药物不良反应
Adverse Drug Reactions

基于美国 FAERS 数据库的药源性伪膜性结肠炎不良事件风险信号挖掘

Risk signal mining of adverse events in drug – induced pseudomembranous colitis based on the US FAERS database

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摘要:目的 基于美国食品药品监督管理局(FDA)不良事件报告系统(FAERS)数据库,挖掘与伪膜性结肠炎(PMC)相关的药品,为临床安全用药提供参考。**方法** 提取 FAERS 数据库 2004 年第 1 季度至 2024 年第 4 季度数据中药源性 PMC 不良事件(AEs)报告,通过报告比值比(ROR)法和比例报告比值比(PRR)法筛选符合风险信号检测的药品,对报告数量前 20 位及信号值前 20 位药品进行分析。**结果** 获取 18 356 例与药源性 PMC 有关数据,筛选出风险信号药品 485 种。女性比例最高,占 52.09%(9 562 例/18 356 例),>60 岁患者数量最多,占 36.88%(6 769 例/18 356 例),药物相关诊断中,克罗恩病占 5.67%(1 040 例/18 356 例)、溃疡性结肠炎占 5.53%(1 016 例/18 356 例),病例数较多,患者转归中住院治疗或住院时间延长比例最高,占 50.43%(9 257 例/18 356 例)。报告数量前 20 位的药品中英夫利西单抗报告数量最多,按照解剖学治疗学及化学(ATC)分类,抗肿瘤药和免疫机能调节药及系统用抗感染药数量较多,各占 30%(6 种/20 种),其中维得利珠单抗在说明书中未提及 PMC。ROR 值信号强度排序前 20 位药品中,系统用抗感染药物占 60%(12 种/20 种),比例最高,颠茄在说明书中未提及 PMC。**结论** 多种药品可发生 PMC,临床需关注,及时进行检查、停用相关药物并治疗,保障用药安全。

关键词:药源性伪膜性结肠炎;美国食品药品监督管理局不良事件报告系统;数据挖掘;比例失衡法

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Abstract: Objective Based on the adverse event reporting system (FAERS) database of the US Food and Drug Administration (FDA), drugs related to pseudomembranous colitis (PMC) were identified to provide a reference for clinical safe medication. **Methods** Extract the reports of drug – related adverse events (AEs) of PMC from the FAERS database for the period from the first quarter of 2004 to the fourth quarter of 2024. Risk signal detection was performed using the reporting odds ratio (ROR) and proportional reporting ratio (PRR) methods. Analysis was conducted on the top 20 drugs in terms of the number of reports and the top 20 drugs in terms of signal values. **Results** A total of 18 356 cases of drug induced PMC were retrieved, and 485 drugs with positive risk signals were identified. The proportion of females was the highest, accounting for 52.09% (9 562 cases/18 356 cases). The number of patients over 60 years old was the largest, accounting for 36.88%

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(6 769 cases/18 356 cases). Among drug-related diagnoses, Crohn's disease accounted for 5.67% (1 040 cases/18 356 cases) and ulcerative colitis for 5.53% (1 016 cases/18 356 cases), with a larger number of cases. Among the patient outcomes, the hospitalization - initial or prolonged rate was the highest, accounting for 50.43% (9 257 cases/18 356 cases). Among the top 20 drugs by number of reports, infliximab ranked first. According to the ATC classification, antineoplastic and immunomodulating agents and anti-infectives for systemic use were the most numerous, each accounting for 30% (6 varieties/20 varieties), among which vedolizumab was not mentioned PMC in the label. In the top 20 drugs ranked by ROR signal intensity, anti-infective drugs accounted for the highest proportion of 60% (12 varieties/20 varieties), and belladonna was not mentioned in relation to PMC in the label. **Conclusion** A variety of drugs can cause PMC. Clinicians should remain vigilant, promptly perform diagnostic evaluations, discontinue the offending drugs, and initiate appropriate treatment to ensure medication safety.

Key words: drug-induced pseudomembranous colitis; US Food and Drug Administration adverse event reporting system; data mining; disproportionality analysis

伪膜性结肠炎(pseudomembranous colitis,PMC)是由细菌、病毒、寄生虫、血管损伤、化学物质、药物等引起的结肠内炎症性疾病,内窥镜可见结肠假膜的典型特征[1]。临床症状轻重不同,常见腹痛、恶心、带血腹泻、发热、心动过速、低血压,可发生严重并发症:全身炎症反应综合征、败血症、肠麻痹、中毒性巨结肠、结肠穿孔伴腹膜炎和感染性休克伴器官衰竭,甚至诱发死亡[2-3]。药物诱发 PMC 是个不可忽略的因素,抗生素、免疫检查点抑制剂、质子泵抑制剂等均有诱发 PMC 的报道[4-6]。目前对于药源性 PMC 只有个案或一类药物报道,没有全面性的汇总分析。美国食品药品监督管理局不良事件报告系统(U.S. Food and Drug Administration adverse event reporting system,FAERS)是药物警戒常用数据库,包括 FDA 收到的所有上市后药物、生物制剂及其他药品的不良事件(adverse event,AE)[7],本研究采用 FAERS 数据库,挖掘与 PMC 发生相关的药物,为临床用药提供参考。

资料与方法

1 数据来源

FAERS 数据库包括医疗保健人员、患者、制造商及其他人员上报的药物相关 AE 或用药错误信息,每季度更新一次并向公众开放,因信息复杂,需要识别并清理以保证数据的可用性[8]。Open Vigil 2.1 软件具有对 FAERS 数据进行清理、验证和处理的功能,且符合 FDA 的调查标准[9],因此本研究采用此软件获取 2004 年第 1 季度至 2024 年第 4 季度数据,收集与药源性 PMC 相关的可疑药物、病例识别号、报告日期、患者结局、性别、年龄、报告国家或地区等相关信息。

2 数据处理

用《国际医学用语词典》[10](medical dictionary for regulatory activities,MedDRA)作为词典,查询狭义标准 MedDRA 查询(standardised MedDRA queries,SMQ)术语,术语集定义为"pseudomembranous colitis"(编码为 20000080),选择"首要怀疑的药物",收集药源性 PMC 相关 AE 报告。删除重复及报告不完整信息,对于病历号(case report number,Case ID)相同的,选择最新报告日期数据。因 FAERS 数据库提取的药品名称包括原研药、仿制药、通用名、商品名等多种形式,使用 DrugBank 数据库(https://go.drugbank.com)进行药品通用名称标准化,删除 DrugBank 不能准确识别的数据[11],将相同通用名称的药品进行合并。为减少混杂因素影响,排除用于治疗 PMC 的甲硝唑、万古霉素、非达霉素、贝洛托单抗、粪便菌群[12],并对药品进行解剖学治疗学及化学(anatomical therapeutic chemical,ATC)法分类[13]。

3 数据分析[14]

对于获得的数据进行描述性分析,用百分比的形式表述数据基本信息特征。用基于比例失衡测量法四格表的报告比值比(reporting odds ratio,ROR)法和比例报告比值比(proportional reporting ratio,PRR)法进行风险信号检测,见表 1 和表 2。

表 1 比例失衡测量法四格表

Table 1 Four-fold table of disproportionality analysis method

Item	Target adverse events	Other adverse events	Total
Target drugs	a	b	a+b
Other drugs	c	d	c+d
Total	a+c	b+d	a+b+c+d

表 2 报告比值比法(ROR)和比例报告比值比法(PRR)计算公式及信号检测标准

Table 2 Equations and criteria of reporting odds ratio(ROR) and proportional reporting ratio(PRR)

Algorithms	Equation	Criteria
ROR	$ROR = (a/c) \div (b/d)$	$a \geqslant 3$,
	$95\%\ CI = e^{1n}(ROR) \pm 1.96\sqrt{1/a + 1/b + 1/c + 1/d}$	lower limit of 95% CI > 1
PRR	$PRR = [a/(a+b)] \div [c/(c+d)]$	$a \geqslant 3$, $PRR \geqslant 2$, $\chi^2 \geqslant 4$
	$\chi^2 = \frac{(\lvert ad - bc \rvert - n/2)^2 n}{(a+b)(a+c)(c+d)(b+d)}$	

结 果

1 描述性分析

通过 Open Vigil 2.1 软件收集 18 356 例与 PMC 有关报告。首次报告为 2004 年 239 例,2004 年至今报告呈现递增趋势,2024 年达到最高 2 475 例。女性比例最高,占 52.09%(9 562 例/18 356 例),>60 岁患者数量最多,占 36.88%(6 769 例/18 356 例),药物相关诊断中,克罗恩病占 5.67%(1 040 例/18 356 例)、溃疡性结肠炎占 5.53%(1 016 例/18 356 例),病例数较多。17 576 例患者报告转归情况,其中住院治疗或住院时间延长比例最高,占 50.43%(9 257 例/18 356 例),死亡报告占 13.09%(2 402 例/18 356 例)。报告国家或地区中美国数量最多,占 54.82%(10 062 例/18 356 例),见表 3。

2 比例失衡分析

通过 ROR 法及 PRR 法进行风险信号检测,获得同时满足两种方法的药物 485 种。

按照报告数量排序,前 20 位药品中英夫利西单抗报告数量最多,其次是泼尼松、泮托拉唑、阿莫西林、地塞米松。按照 ATC 分类,药品数量最多的是抗肿瘤药和免疫机能调节药及系统用抗感染药物,各占 30%(6 种/20 种),其它依次是消化道及代谢药占 15%(3 种/20 种),非性激素和胰岛素的激素类系统药占 10%(2 种/20 种),肌肉-骨骼系统、心血管系统、其它各占 5%(1 种/20 种)。其中维得利珠单抗在说明书中未提及 PMC。

按照 ROR 信号值排序(PRR 值排序一致),值越大说明与 PMC 相关性越高,前 20 位药品中系统用抗感染药物占 60%(12 种/20 种),比例最高。颠茄在说明书中未提及 PMC,见表 4。

导致患者死亡及住院治疗或住院时间延长的前五种药品,见表 5。导致死亡最多的药品是环丙沙星,住院治疗或住院时间延长最多的药品是英夫利西单抗,两种结局均包括环丙沙星和来那度胺,11 种药品中(含并列)除阿达木单抗,均呈现积极的风险信号。

表 3 药源性伪膜性结肠炎患者基本信息(n = 18 356)

Table 3 Clinical characteristics of reported drug-induced pseudomembranous colitis (n = 18 356)

Item	n	Percentage
Gender		
Female	9 562	52.09%
Male	6 753	36.79%
Missing	2 041	11.12%
Age		
<18	926	5.04%
18-40	1 823	9.93%
41-60	3 478	18.95%
>60	6 769	36.88%
Missing	5 360	29.20%
Indication (Top 5)		
Crohn's disease	1 040	5.67%
Colitis ulcerative	1 016	5.53%
Plasma cell myeloma	809	4.41%
Multiple sclerosis	671	3.66%
Rheumatoid arthritis	518	2.82%
Report to the state/country (Top 5)		
America	10 062	54.82%
Canada	2 739	14.92%
Britain	859	4.68%
France	582	3.17%
Germany	573	3.12%
Adverse drug outcome		
Death	2 402	13.09%
Life-threatening	798	4.35%
Disability	287	1.56%
Hospitalization-initial or prolonged	9 257	50.43%
Required intervention to prevent	37	0.20%
Other	4 795	26.12%

表 4 药源性伪膜性结肠炎 ROR 值前 20 位的不良事件风险信号

Table 4 The top 20 risk signals of drug – induced pseudomembranous colitis adverse events according to the ROR intensity

Drug	Case Count	ROR (95% CI)	PRR(χ2)	ATC classification
Carbenicillin	3	340.35(85.11,1 360.99)	227.23(469.03)	Anti – infectives for systemic use
Cefditoren	123	93.39(77.32,112.81)	82.31(9 750.18)	Anti – infectives for systemic use
Amdinocillin	9	90.12(44.96,180.64)	79.70(623.57)	Anti – infectives for systemic use
Pivmecillinam	11	54.68(29.58,101.07)	50.69(487.68)	Anti – infectives for systemic use
Piperacillin – tazobactam	82	44.94(35.92,56.22)	42.23(3 250.58)	Anti – infectives for systemic use
Brivudine	8	40.05(19.63,81.72)	37.88(251.83)	Anti – infectives for systemic use
Flomoxef	3	39.27(12.26,125.76)	37.18(72.64)	Anti – infectives for systemic use
Cefotiam	5	35.46(14.43,87.14)	33.75(127.99)	Anti – infectives for systemic use
Netilmicin	5	34.73(14.14,85.32)	33.10(125.34)	Anti – infectives for systemic use
Ertapenem	221	31.15(27.20,35.67)	29.84(6 070.48)	Anti – infectives for systemic use
Cefazolin	231	26.90(23.57,30.70)	25.92(5 452.58)	Anti – infectives for systemic use
Cefixime	77	25.29(20.14,31.76)	24.42(1 702.19)	Anti – infectives for systemic use
Rethymic	4	151.27(51.19,447.02)	123.95(373.10)	Various
Dexrazoxane	176	100.72(85.93,118.06)	87.97(14 931.08)	Various
Belladonna *	3	70.42(21.45,231.18)	63.91(128.36)	Various
Saccharomyces cerevisiae	31	31.68(22.09,45.43)	30.32(849.69)	Various
Nifuroxazide	26	466.29(283.09,768.05)	277.27(6 884.27)	Alimentary tract and metabolism
Itopride	25	132.07(86.04,202.72)	110.79(2 611.73)	Alimentary tract and metabolism
Rasburicase	137	73.07(61.23,87.19)	66.13(8 673.49)	Musculo – skeletal system
Amsacrine	9	25.01(12.86,48.65)	24.16(177.51)	Antineoplastic and immunomodulating agents

* Indicates new signals not mentioned in the label

表 5 导致死亡及住院治疗或住院时间延长的前 5 种药品

Table 5 Top 5 drug with outcomes of death or hospitalization – initial or prolonged

No.	Death			Hospitalization – Initial or Prolonged		
	Drug	*n*	Percentage	Drug	*n*	Percentage
1	Ciprofloxacin	80	3.33%	Infliximab	354	3.82%
2	Tacrolimus	59	2.46%	Adalimumab	316	3.41%
3	Lenalidomide	57	2.37%	Lenalidomide	311	3.36%
4	Mycophenolate mofetil	41	1.71%	Ciprofloxacin	242	2.61%
5	Dexamethasone	39	1.62%	Vedolizumab	233	2.52%
	Rituximab	39	1.62%			

讨　论

本研究通过 FAERS 数据库收集发生 PMC 的主要可疑药物，患者中女性较多，与之前报道一致[15]，可能与女性更多的使用药物有关。> 60 岁患者占 36.88%(6 769 例/18 356)，95% ~ 100% 的 PMC 由 CDI 引起[16]，我国一项关于东部地区的研究表明，≥55 岁是 CDI 的危险因素[17]，提示老年人易发生 PMC。克罗恩病与溃疡性结肠炎是药物相关诊断中最高的两种疾病，属于炎症性肠病(inflammatory bowel disease，IBD)，患有 IBD 患者发生 CDI 的风险是未患 IBD 患者的 4.8 倍，均有腹痛、腹泻、疲劳等典型临床症状[18]，而 PMC 导致的腹泻易被忽略，一项回顾性分析显示，PMC 的首诊误诊和漏诊率高达 66.67%[15]，提示临床需关注 PMC，及时进行检查、停用相关药物并治疗。

本研究报告数量前 20 位的药品中，涉及免疫抑

制剂5种,免疫抑制剂广泛应用于抗肿瘤、抗风湿、银屑病等各个领域,随着使用的增多,AE报告也增多,免疫抑制剂诱发的PMC可能与其对免疫系统的破坏,增加CDI风险有关[19]。英夫利西单抗是报告数量最多的药品,属于人-鼠嵌合单克隆抗体,可抑制肿瘤坏死因子-α,用于治疗克罗恩病、溃疡性结肠炎、类风湿关节炎等,具有诱发严重感染的风险[20]。在一项对英夫利西单抗进行的回顾性研究中,CDI发生率为2.11%[21],RAZIK等[22]研究发现,英夫利西单抗与复发性CDI风险升高有关,机制可能是英夫利西单抗的免疫抑制作用,也可能是药品使用无效后IBD的疾病进展。维得利珠单抗说明书未提及PMC,研究表明其具有诱发CDI的风险[23],维得利珠单抗通过抑制α4β7整合素而降低特定免疫细胞活性而发挥减轻炎症的作用,发挥抑制作用的同时可能会影响肠道内免疫细胞的分布及功能,破坏肠道黏膜屏障完整性,增加机会性感染,从而诱发PMC[24]。

本研究信号强度前20位药品主要为系统用抗感染药物,不规范和长期使用广谱抗生素是导致PMC发病率上升的原因,部分患者使用广谱抗生素后破坏肠道内菌群平衡,造成艰难梭菌(Clostridium difficile,CD)快速繁殖并产生肠毒素A、细胞毒素B,破坏结肠黏膜天然屏障,导致内皮损伤及上皮坏死,诱发结肠炎症,发生腹泻、出血、PMC等[15],目前认为导致CDI风险较高的抗生素包括第三代头孢菌素、氟喹诺酮、克林霉素以及青霉素类药物[19]。本研究中氟喹诺酮类药物环丙沙星是导致患者死亡及住院病例数较高的药品,体外研究发现,环丙沙星会破坏结肠上皮细胞粘膜屏障,导致免疫功能丧失,增加CDI风险[25]。

FAERS数据库常用于监测和评估药物安全性[26],因用自发报告模式,存在错报、漏报、识别错误等情况,具有一定局限性,本研究采用歧化分析,对AE识别具有一定敏感性,可提示增加PMC风险的药物,对于因果关系的确定需进一步临床试验加以验证。

本研究基于FAERS数据库进行的药源性PMC风险信号挖掘提示:女性、>60岁、患有IBD是高发因素,抗肿瘤药和免疫机能调节药诱发PMC数量较多,系统用抗感染药物诱发PMC数量较多且风险信号较强,环丙沙星、来那度胺导致数量较多的严重临床结局,维得利珠单抗和颠茄说明书中未提及PMC,需警惕。

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·科学文摘·

从靶点筛选到化合物鉴定的 AI 指导抗生素研发流程

引自:SCHUH M G, HESSE J, SIEBER S A. AI – guided antibiotic discovery pipeline from target selection to compound identification [EB/OL]. 2025 – 04 – 15[2026 – 04 – 30]. https://doi.org/10.48550/arXiv.2504.11091.

抗生素耐药已成为全球性公共卫生危机,亟需针对全新细菌机制的治疗策略。蛋白质结构预测与机器学习分子生成技术为加速药物研发提供可能,但相关模型选择与流程整合的实用指导仍不足。本研究建立端到端人工智能(AI)指导抗生素研发全流程,覆盖靶点识别至化合物确定环节:基于多病原体预测蛋白质组的结构聚类,筛选保守、必需且非人源同源的靶点;系统评估扩散、自回归、图神经网络、语言模型共 6 种主流三维结构感知生成模型的可用性、化学有效性与生物学相关性;经严格后处理筛选与商业类似物检索,将 10 万余种生成化合物精简为可合成的核心集合。结果显示深度学习分子砌块生成模型与靶点感知分子生成模型的综合表现最优,同时明确模型复杂度、易用性与输出质量间的关键权衡。本研究为早期抗生素研发中 AI 的落地应用提供对比基准与实施蓝图。