能异常在摄入后72-96小时达到峰水平。阶段 I 的全身性症状会再次出现，并伴黄疸、意识模糊(肝性脑病)、肝酶水平显著升高、高血氨症和出血素质(影像 1)。严重肝毒性的征象包括：血浆ALT和AST水平通常超过10,000U/L、PT延长/INR增加、低血糖、乳酸酸中毒，以及总胆红素浓度超过4.0mg/dL或68μmol/L(主要为间接胆红素)。10%-25%的显著肝毒性患者以及50%以上有明确肝功能衰竭的患者会出现急性肾衰竭[38,122,126,127]。死亡最常发生在该阶段，通常由多器官系统功能衰竭引起[38]。(参见下文‘急性肾损伤(急性肾衰竭)’)

阶段 IV (4日-2周) — 阶段 III 中存活的患者会进入恢复期，通常从药物过量后4日开始，到7日时结束[73]。重症患者恢复更慢，症状和实验室检查指标可能持续几周才恢复正常。肝脏的组织学变化包括肝细胞溶解到小叶中心坏死。小叶中央区(III带)的CYP2E1浓度最高，从而NAPQI的生成量也最大，因此该区域首先受累。组织学恢复滞后于临床恢复，可能需要3个月。如果患者恢复，则会完全恢复，慢性肝功能障碍并不是对乙酰氨基酚中毒的后遗症。

急性肾损伤(急性肾衰竭) — 肾功能不全的发生率与对乙酰氨基酚摄入的严重程度有关。据估计，肾损害的发生率为：所有患者(包括轻微病变患者)中不到2%、无肝功能衰竭的肝脏受累患者中5%、重度中毒患者中10%，而在急性肝功能衰竭患者中可达53%[122,127,128]。在最后一种情况中，肝肾综合征和药物直接毒性可能促进发生肾衰竭。

急性肾损伤表现为血尿素氮和肌酐水平升高，伴有尿液分析发现蛋白尿、血尿以及颗粒管型和上皮细胞管型。

急性肾损伤主要由急性肾小管坏死引起[116,129]。也可发生血管内皮损伤，因此直接肾毒性和缺血都可能促进肾小管损伤[129]。

肾功能会在1-4周内自行恢复至之前的基线水平，但急性发作期间可能需要透析[127]。给予乙酰半胱氨酸能尽量减轻肾毒性，但没有证据表明其对肾脏有任何保护作用。

评估和诊断

一般方法和对乙酰氨基酚的血清浓度 — 常需保持高度警惕才能诊断出对乙酰氨基酚中毒。由于对乙酰氨基酚血清浓度是诊断急性中毒及确定是否需要治疗的基础，所以**每名**疑似故意或非故意过量的患者都应测定血药浓度。

任何中毒患者的一般方法都应包括以下要素：

- 评估应尽可能包括确认涉及药物、评估严重程度以及预测毒性。对于任何疑似对乙酰氨基酚过量患者，应询问病史以了解使用剂量、使用目的(自杀或非自杀)、使用方式(如单次或多次)、摄入时间、是否同时摄入其他物质、是否存在可能诱发肝损伤的共存状况，例如饮酒、Gilbert病、使用抗癫痫药和近期禁食。(参见上文‘可能影响毒性的临床因素’)

- 有明确对乙酰氨基酚过量史的患者都应检测血药浓度。如果对摄入时间存在任何疑问，应在就诊时立即测定血清药物浓度。还应在就诊或急性摄入后4小时测定血药浓度。

  对于已经确认中毒的患者，或根据病史和初始血药浓度预测会发生中毒的患者，还应进一步开展其他实验室检测，包括电解质、血尿素氮和肌酐、血清总胆红素水平、PT和INR、AST、ALT、淀粉酶、尿液分析。对于故意摄入或病史不可靠的患者，应行血液和尿液毒物筛查，以判断是否摄入了其他物质。(参见 “成人药物中毒的一般处理方法”)

- 处理包括支持治疗、防止药物吸收，以及适时给予解毒剂和增强药物清除。对乙酰氨基酚中毒的治疗详见其他专题。(参见 “成人对乙酰氨基酚(扑热息痛)中毒的治疗”和 “中毒患者的胃肠道去污染”和 “毒物的强化清除”)

急性过量后的评估

摄入速释对乙酰氨基酚 — 联合摄入时间与对乙酰氨基酚血清浓度来预测中毒风险的效果最好。一些研究发现，患者报告的对乙酰氨基酚摄入量与所测定的血清浓度无关，因此不应通过剂量史来预测肝毒性[130,131]。

速释制剂单次急性过量后，应在患者报告的摄入时间后4小时测定对乙酰氨基酚血药浓度。如果就诊时距离摄入已超过4小时，应立即测定对乙酰氨基酚血药浓度。应根据改良版Rumack-Matthew列线图来评估测得的浓度，以确定是否需要NAC治疗(图 3)[132]。摄入后4小时内测得的血药浓度可能不是峰浓度，因此不应使用[73,133]。

如果不知道或不清楚摄入的时间，则应立即测定对乙酰氨基酚血清浓度并在4小时后重复测定。如果最初未能检测出浓度，一定**不能**将其错误地解读为没有肝毒性。应继续观察患者并在4小时时再次测定浓度。

如果最初未能检测出浓度，则应根据是否存在肝毒性的临床和实验室征象来确定是否进行NAC治疗。如果有任何疑问，应开始NAC治疗。如果摄入时间不明，或距推测的摄入时间已过去8小时，应在对乙酰氨基酚血药浓度及肝功能测定结果出来之前开始经验性NAC治疗。(参见 “成人对乙酰氨基酚(扑热息痛)中毒的治疗”和 “中毒患者的胃肠道去污染”和 “毒物的强化清除”)

使用治疗列线图 — 虽然普遍认为在对乙酰氨基酚过量后立即给予NAC可有效防止肝损伤，但世界各地关于开始治疗的确切指南各不相同。改良版Rumack-Matthew治疗列线图(4小时浓度为150mg/L)已使用多年且安全有效，是我们指导治疗的首选工具(图 3)[132,134]。采用该工具时，如果血清对乙酰氨基酚浓度高于图中4小时150μg/mL(990μmol/L)与16小时18.8μg/mL(125μmol/L)这两个点的连接线，则认为具有发生肝毒性的“潜在风险”，标准疗法为NAC(图 3)[66,135]。其他采用不同治疗阈值的指南也已发布，可在一些国家使用[136,137]。

原始版Rumack-Matthew列线图的基础为大量未接受解毒剂的过量患者的数据，其结合了对乙酰氨基酚血清浓度和摄入时间来预测肝毒性(图 2)。血清对乙酰氨基酚浓度超过4小时200μg/mL(1320μmol/L)与16小时25μg/mL(165μmol/L)这两个点的连接线(“可能有肝毒性”)的患者若不进行解毒剂治疗，严重肝毒性(AST>1000U/L)的发生率为60%，死亡率为5%[24,138]。血清对乙酰氨基酚浓度超过4小时300μg/mL(1980μmol/L)与16小时37.5μg/mL(250μmol/L)这两个点的连接线(“高度肝毒性”)的患者若不进行治疗，严重肝毒性的发生率为90%，死亡率可达24%[24,138]。正如最初报道所示，对乙酰氨基酚血药浓度低于“可能有肝毒性”线的患者没有发生严重肝毒性，也没有死亡病例报道[24,132,138]。

改良版Rumack-Matthew治疗列线图的治疗线比原始版治疗线(“可能有肝毒性”)低25%[82,135]。考虑到不同实验室测定的对乙酰氨基酚浓度存在差异以及估计的摄入时间可能有误，便制定了该安全范围。采用改良版列线图不准确的发生率极低[75]。25%的安全范围也可能保护发生肝毒性风险更高的易感患者(如酗酒者)。一些机构建议进一步降低此类患者的治疗线，但尚无证据支持[38,139,140]。

血清对乙酰氨基酚浓度低于“可能有肝毒性”线的患者，即使接受了NAC治疗，偶尔也会发生严重肝毒性(AST>1000U)。一项研究纳入2023例口服NAC治疗急性对乙酰氨基酚过量的患者，发现血清对乙酰氨基酚浓度低于“可能有肝毒性”线的患者发生严重肝毒性的比例为0-3%[82,135]。该治疗组没有患者死亡[135]。

摄入缓释对乙酰氨基酚 — 关于Rumack-Matthew列线图能否准确评估对乙酰氨基酚缓释制剂急性过量后的风险，现有经验不足。一些机构(包括生产商)推荐在4小时和8小时测定对乙酰氨基酚的血清浓度，如果任一浓度高于列线图中的“可能有肝毒性”线，则应开始NAC治疗[29,141]。如果在列线图上描出的对乙酰氨基酚单个浓度在治疗线之下，则很可能不需要NAC治疗[73]。在获得更多临床经验之前，我们推荐遵循生产商提供的保守方法。(参见 “成人对乙酰氨基酚(扑热息痛)中毒的治疗”)

反复超治疗剂量摄入后的评估 — 反复超治疗剂量摄入(repeated supratherapeutic ingestion, RSTI)对乙酰氨基酚所致中毒往往难以诊断，需要采集高质量的病史，并识别典型的临床和实验室异常。起病时的症状和体征较隐匿，通常为非特异性，很容易与其他诊断相混淆(例如，病毒性综合征)。在询问可能的毒性药物时，临床医生应问及对乙酰氨基酚，包括关于剂量和使用方式的具体问题。慢性过量或RSTI人群的血清对乙酰氨基酚浓度常在治疗水平，并且浓度与毒性无关，这一点不同于急性过量[5,8,76,142]。这种情况下，Rumack-Matthew列线图并**不**适用。

评估肝毒性风险 — 如果已知或疑似对乙酰氨基酚RSTI，评估目标是基于病史、临床和实验室数据识别出需要NAC治疗的患者。患者有以下**任何**表现时，发生对乙酰氨基酚所致肝毒性的风险升高：

- 24小时摄入对乙酰氨基酚超过7.5-10g，或者24小时摄入量超过4g**且**肝毒性易感性增加，例如长期饮酒、禁食、使用细胞色素P450诱导剂(表 2)[23,73]。
- 腹痛或肝区压痛、恶心、呕吐、黄疸或一般状况差。
- 血清对乙酰氨基酚浓度超过治疗水平(>20μg/mL或130μmol/L)伴或不伴ALT升高[11,143,144]。
- 就诊时ALT或AST浓度升高(≥50U/L)。如果患者有对乙酰氨基酚RSTI史，并且氨基转移酶升高，无论测得血药浓度如何，都应考虑该药引起肝毒性。
- 就诊时对乙酰氨基酚与氨基转移酶的乘积较高。该表现可以预测显著肝毒性而不受摄入时间影响[145]。

N-乙酰半胱氨酸治疗的需求 — 在RSTI情况下，根据末次摄入时间用列线图进行评估，如果血清对乙酰氨基酚浓度可能引起中毒，则明确需要NAC治疗。对于有RSTI和中毒临床征象(如肝区压痛)、氨基转移酶升高(ALT或AST≥50U/L)、血清对乙酰氨基酚浓度超过治疗水平(>20μg/mL或130μmol/L)的所有患者，以及有过量摄入史、中毒危险因素、血清对乙酰氨基酚浓度>10μg/mL(65μmol/L)的患者，推荐进行NAC治疗。此外，鉴于对乙酰氨基酚中毒在工业化国家中是急性肝衰竭的首要原因，急性肝衰竭患者尚未确定病因时，推荐早期给予NAC经验性治疗。(参见“成人对乙酰氨基酚(扑热息痛)中毒的治疗”和“儿童和青少年对乙酰氨基酚(扑热息痛)中毒的治疗”)

如果可检测到患者的对乙酰氨基酚浓度，但其没有中毒的症状、体征或危险因素且氨基转移酶未升高，则极可能不需要治疗[11,73]。如果血清对乙酰氨基酚浓度低于检测水平(<10μg/mL或65μmol/L)且氨基转移酶水平正常(ALT或AST<50U/L)，则不需要NAC治疗。就诊时，ALT<50U/L和对乙酰氨基酚-氨基转移酶乘积<1500μg/mL(9,900μmol/L)×U/L似乎可有力预测患者不会发生显著肝毒性(ALT>1000U/L)。

4项总共纳入625例对乙酰氨基酚RSTI患者的研究一致发现，只要就诊时对乙酰氨基酚浓度较低，**所有**ALT<50U/L的患者都不会发生显著肝毒性(ALT>1000U/L)[146-149]。其中两项研究显示，初始对乙酰氨基酚-氨基转移酶乘积<1500μg/mL(9,900μmol/L)×U/L能够预测患者不会发生显著肝毒性(ALT>1000U/L)。目前无法根据这些研究给出确切推荐，因为它们基本采用回顾性和非随机设计，对

患者的随访情况不一，而且最重要的是，ALT<50U/L和/或初始对乙酰氨基酚-氨基转移酶乘积＜1500μg/mL(9,900μmol/L)×U/L但仍接受NAC治疗的患者比例差异很大(各研究中为40%-100%)。

延迟就诊后的评估 — 患者摄入后超过24小时至数日才就诊时，确定对乙酰氨基酚中毒的诊断具有挑战。就诊较晚的显著对乙酰氨基酚中毒患者总是存在血清肝毒性，但血清对乙酰氨基酚浓度可能无法再检出。在这些患者中，很难区分对乙酰氨基酚与其他因素引起的急性肝损伤，对乙酰氨基酚暴露史可能不存在或不可靠。

目前正在研究这种情况下做出诊断的分析方法。一项观察性队列研究报道，检测血清对乙酰氨基酚-蛋白加合物的免疫测定可快速准确识别出该药诱导的肝损伤患者[150]。该研究发现，相比高效液相色谱分析结果(参考标准)，即时免疫测定(AcetaSTAT)识别对乙酰氨基酚诱导性急性肝损伤的敏感性和阴性预测值均为100%。如果未来的临床试验能验证这些结果，该方法就可快速鉴别对乙酰氨基酚与其他因素引起的急性肝损伤，并开始适当治疗。

治疗

急性对乙酰氨基酚过量的治疗，包括NAC解毒治疗，详见其他专题。(参见 “成人对乙酰氨基酚(扑热息痛)中毒的治疗”和 “儿童和青少年对乙酰氨基酚(扑热息痛)中毒的治疗”)

其他资源

美国区域性中毒控制中心随时都可以为危重、需入院或临床情况不明确的患者提供咨询(1-800-222-1222)。此外，某些医院也会有临床和/或医学毒理学家可为患者提供床旁会诊和/或住院治疗。只要可用，这些都是有助于诊断和处理毒物摄入或过量使用的宝贵资源。世界各地中毒控制中心的联系方式参见链接中的网站[151]。

除了中毒控制中心，通常还可随时电话联系肝移植中心的移植肝脏病学家，以帮助治疗对乙酰氨基酚中毒患者。

学会指南链接

部分国家及地区的学会指南和政府指南的链接参见其他专题。(参见 “Society guideline links: General measures for acute poisoning treatment”和 “Society guideline links: Treatment of acute poisoning caused by specific agents other than drugs of abuse”)

患者教育

UpToDate提供两种类型的患者教育资料： “基础篇”和“高级篇” 。基础篇通俗易懂，相当于5-6年级阅读水平(美国)，可以解答关于某种疾病患者可能想了解的4-5个关键问题；基础篇更适合想了

解疾病概况且喜欢阅读简短易读资料的患者。高级篇篇幅较长，内容更深入详尽；相当于10-12年级阅读水平(美国)，适合想深入了解并且能接受一些医学术语的患者。

以下是与此专题相关的患者教育资料。我们建议您以打印或电子邮件的方式给予患者。(您也可以通过检索“患者教育”和关键词找到更多相关专题内容。)

- 基础篇(参见 “患者教育：对乙酰氨基酚中毒(基础篇)”)

总结与推荐

对乙酰氨基酚过量的临床表现及诊断的要点如下。对乙酰氨基酚过量的治疗详见其他专题。(参见“成人对乙酰氨基酚(扑热息痛)中毒的治疗”和 “儿童和青少年对乙酰氨基酚(扑热息痛)中毒的治疗”)

- 对乙酰氨基酚过量可能致命，但公众常常低估该药的潜在危险。治疗剂量为儿童一次10-15mg/kg，成人一次325-1000mg，每日最大推荐剂量为儿童80mg/kg或成人4g。中毒剂量因人而异，但儿童单次剂量不到150mg/kg或成人单次剂量不到7.5-10g不太可能导致中毒。单次摄入超过250mg/kg或24小时内摄入超过12g很可能会导致中毒。(参见上文‘流行病学’和‘药代动力学’)

- 对乙酰氨基酚经胃肠道迅速完全吸收。口服治疗剂量后，血清浓度在0.5-2小时达到峰值，但存在食物可能使该过程减慢。过量使用速释制剂后4小时内可达到血清峰浓度，但如果同时使用可延迟胃排空的药物(如阿片类、抗胆碱能药物)或在过量使用缓释制剂后，达峰时间可能延迟。导致中毒的生化途径见正文。(参见上文‘药代动力学’和‘生化毒性’)

- 特定临床因素可使患者在摄入对乙酰氨基酚后容易发生损伤，包括影响肝脏CYP2E1酶系统的药物、营养不良、基因多态性和高龄。长期饮酒的作用尚不明确。(参见上文‘可能影响毒性的临床因素’)

- 与多数其他因素引起的肝炎不同，对乙酰氨基酚引起的肝炎起病急、进展快，特征为血浆氨基转移酶明显升高(通常>3000U/L)，伴有凝血酶原时间(PT)延长/国际标准化比值(INR)升高。饮酒者发生慢性对乙酰氨基酚中毒的特征也是氨基转移酶明显升高(>3000U/L)，伴有低血容量、黄疸、凝血病、低血糖，50%以上的患者还会出现急性肾衰竭。(参见上文‘鉴别诊断’)

- 对乙酰氨基酚中毒的初始表现通常轻微且无特异性，不能可靠预测随后的肝毒性。因此，一旦怀疑药物过量，测定该药血清浓度至关重要。对乙酰氨基酚过量4个阶段的症状和体征见上文。严重过量可致肝衰竭。(参见上文‘临床表现’)

- 联合摄入时间与对乙酰氨基酚血清浓度预测中毒风险的效果最好。血清治疗浓度范围为10-20μg/mL(65-130μmol/L)。速释制剂单次急性过量后，应在患者报告摄入后的4小时测定对乙酰氨基酚血清浓度。对于摄入后超过4小时才就诊的患者，应立即检测血清药物浓度。应根据改良版Rumack-Matthew列线图来评估测得的浓度，以确定是否需要N-乙酰半胱氨酸(NAC)

治疗(图 3)。(参见上文‘一般方法和对乙酰氨基酚的血清浓度’和‘摄入速释对乙酰氨基酚’)

- 某些临床情况下，很难确定对乙酰氨基酚暴露相关风险和恰当治疗。一些最常见困难情况的处理方法详见相应专题：
  - 摄入时间不明(参见 “成人对乙酰氨基酚(扑热息痛)中毒的治疗”，关于‘不清楚或不知道摄入时间’一节)
  - 妊娠患者(参见 “成人对乙酰氨基酚(扑热息痛)中毒的治疗”，关于‘妊娠期的治疗’一节)
  - 摄入缓释剂型(参见上文‘摄入缓释对乙酰氨基酚’)
  - 反复超治疗剂量摄入(RSTI)(参见上文‘反复超治疗剂量摄入后的评估’)

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图表

Common dosage forms of acetaminophen (paracetamol)

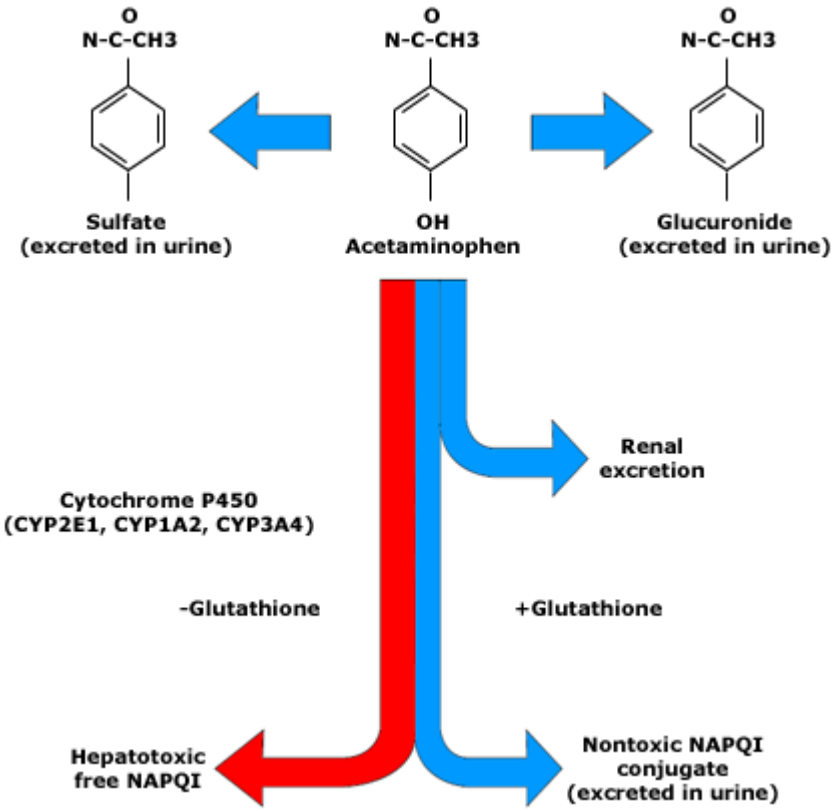
Preparation	Strength	Examples of US trade names
Extended release caplet	650 mg	Tylenol Arthritis Pain
Extra strength tablets, capsules, caplets, gelcaps, geltabs	500 mg	Genapap Extra Strength, Genebs Extra Strength, Tylenol Extra Strength, Medpap Extra Strength, Aspirin Free Anacin® Maximum Strength, Cetafen Extra, Redutemp, Valorin Extra
Tablets	325 mg	Cetafen, Genapap, Genebs ,Tylenol, Valorin, Mapap
	160 mg	Mapap
Chewable tablets	80 mg	Children's Genapap, Children's Mapap, Children's Tylenol
	160 mg	Junior Strength Tylenol
Liquid, syrup, elixir, suspension	160 mg/5 mL (32 mg/mL)	Redutemp, Children's Genapap, Children's Silapap, Children's Mapap Children's Tylenol
	500 mg/15 mL (33.3 mg/mL)	Tylenol Sore Throat
Drops*	100 mg/mL (80 mg/0.8 mL)	Infant Genapap, Infantaire, Infant's Silapap Liquiprin for Children, Infant's Mapap, Infant's Tylenol
Suppositories	80, 120, 325, 650 mg	Acephen, Feverall, Mapap
Intravenous solution¶	10 mg/mL	Ofirmev

* As of 2011, in an effort to minimize pediatric dosing errors, the Consumer Healthcare Products Association, in conjunction with the US Federal Drug Administration, is phasing out formulations that contain 100 mg per mL (infant acetaminophen drops) so that pediatric liquid preparations obtained in the United States after that time will all contain a concentration of 32 mg/mL (160 mg per 5 mL). However, 100 mg per mL solutions are likely to continue to be given to children from infant acetaminophen drops preparations purchased by caregivers before this phase out.

¶ NOTE: Tenfold dosing errors and toxicity from intravenous acetaminophen have occurred in small children when the calculated dose in mg is INCORRECTLY administered as the volume in mL because the concentration of the solution is 10 mg/mL. In the United States, intravenous acetaminophen is not licensed for use in children under two years of age.

Graphic 79854 Version 5.0

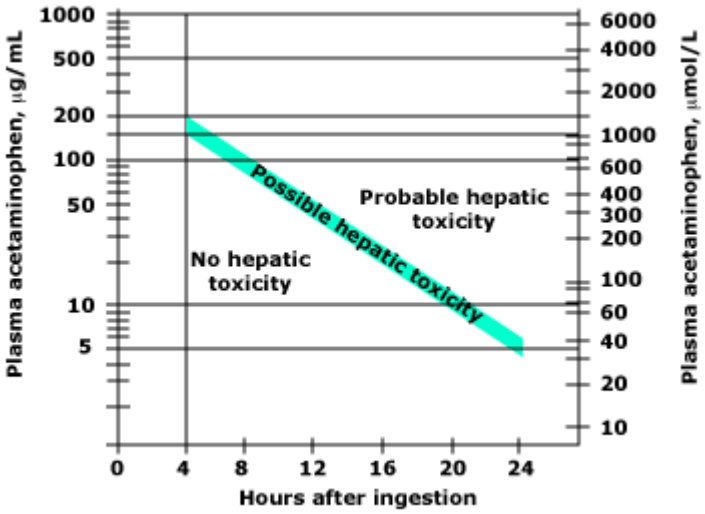
Acetaminophen metabolism



At therapeutic doses, 90 percent of acetaminophen is metabolized in the liver to sulfate and glucuronide conjugates that are then excreted in the urine. One-half of the remaining acetaminophen is excreted unchanged in the urine and one-half is metabolized via the hepatic cytochrome P450 (CYP2E1, CYP1A2, CYP3A4 subfamilies) mixed function oxidase pathway to N-acetyl-p-benzoquinoneimine (NAPQI), which is hepatotoxic. With normal doses (blue arrows), NAPQI is rapidly conjugated to hepatic glutathione, forming nontoxic cysteine and mercaptate compounds that are excreted in the urine. With toxic doses (red arrow), the sulfate and glucuronide pathways become saturated, resulting in an increased fraction of acetaminophen being metabolized by cytochrome P450 enzymes. Once glutathione stores are depleted, NAPQI begins to accumulate and hepatic injury ensues.

Graphic 68213 Version 2.0

Severity of acetaminophen intoxication

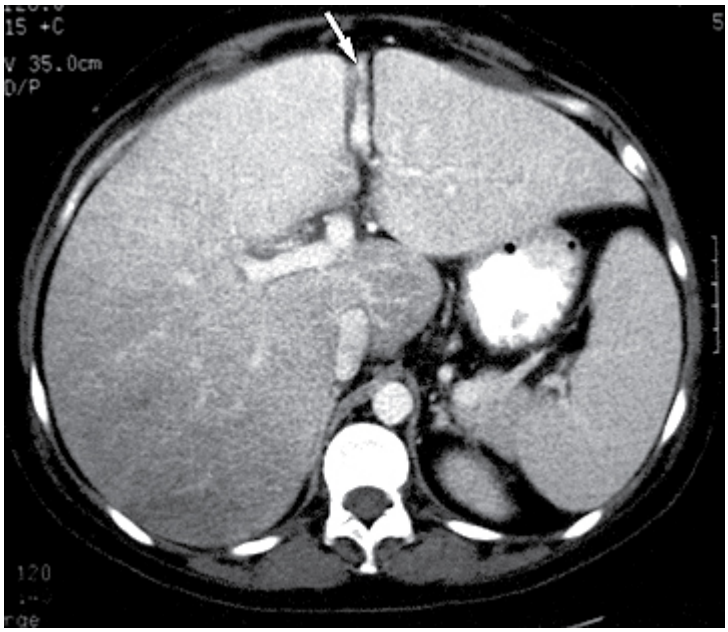


The Rumack-Matthews nomogram summarizes the relationship between plasma acetaminophen concentration (in µg/mL or µmol/L), the time after drug ingestion, and the risk of hepatic toxicity. The thick diagonal line of possible hepatic toxicity represents a 25 percent likelihood of disease. A relatively low level (such as 10 µg/mL) is safe soon after ingestion, but associated with appreciable risk at 24 hours since it reflects a high initial load which has now distributed into the tissues.

Adapted from Rumack, BH, Matthews, H, Pediatrics 1975; 55:873.

Graphic 61338 Version 2.0

Acute liver failure

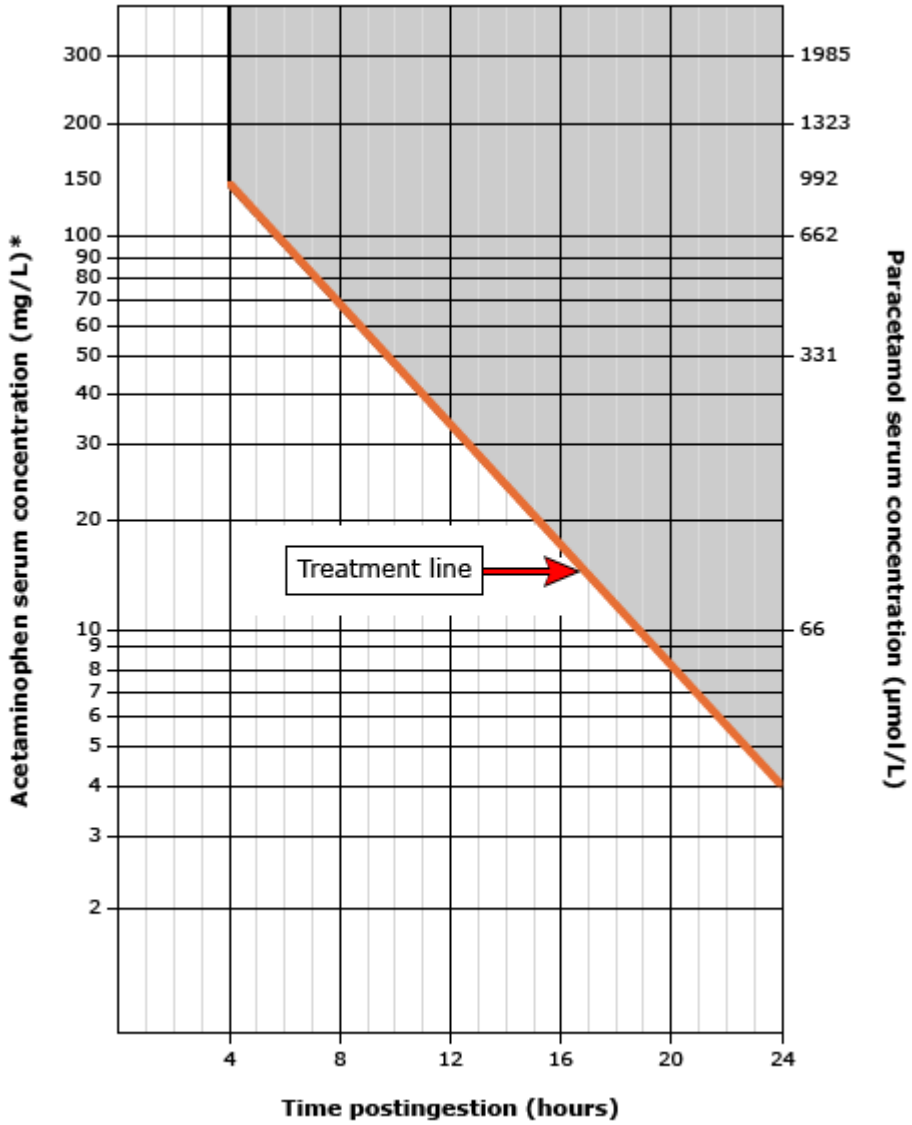


Contrast-enhanced CT scan of the liver in a 35-year-old female who took an overdose of acetaminophen demonstrates a heterogenous poorly enhancing liver with areas of lower attenuation due to acute fatty replacement. Note also the patent recanalized paraumbilical vein coursing through the ligamentum teres (arrow).

Courtesy of Jonathan Kruskal, MD.

Graphic 63610 Version 2.0

Acetaminophen poisoning nomogram



This nomogram should only be used after a single acute acetaminophen ingestion. The line indicates the level at which toxicity is possible after acetaminophen overdose. A serum acetaminophen level should be obtained four or more hours after an ingestion to ensure that a peak level has occurred. Patients who ingest extended-release preparations should have a second level drawn four hours after the first level to assess for an additional rise in serum concentration. The level should be plotted in relationship to the time of ingestion to determine the likelihood of toxicity and the need for treatment. Caution should be used in assessing the reliability of the time of ingestion. This nomogram cannot be used for ingestions that occurred greater than 24 hours prior to presentation, repeated supratherapeutic oral ingestions, or iatrogenic intravenous overdose.

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* Note that mg/L is the same concentration as mcg/mL.

Original nomogram from: Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. Pediatrics 1975; 55:871. Copyright © 1975 by the AAP. Updated version reproduced with permission from: Dart RC, Rumack BH. Acetaminophen (Paracetamol). In: Medical Toxicology, 3rd ed, Dart RC (Ed), Lippincott Williams & Wilkins, Philadelphia 2004. Copyright © 2004 Lippincott Williams & Wilkins.

Graphic 83590 Version 8.0

Cytochrome P450 3A (including 3A4) inhibitors and inducers

Strong inhibitors	Moderate inhibitors	Strong inducers	Moderate inducers
▪ Atazanavir ▪ Ceritinib ▪ Clarithromycin ▪ Cobicistat and cobicistat-containing coformulations ▪ Darunavir ▪ Idelalisib ▪ Indinavir ▪ Itraconazole ▪ Ketoconazole ▪ Levoketoconazole ▪ Lonafarnib ▪ Lopinavir ▪ Mifepristone ▪ Nefazodone ▪ Nelfinavir ▪ Ombitasvir-paritaprevir-ritonavir ▪ Ombitasvir-paritaprevir-ritonavir plus dasabuvir ▪ Posaconazole ▪ Ritonavir and ritonavir-containing coformulations ▪ Saquinavir ▪ Telithromycin ▪ Tucatinib ▪ Voriconazole	▪ Amiodarone* ▪ Aprepitant ▪ Berotralstat ▪ Cimetidine* ▪ Conivaptan ▪ Crizotinib ▪ Cyclosporine* ▪ Diltiazem ▪ Duvelisib ▪ Dronedarone ▪ Erythromycin ▪ Fedratinib ▪ Fluconazole ▪ Fosamprenavir ▪ Fosaprepitant* ▪ Fosnetupitant-palonosetron ▪ Grapefruit juice ▪ Imatinib ▪ Isavuconazole (isavuconazonium sulfate) ▪ Lefamulin ▪ Letermovir ▪ Netupitant ▪ Nilotinib ▪ Ribociclib ▪ Schisandra ▪ Verapamil	▪ Apalutamide ▪ Carbamazepine ▪ Enzalutamide ▪ Fosphenytoin ▪ Lumacaftor ▪ Lumacaftor-ivacaftor ▪ Mitotane ▪ Phenobarbital ▪ Phenytoin ▪ Primidone ▪ Rifampin (rifampicin)	▪ Bexarotene ▪ Bosentan ▪ Cenobamate ▪ Dabrafenib ▪ Dexamethasone¶ ▪ Dipyrone ▪ Efavirenz ▪ Elagolix, estradiol, and norethindrone therapy pack$^{\Delta}$ ▪ Eslicarbazepine ▪ Etravirine ▪ Lorlatinib ▪ Mitapivat ▪ Modafinil ▪ Nafcillin ▪ Pexidartinib ▪ Rifabutin ▪ Rifapentine ▪ Sotorasib ▪ St. John's wort

- For drug interaction purposes, the inhibitors and inducers of CYP3A metabolism listed above can alter serum concentrations of drugs that are dependent upon the CYP3A subfamily of liver enzymes, including CYP3A4, for elimination or activation.
- These classifications are based upon US Food and Drug Administration (FDA) guidance.[1,2] Other sources may use a different classification system resulting in some agents being

classified differently.

- Data are for systemic drug forms. Degree of inhibition or induction may be altered by dose, method, and timing of administration.
- Weak inhibitors and inducers are not listed in this table with exception of a few examples. Clinically significant interactions can occasionally occur due to weak inhibitors and inducers (eg, target drug is highly dependent on CYP3A4 metabolism and has a narrow therapeutic index). Accordingly, specific interactions should be checked using a drug interaction program such as the Lexicomp drug interactions program included within UpToDate.
- Refer to UpToDate topics on specific agents and indications for further details.

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* Classified as a weak inhibitor of CYP3A4 according to FDA system.[1]

¶ Classified as a weak inducer of CYP3A4 according to FDA system.[1]

Δ The fixed-dose combination therapy pack taken in the approved regimen has moderate CYP3A4 induction effects. When elagolix is used as a single agent, it is a weak CYP3A4 inducer. Norethindrone and estradiol are not CYP3A4 inducers.

References:

1. *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry (January 2020) available at: http://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-drug-interaction-studies-cytochrome-p450-enzyme-and-transporter-mediated-drug-interactions.*
2. *US Food & Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Available at: FDA.gov website.*

Graphic 76992 Version 86.0

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