·指南与共识·

小肠克罗恩病的内镜诊治共识(2024,上海)

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【摘要】 小肠克罗恩病是好发于小肠的多发溃疡性病变,容易导致肠道梗阻、狭窄及出血。随着胶囊内镜及气囊辅助式小肠镜等技术的临床推广应用,小肠克罗恩病的发现较前明显增多,但小肠克罗恩病的治疗依然是困扰临床的难题。如何规范小肠克罗恩病的诊治流程并优化诊治策略,进一步提高诊治效率具有重要现实意义,有必要制定小肠克罗恩病的内镜诊治专家共识。本共识基于循证医学依据及专家经验,聚焦小肠克罗恩病的流行病学、内镜及影像学诊断、小肠镜治疗、药物治疗及随访等临床问题,形成相关推荐意见,以便规范小肠克罗恩病诊治流程,改善患者预后。

【关键词】 小肠; 克罗恩病; 胶囊内镜; 双气囊小肠镜; 诊断与治疗
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Consensus on the endoscopic diagnosis and treatment for small bowel Crohn´s disease (2024, Shanghai)

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【Abstract】 Small bowel Crohn's disease (CD) is a multi-ulcerative lesion that tends to occur in the small intestine, which leads to intestinal obstruction, stricture, and bleeding easily. With the clinical application of capsule endoscopy and balloon-assisted enteroscopy, the detection of small bowel CD has increased significantly, however, the treatment of the small bowel CD is still a difficult issue which troubles clinical practice. It is of great practical significance to standardize the diagnosis and treatment process, optimize the diagnosis and treatment strategy of the small bowel CD, and further improve the diagnosis and treatment efficiency. It is necessary to formulate an expert consensus on the endoscopic diagnosis and treatment of the small bowel CD. Based on evidence-based medicine and expert experience, the consensus focuses on clinical issues including the epidemiology, endoscopic and imaging diagnosis, enteroscopy treatment, drug treatment and follow-up of the small bowel CD, and formulates relevant recommendations, so as to standardize the diagnosis and treatment process of the small bowel CD and improve the prognosis of patients.

【Key words】 Intestine, small; Crohn's disease; Capsule endoscopy; Double balloon enteroscopy; Diagnosis and treatment
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克罗恩病是一类与免疫异常相关的非特异性慢性肠道炎性疾病,属于炎症性肠病(inflammatory bowel disease, IBD),通常按照发病部位可分为结肠型克罗恩病、回肠-结肠型克罗恩病、回肠末端型克罗恩病、上消化道克罗恩病。其中,有30%左右的克罗恩病仅累及小肠[1-2],而回肠末端型克罗恩病病变仅位于回肠末端,未能充分反映出小肠克罗恩病的临床特点,有必要单独列出一型小肠克罗恩病。小肠克罗恩病仅累及小肠,可包括回肠、空肠或泛小肠型克罗恩病,其在发病机制、临床表现、内镜诊治和药物治疗反应方面有其特殊性,需要对该类型克罗恩病的诊断和治疗加以重视。回肠-结肠型克罗恩病也可累及小肠,部分临床表现近似于小肠克罗恩病,伴有结肠克罗恩病的特点。随着胶囊内镜和气囊辅助式小肠镜(balloon-assisted enteroscopy,BAE)技术临床应用的普及,越来越多的小肠克罗恩病被确诊,对药物治疗和内镜治疗的临床需求日益增多,有必要针对小肠克罗恩病单独制定相关共识,以指导临床实践。本共识联合国内

IBD、小肠内镜、胶囊内镜以及外科领域相关专家,共同针对小肠克罗恩病的诊治要点进行汇总分析,按照Delphi法提出临床问题,通过"推荐等级的评估、制定与评价(the grading of recommendations assessment, development and evaluation, GRADE)系统"对循证医学证据进行分级评价,最终共提出16个临床问题,获得24条陈述意见和建议,并经定稿、投票,有望为小肠克罗恩病的临床诊治提供指导。

一、共识制定方法

共识的制定采用国际通用的Delphi法。共识起草小组通过系统性文献检索制定共识草案。共识草案由专家委员会讨论与修改,进行投票,最终达成共识。临床证据质量评估采用GRADE系统,分为高、中、低、极低。投票意见的推荐等级分为A~D 4级(A为完全赞成;B为部分赞成,推荐;C为视情况而定;D为不赞成),共识水平(达到A级、B级的意见)>90%的陈述意见加入共识中,达不到上述标准的陈述意见放弃。

二、临床问题及陈述意见

临床问题1:小肠克罗恩病的发病率及流行病学现状如何?

【陈述意见1】小肠克罗恩病的年发病率为0.11/10万~0.12/10万,单纯累及小肠的克罗恩病患者约占总体克罗恩病患者的30%,同时累及小肠和结肠的克罗恩病患者约占总体克罗恩病患者的40%。(证据质量/推荐等级:高/A;共识水平:100.0%)

目前尚无关于小肠克罗恩病的准确流行病学数据,一般认为克罗恩病患者中约有70%累及小肠,包括约1/3以上的克罗恩病为单纯小肠受累[1-2],均为小肠克罗恩病定义范畴。亚太地区大型流行病学研究显示,我国各地区克罗恩病的平均年发病率为0.36(95%*CI*:0.28~0.46)/10万[3]。一项Meta分析综述47篇中国人群克罗恩病流行病学数据,结果显示克罗恩病的发病率为0.40(95%*CI*:0.23~0.57)/10万[4]。根据克罗恩病整体流行病学数据推测,小肠克罗恩病的年发病率为0.11/10万~0.12/10万。

我国不同地区的克罗恩病发病率变化与人口密度相关,呈南北梯度和东西梯度差异,南部和东部地区发病率较高[3,5]。中国北方地区IBD发病率的调查显示,克罗恩病粗发病率为0.15(95%*CI*:0.02~0.54)/10万,年龄标准化发病率为0.13(95%*CI*:0.02~0.47)/10万[6]。一项前瞻性基于人群的IBD发病率研究覆盖武汉中部17家医疗机构2010年全年数据结果显示,克罗恩病的粗发病率为0.56(95%*CI*:0.37~0.75)/10万,年龄校正发病率为0.51(95%*CI*:0.33~0.68)/10万[7]。目前,我国克罗恩病发病率及患病率相较于欧美国家仍较低,但我国克罗恩病的发病率正快速上升[5]。

临床问题2:小肠克罗恩病的好发人群和遗传特征有哪些?

【陈述意见2】小肠克罗恩病好发于青壮年,该病具有一定的遗传易感性,但环境等外部因素仍是其发生的重要决定因素。(证据质量/推荐等级:高/A;共识水平:100.0%)

相较于结肠型克罗恩病患者,小肠克罗恩病患者发病年龄更轻,且基因图谱有所差异[8]。Bayless等[9]报道了同一家族内克罗恩病患者的肠道病变部位和临床类型的高度一致性,首个确定的克罗恩病遗传风险变异是*NOD2*基因,其与起病年龄早、病变位于回肠和纤维狭窄有关;*HLA-DRB1*01:03*也与克罗恩病小肠受累相关[10-14]。新近的一项研究表明,近端小肠受累为主的克罗恩病和结肠受累为主的克罗恩病患者的遗传学特征存在差异,该研究鉴定出97个基因相关的115个单核苷酸多态性在近端小肠受累为主的克罗恩病和结肠受累为主的克罗恩病之间存在显著差异,其中*EFNA3*基因可较好区分两种表型不同的克罗恩病,*EFNA3 rs17723260*在结肠受累为主的克罗恩病中的等位基因频率(4.5%)显著低于其在近端小肠受累为主的克罗恩病的频率(37.5%)[15]。加拿大一项研究表明,华人移民的克罗恩病标准化发病率为1.58/10万,远低于当地人群的10.6/10万[16],进一步说明遗传因素是克罗恩病发生的重要因素。肠道生态失调是克罗恩病的特征表现之一,大量研究表明饮食习惯是最有可能影响肠道微生物群的环境因素[17-18]。一项涉及21个国家及11 600例参与者的前瞻性研究结果表明摄入较多超加工食品与克罗恩病风险呈正相关[19]。地理差异在克罗恩病的发生中也具有重要作用,法国一项回顾性研究表明克罗恩病患病率的地理分布并不均匀,同时与高水平的社会资源匮乏和城市化相关[20]。

临床问题3:小肠克罗恩病的临床表现包含哪些特点?

【陈述意见3】小肠克罗恩病患者多有腹痛、腹泻及消瘦症状,可产生肠梗阻、穿孔、瘘管、出血、肛周病变等并发症,部分患者还存在皮肤、关节等肠外表现。(证据质量/推荐等级:高/A;共识水平:100.0%)

小肠克罗恩病起病隐匿,在疾病早期仅有多发阿弗他样溃疡,通常无明显临床表现。随着疾病进展、发展为肠道纵行溃疡及肠道透壁性炎症病变时可出现腹痛、腹泻、消化道出血。当疾病控制不佳、迁延反复发作时可出现并发症,诸如肠梗阻、肠瘘和腹腔脓肿。小肠溃疡病变症状隐匿,常因梗阻症状首诊,因此小肠克罗恩病在初诊时较结肠型克罗恩病更易合并肠腔狭窄和梗阻并发症[21]。

远端回肠炎的克罗恩病常表现为右下腹痛,近端小肠受累者则表现为脐周腹痛。小肠克罗恩病因肠道炎症、吸收不良等原因可表现为水样泻和脂肪泻,但由于小肠的代偿能力较强,腹泻症状可在很长一段时间内时轻时重。小肠克罗恩病的贫血症状通常与广泛肠道炎症病变导致的吸收不良和溃疡导致的慢性失血相关。偶见小肠克罗恩病以急性小肠大出血为首发表现,此时多为溃疡病变深大,累及肠壁黏膜下小血管所致。

此外,小肠克罗恩病还可有全身性表现和肛周病变。小肠克罗恩病全身性表现主要有体质量减轻、食欲减退、贫血和发热等。肛周病变,如肛周脓肿或肛瘘亦是小肠克罗恩病的常见表现,可先于肠道病变数年发生;肛周病变在小肠克

罗恩病病程中发生率相较于结肠型克罗恩病孰高孰低目前存在争议,回结肠均受累者肛周病变的发生率可能高于其他类型克罗恩病[22-26]。

临床问题4:小肠克罗恩病如何进行规范化诊断?

【陈述意见4】小肠克罗恩病诊断应结合病史、检验、影像学、胶囊内镜和(或)小肠镜检查等,以及内镜活检或手术标本病理进行综合判断。完整的小肠克罗恩病诊断应包括疾病分型、疾病活动程度及并发症。(证据质量/推荐等级:中/A;共识水平:100.0%)

小肠克罗恩病的诊断缺乏"金标准",需综合病史、检验、影像学、内镜及病理结果进行综合判断。对于根据病史、小肠影像学检查和(或)相关临床检验结果临床疑诊小肠克罗恩病者,可进行BAE检查。小肠镜直视检查有利于发现影像学检查阴性的克罗恩病早期病变,如小肠黏膜糜烂、浅溃疡性病变以及小肠纤维性膜状狭窄等。对于发现的可疑病变,可进行镜下活检,从而提高诊断率。同时,病史、小肠影像学检查及内镜检查结果是评估疾病病变范围、疾病行为、是否存在并发症的主要依据。临床表现及炎症指标不能客观反映小肠克罗恩病疾病活动度,小肠克罗恩病疾病活动度评价以影像学和内镜为主要依据,参考陈述意见6和陈述意见12。

目前小肠克罗恩病尚无独立的诊断标准,推荐参照世界胃肠病学组织(World Gastroenterology Organisation, WGO)提出的6条诊断依据进行诊断[27],符合非连续性或节段性病变、铺路石样或纵行溃疡和透壁性炎症者,加上裂沟、瘘管或肛周病变可确诊;符合非干酪性肉芽肿,加上非连续性或节段性病变、铺路石样或纵行溃疡和透壁性炎症者中三者之二可作为确诊依据。

克罗恩病的蒙特利尔疾病分型中包含了诊断年龄、疾病行为和疾病受累部位以及是否存在肛周病变[28]。随着小肠内镜及小肠影像学应用增多,越来越多深部小肠受累的克罗恩病被诊断,使小肠病变范围评估更加精准,同时并发症的评估更加全面,包括对狭窄性质及是否伴有梗阻的判断、是否存在肠瘘伴或不伴有腹腔炎性包块或脓肿、肛周病变。小肠克罗恩病的部位及疾病行为分型推荐在蒙特利尔分型基础上,参考巴黎分型(上消化道受累克罗恩病以屈氏韧带为界分为L4a和L4b亚型)进行具体定义(表1)[28],小肠克罗恩病包含L1及L4b型克罗恩病(图1)。

表1 小肠克罗恩病的临床分型

项目	分型	标准
诊断年龄(A)	A1	<17岁
	A2	17~40岁
	A3	>40岁
病变部位(L)	L1	回肠末端30 cm
	L2	结肠
	L3	回肠末端30 cm及结肠
	L4a	食管、胃及十二指肠(屈氏韧带以上消化道)
	L4b	空肠及回肠其余部分
疾病行为(B)	B1	非狭窄非穿透
	B2	狭窄
	B3	穿透
	P	肛周病变

临床问题5:小肠克罗恩病需与哪些小肠溃疡性疾病相鉴别?

【陈述意见5】小肠克罗恩病应与其他小肠受累的溃疡性疾病鉴别,包括肠结核、肠道淋巴瘤、慢性缺血性小肠炎、非甾体抗炎药相关性小肠炎、贝赫切特综合征、隐源性多灶性溃疡性狭窄性小肠炎(cryptogenetic multifocal ulcerous stenosing enteritis, CMUSE)等。(证据质量/推荐等级:高/A;共识水平:100.0%)

小肠受累的溃疡性疾病较多,小肠克罗恩病诊断时应鉴别感染性疾病、肿瘤性疾病及其他炎性小肠疾病。常见感染性疾病包括肠结核;肿瘤性疾病包括小肠淋巴瘤;炎性疾病包括慢性缺血性小肠炎、非甾体抗炎药相关性小肠炎、贝赫切特综合征、CMUSE、非特异性溃疡等。国内一项小肠克罗恩病与其他小肠溃疡病变鉴别模型研究显示,青壮年起病、腹痛、小肠跳跃性病变、纵行溃疡等表现支持小肠克罗恩病诊断[29]。

肠结核和小肠克罗恩病的鉴别较为困难,肠结核的特点为结核中毒症状、内镜下环形溃疡及回盲瓣固定开放、组织学表现为干酪性、融合的大肉芽肿、结核病原学阳性、影像学可见腹腔感染性淋巴结,其中后3者对肠结核具有确诊意义,但其灵敏度较低。多项研究基于克罗恩病与回盲部肠结核(ileocecal intestinal tuberculosis, ITB)的特征建立了鉴别

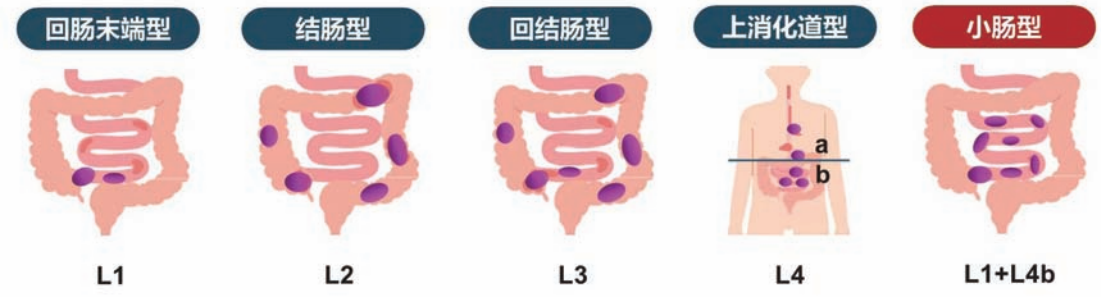


图1 克罗恩病的部位分型(参考蒙特利尔/巴黎分型,小肠克罗恩病为L1+L4b)

诊断模型。一项荟萃分析纳入2 117例克罗恩病和1 589例ITB构建了鉴别ITB和克罗恩病的贝叶斯模型,其诊断ITB的灵敏度、特异度和准确率分别为90.9%、92.6%和91.8%。该模型中支持诊断克罗恩病的因素包括(1)男性、便血、肛周疾病、肠梗阻和肠外表现;(2)内镜纵向溃疡、鹅卵石样外观、管腔狭窄、黏膜桥和直肠受累;(3)病理局部增强型肠炎;(4)影像肠壁不对称增厚、肠壁分层、梳状征和纤维脂肪增生。模型中支持ITB的因素包括(1)发热、盗汗、肺部受累和腹水;(2)内镜下环形溃疡、回盲瓣扩张和盲肠受累;(3)病理融合性或黏膜下肉芽肿;(4)小肠电子计算机断层扫描成像(computed tomography enterography, CTE)显示短节段受累、γ-干扰素释放试验阳性[30]。鉴于误诊为小肠克罗恩病的肠结核采用免疫抑制治疗后可能导致结核播散的严重不良后果,使用上述模型诊断克罗恩病概率低于90%时,推荐先行诊断性抗结核治疗。目前尚无单独针对小肠结核和克罗恩病鉴别诊断的模型,约20%克罗恩病患者在诊断性抗结核治疗失败后转而诊断为克罗恩病,这导致了部分小肠克罗恩病诊断延迟及治疗延误[31-32]。此外,多数狭窄性肠结核在诊断性抗结核治疗后狭窄无法缓解或恢复,外科手术肠段切除可作为明确诊断和解除狭窄的有效方法[33]。

小肠原发淋巴瘤约有10%表现为多灶病变,尤其一些惰性淋巴瘤可类似克罗恩病纵行溃疡表现,两者在影像学及内镜下表现鉴别困难[34-35],组织病理证据是鉴别诊断的关键[36]。

慢性缺血性小肠炎在小肠镜检查中并非罕见,表现为地图状、条带状及环形溃疡和(或)形成环形疤痕或纵行疤痕样狭窄,与克罗恩病鉴别存在一定的困难,传统的诊断标准为以下3条符合(1)或(2)+(3):(1)内镜活检标本或切除肠段的组织病理学结果与缺血性肠炎相符;(2)临床上和影像学的病情演变提示缺血性肠炎;(3)排除其他已知疾病,如克罗恩病、感染性疾病如肠结核、非甾体抗炎药相关溃疡、慢性非特异性小肠多发溃疡、放射性肠炎或恶性肿瘤[37]。

CMUSE临床表现可为腹痛、黑便、贫血或反复发作的不完全性肠梗阻,内镜和影像学表现为小肠多发环形溃疡伴狭窄,呈多灶性表现,患者易并发肠梗阻或胶囊内镜滞留,仅部分患者对激素治疗存在应答,免疫抑制剂及生物制剂治疗效果尚不明确[38]。

临床问题6:小肠克罗恩病的影像学检查方法包括哪些?

【陈述意见6】推荐CTE和磁共振小肠成像(magnetic resonance enterography, MRE)均可作为小肠克罗恩病患者的一线检查方法,有小肠梗阻症状者应首选CTE和(或)MRE检查。(证据质量/推荐等级:高/A; 共识水平:100.0%)

疑诊为小肠克罗恩病的患者,可选择小肠影像学检查,如CTE或MRE作为一线检查方法;CTE或MRE可观察到小肠克罗恩病的病变部位、范围,同时可评估是否存在狭窄、肠内外瘘等并发症。小肠克罗恩病在小肠影像学中的表现主要包括小肠的节段性肠壁增厚、肠黏膜强化伴肠壁分层改变、肠系膜血管增多伴扩张扭曲(梳样征)。在诊断小肠克罗恩病方面,MRE和内镜检查准确率几乎相当,并且因其无创性、无辐射性的优势而更易被患者接受[39]。相较于MRE,CTE的空间分辨率更高,放射学医师阅片一致性更高,耗时短,对设备要求比MRE低,因此国内开展CTE检查的单位多于MRE。研究表明CTE和MRE在检测小肠克罗恩病活动度及肠道并发症的灵敏度和特异度相似[40]。在评估肠道狭窄方面,胶囊内镜可能在检查过程中存在滞留风险,而BAE仅能对内镜可及的肠壁黏膜组织进行活检,对小肠狭窄病变远端的炎症和纤维化评估不完整。CTE和(或)MRE可对肠壁进行全层评估,从而克服上述小肠镜的各种局限性[41]。

在评价小肠克罗恩病对治疗的应答方面,国际炎症性肠病研究组织(the international organization for the study of IBD, IOIBD)发布的2021年版炎症性肠病治疗目标选择Ⅱ(selecting therapeutic targets in inflammatory bowel disease Ⅱ, STRIDE-Ⅱ)共识将"透壁愈合"作为未来更高要求的克罗恩病愈合标准[42],CTE、MRE均可以直观了解小肠克罗恩病患者全层肠壁的病变情况(图2A,2B),可用于透壁愈合的评估[43-44]。CTE诊断透壁愈合的定义是肠壁厚度≤3 mm以及其他正常影像学表现,即壁层信号正常、无壁层过度强化、无肠周浸润或穿透性并发症(未见肠道狭窄、脓肿、瘘管、窦道、肠周炎症、狭窄、纤维脂肪增生、靶征、梳状征、淋巴结长径超过1 cm、腹腔游离液体);MRE诊断透壁愈合的定义是磁共振活动指数(magnetic resonance index of activity, MaRiA)评分<7分。具体评分计算方法如下(其中肠壁厚度以mm为单位,有水肿或有溃疡分别计为1,无则计为0):MaRiA评分=1.5×肠壁厚度+0.02×相关对比度增强(即增强前后肠壁信号变化率)+5×水肿(有/无)+10×溃疡(有/无)[45]。

【陈述意见7】经腹肠道超声有助于小肠克罗恩病及其并发症的诊断,以及疾病活动性的评估。(证据质量/推荐等级:高/A; 共识水平:96.4%)

IBD肠道超声通常指经腹肠道超声,广义上还包括小肠对比超声成像(small intestinal contrast ultrasound, SICUS)、经直肠超声、经会阴超声和内镜超声(endoscopic ultrasound, EUS)等。肠道超声因其操作简便、无辐射、实时动态观察等优点成为IBD长期随访的理想检查手段(图2C,2D)。肠道超声诊断IBD的病变灵敏度和特异度分别为85%和91%,对IBD肠道或腹腔并发症的诊断准确率高于80%[46];对小肠病变的活动性判断灵敏度和特异度分别为90%和77%[47]。近期已发布的我国IBD肠道超声检查及报告规范专家指导意见及国际共识具有参考价值[48-49]。

SICUS在患者检查前口服助显剂,加大肠腔内外结构的对比,有利于肠道超声对肠道病变的观察,可用于小肠克罗恩病的诊断。既往Meta分析显示,SICUS对小肠克罗恩病的诊断灵敏度和特异度分别达到88%~95%和77%~86%[50-51]。SICUS对小肠克罗恩病相关并发症如腹腔脓肿的诊断灵敏度及特异度分别达到100%和90%;对肠道狭窄的诊断灵敏度和特异度分别为78%和96%;对于瘘管诊断的灵敏度和特异度分别为77%和92%[51]。

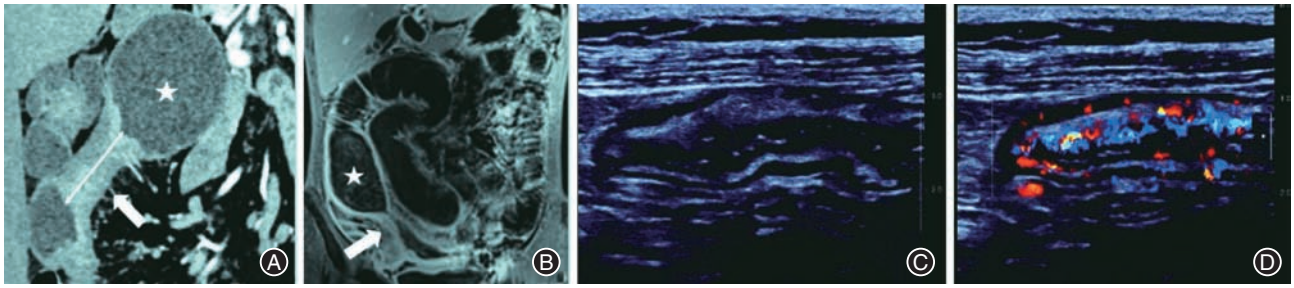


图2 活动期小肠克罗恩病的典型影像学表现 A:小肠电子计算机断层扫描成像示小肠肠壁增厚强化并肠腔狭窄(箭头所示),近端肠腔扩张(星号所示);B:磁共振小肠成像示小肠肠壁增厚、肠腔狭窄(箭头所示),近端肠腔扩张(星号所示);C:经腹肠道超声示回肠肠壁增厚5 mm;D:经腹肠道超声示彩色多普勒血流信号Limberg Ⅳ级

EUS不同于其他肠道超声检查,超声探头位于肠腔内,可由内至外观察肠壁各层结构。小肠EUS可避免腹腔脏器对超声检查的影响,在一定程度上更有利于判断克罗恩病病变的肠壁累及深度,目前相关临床研究较少。

临床问题7:小肠克罗恩病的内镜诊断方法包括哪些?

【陈述意见8】胶囊内镜检查主要用于疑诊克罗恩病但结肠镜及小肠影像学检查未能明确诊断者,建议检查前评估肠道狭窄情况,以降低内镜胶囊滞留风险。(证据质量/推荐等级:高/A ;共识水平:100.0%)

小肠克罗恩病因溃疡病变局限于小肠,因此当结肠镜及小肠影像学检查未能明确诊断时,可考虑行胶囊内镜检查协助诊断(图3)。对于疑诊小肠克罗恩病患者,胶囊内镜的病变检出率相较于小肠钡餐造影联合CTE显著提高32%~47%[52]。一项荟萃分析研究发现,胶囊内镜、小肠超声与MRE对小肠克罗恩病的病变检出率相当,但对于近段小肠受累者,胶囊内镜检出率较MRE显著提高[53]。此外,胶囊内镜用于排除克罗恩病的阴性预测值可达到96%,小肠克罗恩病漏诊率低[54]。

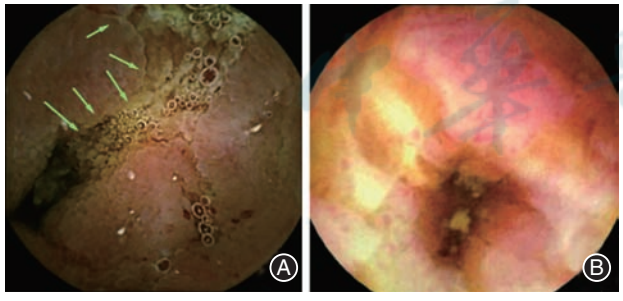


图3 活动期小肠克罗恩病的典型胶囊内镜表现 A:胶囊内镜图像可见回肠纵行溃疡;B:胶囊内镜图像可见回肠狭窄

克罗恩病在胶囊内镜下的表现缺乏特异度,多种类型的小肠溃疡均可在胶囊内镜检查中发现,非甾体抗炎药相关肠炎、肠型贝赫切特综合征、CMUSE、小肠结核等在胶囊内镜下的表现与克罗恩病类似。有研究发现,在排除近1个月内非甾体抗炎药药物使用后,胶囊内镜发现≥3处小肠溃疡性病变,对小肠克罗恩病也有较高诊断价值[55]。因此,若胶囊内镜发现阳性溃疡病灶,需结合后续小肠镜检查及活检病理进行综合评估[56]。此外,胶囊内镜还可对疑诊克罗恩病病变进行Lewis评分,总分≥135者诊断克罗恩病的灵敏度和特异度分别达到89.5%和78.9%[57]。

但内镜胶囊存在滞留风险,在疑诊及确诊克罗恩病时,总体滞留风险高达3.6%~10.4%[58-61]。有研究表明,对于无梗阻症状、无既往小肠手术史以及无已知肠道狭窄的疑诊克罗恩病患者,内镜胶囊滞留风险与消化道出血人群相当,仅为1%~2%[61]。一旦发生胶囊内镜滞留亦不必担忧,多数患者无临床表现,少部分患者出现腹痛,小肠镜取出滞留的内镜胶囊有较高的成功率,仅约15%患者可能出现梗阻症状,而最终需要手术干预[62]。胶囊内镜检查前需常规进行滞留风险评估,主要包括针对肠道狭窄情况的评估,影像学检查如CTE、MRE是评估肠道狭窄情况的主要方法,CTE/MRE评估可显著降低克罗恩病患者内镜胶囊滞留风险[63]。国外有可自溶的探路胶囊来降低胶囊内镜滞留率[64],国内的探路胶囊也即将上市。

【陈述意见9】BAE是诊断小肠克罗恩病的重要内镜检查方式,经CTE和(或)MRE和(或)胶囊内镜检查疑诊小肠克罗恩病者,可行小肠镜检查并行黏膜活检;小肠镜可精确判断克罗恩病溃疡的部位、范围、疾病活动度、有无伴有狭窄及活动性出血等,对于明确小肠克罗恩病的严重程度有重要价值。(证据质量/推荐等级:高/A ;共识水平:100.0%)

CTE和(或)MRE和(或)胶囊内镜是评估克罗恩病小肠病变的常用方法,当上述方法疑诊小肠克罗恩病,但因疾病部位、病变不典型等原因无法通过结肠镜确诊的患者,建议行BAE检查。小肠镜操作一般需在麻醉状态下进行,耗时较长,安全性较好,目前国内已有较多的医疗中心可以开展[65]。在疑诊小肠克罗恩病的病例中,小肠镜下黏膜活检的检出率可高达80%[66-68]。有研究表明,当CTE和(或)MRE和(或)胶囊内镜有阳性发现,小肠镜检查阳性率较直接小肠镜检查显著提高(77.8%比40.0%)[69]。

70%的克罗恩病病变累及小肠[70]。小肠克罗恩病病变以间断、不连续、透壁性溃疡为主要特点(图4),内镜结合组织病理学检查是小肠克罗恩病的重要诊断依据[71]。BAE现已广泛应用于临床小肠相关疾病的诊治,具有检查范围广(全小肠检查)、可获取小肠黏膜高清图像、可视化小肠黏膜组织活检的优点[64],已成为诊断小肠克罗恩病的重要内镜检查方式。对于小肠克罗恩病而言,溃疡和狭窄是小肠克罗恩

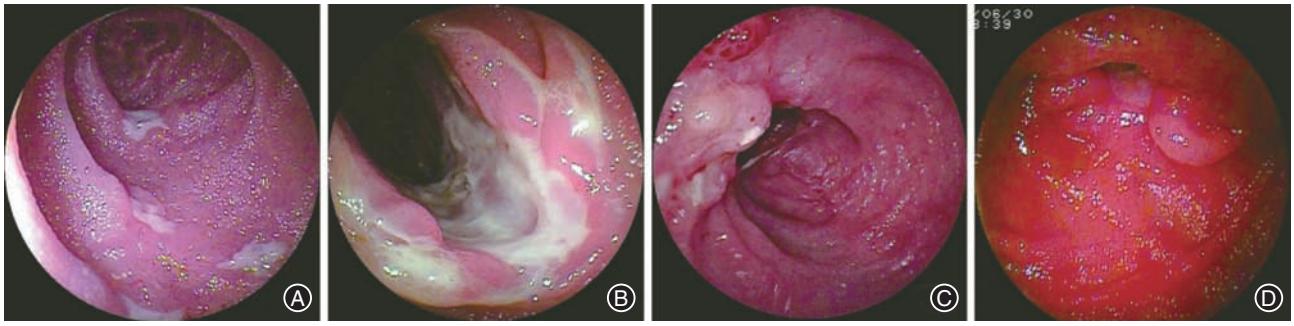


图4　活动期小肠克罗恩病的典型小肠镜表现　A:空肠克罗恩病小肠镜下溃疡表现; B:回肠克罗恩病小肠镜下溃疡表现; C: 空肠克罗恩病小肠镜下狭窄表现;D:回肠克罗恩病小肠镜下狭窄表现

病的典型病理生理学改变,相较于影像学(MRE/CTE)和胶囊内镜检查,小肠镜可精准判断溃疡部位、局部特征、整体分布特点,同时取活检病理与其他小肠溃疡性疾病相鉴别[72]。值得注意的是,空肠克罗恩病和回肠克罗恩病镜下表现不一,空肠克罗恩病多呈阿弗他样、非纵行溃疡改变[73-74]。随着病情加重或溃疡愈合,小肠克罗恩病患者小肠肠腔会出现狭窄[75]。肠腔狭窄是胶囊内镜检查的相对禁忌证,而小肠镜诊断小肠克罗恩病狭窄的准确率高达92.7%[76]。通过小肠镜下表现精准判断克罗恩病溃疡的部位、疾病活动度、有无伴有狭窄及活动性出血等,进而辅助评估克罗恩病的严重程度,可有效预测小肠克罗恩病患者手术风险[77]。因此,对于可疑小肠克罗恩病患者,经口和经肛小肠镜检查均应该完成,以获取更多小肠病变信息,但受小肠克罗恩病自身疾病特征(狭窄、透壁溃疡等)影响,不强求实现全小肠对接[78]。对于BAE下的病理取材方法,可参照回肠-结肠型克罗恩病的病理取材方式,于每个小肠肠段取材2块,包括病变及非病变部位。部分小肠淋巴瘤可有类似克罗恩病纵行溃疡样表现,内镜下多块、深取活检提供可靠的组织学诊断是鉴别小肠克罗恩病和小肠淋巴瘤的关键[36]。此外,小肠镜治疗小肠克罗恩病相关狭窄操作成功率高达95%,并发症发生率为3.1%[79],操作者可通过球囊扩张并通过狭窄病变,进而获取狭窄远端肠腔的病变全貌,评估狭窄长度和严重程度。

【陈述意见10】人工智能在胶囊内镜和小肠镜的诊断和鉴别诊断中可发挥辅助作用,从而提高小肠克罗恩病的诊断准确率。(证据质量/推荐等级:中/A; 共识水平:100.0%)

人工智能在临床多个领域发展迅速,尤其在胃肠镜领域,其中卷积神经网络(convolutional neural networks, CNN)在胃肠镜图片的识别中表现出较高的准确率和灵敏度[80]。胶囊内镜检查便利、无侵入性,是诊断小肠克罗恩病重要的检查手段。然而,人工阅片工作量大、耗时长,会造成小肠病变的漏诊和诊断准确率的下降[81]。近年来,有研究已建立了多种CNN模型,包括CE-YOLOv5[82]、基于VGGNET的CNN[83]等神经网络模型,缩短了胶囊内镜的阅片时间、提高了溃疡等病变的诊断准确率。同时,人工智能模型可对胶囊内镜中的阴性图片进行再分析,还可以进一步避免胶囊内镜的漏诊[84]。

BAE虽已广泛应用于小肠克罗恩病的诊断,但内镜医师的操作经验会影响小肠克罗恩病的诊断水平。目前国内已有研究建立EfficientNet-b5模型,用于诊断小肠克罗恩病病变和评估克罗恩病溃疡,准确率均在85%以上[85];另有DRCA-DenseNet169模型,可用于小肠溃疡疾病的鉴别诊断[86]。尽管目前人工智能在小肠镜及小肠克罗恩病应用中的研究刚刚起步,但已有证据表明该领域是今后的热点研究方向,以实时监测图片或视频为基础的人工智能识别有助于提高内镜医师的诊断准确率[87]。

临床问题8:小肠克罗恩病的内镜下活动度评分如何判断?

【陈述意见11】小肠克罗恩病的内镜评分标准可参考简化克罗恩病内镜下评分(simple endoscopic score for Crohn´s disease, SES-CD)评分。(证据质量/推荐等级:中/A;共识水平:93.5%)

克罗恩病的常用内镜评分体系包括克罗恩病内镜下严重程度指数(Crohn′s disease endoscopic index of severity, CDEIS)和SES-CD[88-89],其中SES-CD相对简单,应用较为广泛。SES-CD评分对回肠、右半结肠(回盲瓣、盲肠和升结肠至肝曲)、横结肠、左半结肠(降结肠至脾曲和乙状结肠)和直肠5部分单独评分后相加(表2)。SES-CD最早提出时小肠克罗恩病的理念尚未推广,并未涵盖空肠及近端回肠。因此对于孤立小肠克罗恩病,SES-CD可能低估疾病严重程度。期待未来建立针对于小肠克罗恩病的内镜评分标准,从而使小肠克罗恩病的内镜评判更为准确。

表2　简化克罗恩病内镜下评分

项目	计分(分)			
	0	1	2	3
溃疡大小	无	阿弗他溃疡(长径0.1~0.5 cm)	较大溃疡(长径>0.5~2 cm)	大溃疡(>2 cm)
溃疡表面范围	无	<10%	10%~30%	>30%
肠段受累范围	无	<50%	50%~75%	>75%
狭窄	无	单发,内镜可通过	多发,内镜可通过	内镜不能通过

注:3~6分为轻度活动;7~16分为中度活动;>16分为重度活动

【陈述意见12】胶囊内镜下的胶囊内镜克罗恩病活动指数(capsule endoscopy Crohn´s disease activity index, CECDAI)评分或Lewis评分有助于判断小肠克罗恩病的活动度。(证据质量/推荐等级:中/A;共识水平:96.8%)

胶囊内镜作为小肠克罗恩病重要评估手段之一,目前国际上主要使用CECDAI或Lewis评分评估疾病活动度[90-91]。CECDAI评分已被证实具有较高的评估准确率,其评估内容主要包括炎症、病变范围及狭窄程度,CECDAI对于小肠整体炎症程度具有全面的评估能力,但评分尚缺乏较为可靠的阈值划分(表3)。Lewis评分被证明有较好的观察者间一致性,可用于评估小肠克罗恩病包括绒毛水肿、溃疡、狭窄在内的多种病变形态。已有前瞻性队列建立了可较好区分患者活动度的界值,被证实与粪便钙卫蛋白(fecal calprotectin, FC)及患者预后相关[92-95]。因此,推荐使用Lewis评分用于小肠克罗恩病的黏膜病变活动度的初始评价、随访及疗效评估(表4)。黏膜病变可分为正常(评分<135分)、轻度(评分≥135~<790分)、中重度(评分≥790分),中重度患者激素使用率、住院率均显著高于黏膜正常患者[92]。需注意目前Lewis评分较注重肠道狭窄评估,若黏膜愈合时出现瘢痕狭窄,可能导致评分过高的结果。同时,Lewis评分尚未证实与克罗恩病活动指数(Crohn's disease activity index, CDAI)、C反应蛋白相关,内镜评分与临床活动度的不一致性也提示黏膜缓解与临床缓解的不平行性。Lewis评分和CECDAI评分均能较好地评估小肠克罗恩病活动度,也被验证具有较强的关联性。

临床问题9:小肠克罗恩病的实验室检查包括哪些?

【陈述意见13】小肠克罗恩病患者基线FC水平可以预测近期疾病复发,不推荐使用血清C反应蛋白和红细胞沉降率对小肠克罗恩病活动度进行评估,γ-干扰素释放试验(gamma interferon release assay, IGRA)、T淋巴细胞斑点试验(T-cell spot test, T-SPOT)等检查有助于排查肠结核。(证据质量/推荐等级:高/A;共识水平:93.3%)

FC水平升高可作为多种免疫性疾病的生物标志物,FC水平对IBD和非IBD有较高的鉴别诊断价值[96-97],FC低于检测水平下限对排除成人克罗恩病有较高的准确率[98]。既往研究表明,FC水平与SES-CD、CDAI等疾病活动度指标均存在良好相关性[99],但其对小肠克罗恩病的诊断价值存在一定争议。有研究表明,小肠克罗恩病患者FC水平显著高于非克罗恩病患者(354 μg/g比132 μg/g),但FC水平升高的特异度和阳性预测价值较低[100]。另有研究提示约30%的小肠克罗恩病患者FC处于正常水平[101]。然而,FC的阴性预测价值较高,近期一项荟萃分析表明,FC水平小于50 μg/g对小肠克罗恩病的阴性预测率高于90%[102]。此外,小肠克罗恩病患者基线FC水平可以较好预测近期疾病复发(6个月内),但对于长期复发(2年内)的预测效率较低[103]。

血清C反应蛋白和红细胞沉降率是评估克罗恩病疾病炎症程度的常用指标。然而,类似于FC,血清C反应蛋白和红细胞沉降率在小肠克罗恩病活动度的评估价值有限。回顾性研究发现,在进行胶囊内镜检查的患者中,小肠克罗恩病患者与其他患者血清C反应蛋白水平差异无统计学意义[100]。在行胶囊内镜检查且无手术史的小肠克罗恩病患者中,35%患者血清C反应蛋白水平处于正常范围,而在既往行手术治疗的患者中这一比例达42%[101]。但血清C反应蛋白水平的升高可作为小肠克罗恩病患者3~24个月疾病复发的预测指标[103]。对于红细胞沉降率,既往研究发现,局限于回肠或空肠的克罗恩病患者,血清红细胞沉降率水平处于正常范围内[104],且红细胞沉降率水平与疾病活动度无显著正相关性[105]。因此,不推荐使用血清C反应蛋白和红细胞沉降率对小肠克罗恩病患者疾病活动度进行评估。

肠结核是克罗恩病重要的鉴别诊断之一。肠结核主要累及部位为回盲部,而累及小肠的肠结核少见[106]。一项Meta分析发现,IGRA鉴别肠结核与克罗恩病的灵敏度达到

表4 小肠克罗恩病的胶囊内镜Lewis评分

参数	数量	程度	特殊描述
绒毛	正常-0分	短节段-8分[b]	单发-1分
	水肿-1分[a]	长节段-12分[b]	补丁样-14分
		泛节段-20分[b]	弥漫-17分
溃疡	无-0分	短节段-5分[b]	<1/4-9分[d]
	单发-3分[c]	长节段-10分[b]	1/4~1/2-12分[d]
	少量-5分[c]	泛节段-15分[b]	>1/2-18分[d]
	多发-10分[c]		
狭窄	无-0分	溃疡型-24分	无滞留-7分
	单发-14分	非溃疡型-2分	滞留-10分
	多发-20分		

注:[a]黏膜水肿定义为绒毛宽度等于或大于绒毛高度;[b]受累肠段:短节段为<10%,长节段为10%~50%,泛节段为>50%;[c]溃疡数量:1处为单发,2~7处为稀发,≥8处为多发;[d]溃疡大小:根据最大溃疡占据胶囊内镜照片面积的比例来计算;Lewis评分=病变最严重的1/3肠段的得分[(绒毛数量×程度×特殊描述)+(溃疡数量×程度×特殊描述)]+全肠段的狭窄得分(数量×程度×特殊描述)

表3 胶囊内镜克罗恩病活动指数(CECDAI)评分

项目	0分	1分	2分	3分	4分	5分
炎症(A)	无	轻度至中度水肿、充血、剥脱	重度水肿、充血、剥脱	出血、渗出、口疮样溃疡、糜烂、溃疡(<0.5 cm)	溃疡(0.5~2.0 cm)、假性息肉	溃疡(>2.0 cm)
疾病程度(B)	无	局灶性(单节段)	斑片状(2~3节段)	弥漫性(>3个节段)		
狭窄(C)	无	单发	多发	梗阻		

注:根据胶囊内镜通过小肠的时间确定中点,将小肠分为近端及远端,CECDAI评分=近端得分[(A×B)+C]+远端得分[(A×B)+C]

74%,特异度高达87%[107]。此外,联合IGRA及关键变量(如年龄、环周溃疡、直肠受累、小肠跳跃性病变、靶征及梳齿征)组成的预测模型,可将鉴别诊断的灵敏度提高至84.2%~86.8%,特异度提高至90.9%~100%[108]。有研究报道,T-SPOT在鉴别诊断克罗恩病与肠结核中的阴性预测价值达98.8%[109]。综上所述,若患者IGRA或T-SPOT阴性,则患者罹患肠结核的可能性较低。

临床问题10:小肠克罗恩病的治疗原则包括哪些?

【陈述意见14】小肠克罗恩病患者的治疗原则是通过药物诱导疾病缓解、维持缓解,近期目标为临床症状缓解、血清和(或)粪便炎性指标正常,远期目标为维持临床症状缓解、血清和(或)粪便炎性指标正常、达到内镜下黏膜愈合甚至深度愈合。(证据质量/推荐等级:中/A;共识水平:100.0%)

2021年发表的STRIDE-Ⅱ专家共识中提出,将启动克罗恩病治疗后3~6个月临床缓解、血清和(或)粪便炎症指标恢复作为短期目标,而将治疗9~12个月后内镜下黏膜愈合作为远期目标[42]。小肠克罗恩病的治疗原则及治疗目标同其他类型克罗恩病[110]。既往研究表明,相较于结肠型克罗恩病,小肠克罗恩病对生物制剂的疗效反应较差[111-112]。为了实现小肠病变内镜下缓解,相较于其他克罗恩病患者,生物制剂等药物需要达到更高的血清谷浓度[113]。截至2024年,大多数临床研究并没有根据克罗恩病疾病部位对药物疗效进行亚组分析,所以对小肠克罗恩病治疗目标及疗效的评估仍需后续研究。

临床问题11:小肠克罗恩病如何诱导缓解?

【陈述意见15】轻度活动期且无其他高危因素的小肠克罗恩病患者可应用糖皮质激素进行诱导缓解,肠内营养亦有相当的诱导缓解效果。(证据质量/推荐等级:中/A;共识水平:96.7%)

当前小肠克罗恩病疗效的研究数据相对较少。在克罗恩病的传统治疗中,随机对照研究(randomized controlled trial, RCT)已证实系统性糖皮质激素(以下简称激素)可有效诱导活动期克罗恩病缓解,有效率明显高于安慰剂[114-115]。对于轻度局限性回肠或回盲部受累的小肠克罗恩病患者,推荐局部作用的布地奈德用于诱导缓解,布地奈德相较于系统性糖皮质激素不良反应更少[116]。此外,肠内营养诱导小肠克罗恩病的效果优于结肠型克罗恩病,以儿童患者为甚。多项研究从CDAI、内镜评分和病理评分多方面进行了比较,儿童克罗恩病全肠内营养诱导缓解率L1型和L2型明显高于L3型,分别为91.7%、82.1%和50%[117]。成人小肠克罗恩病全肠内营养诱导缓解率为68.3%,高于结肠型克罗恩病(51.9%)[118]。

【陈述意见16】中重度活动期小肠克罗恩病或存在高危因素者,推荐生物制剂进行诱导缓解,小分子药物也有良好疗效。(证据质量/推荐等级:高/A;共识水平:100.0%)

对于伴有高危因素或传统药物治疗失败的中重度活动期克罗恩病可推荐使用生物制剂,诸如抗肿瘤坏死因子(tumor necrosis factor, TNF)-α单克隆抗体(以下简称单抗)、维得利珠单抗(vedolizumab, VDZ)、乌司奴单抗(ustekinumab, UST)等治疗。选择性Janus激酶(Janus kinase, JAK)抑制剂可用于抗TNF-α单抗治疗失败的中重度活动期克罗恩病患者的诱导缓解。多项研究表明生物制剂治疗小肠克罗恩病通常需要更高的药物谷浓度水平才能实现内镜下黏膜愈合[112, 119-121]。2022年,一项荟萃分析显示,英夫利西单抗(infliximab, IFX)、阿达木单抗(adalimumab, ADA)、UST和VDZ在基线时回肠SES-CD评分<3分的患者中治疗后1年内镜下黏膜愈合率差异无统计学意义;但对于回肠存在较大溃疡(长径>0.5 cm)的患者,IFX治疗后1年回肠溃疡愈合率(40.9%)最高,其次是ADA(30.0%)和UST(17.7%),VDZ的内镜下溃疡愈合率则为8.7%[122]。一项Ⅲ期临床试验表明,VDZ在第26周和第52周的回肠组织学应答率分别为28.3%和34.3%[123]。总体而言,克罗恩病小肠病变相较结肠病变通常对生物制剂反应不足。

高选择性JAK1抑制剂乌帕替尼是目前国内唯一获批克罗恩病适应证的口服小分子药物,全球多中心的Ⅲ期RCT及系统评价均证实其在中重度克罗恩病(小肠克罗恩病占比在50%以上)诱导缓解及维持治疗中的有效性,但均未专门披露小肠克罗恩病的结局[124-126]。小样本真实世界研究显示,结肠型克罗恩病患者第8周时80%的基线疾病活动度的患者达到临床应答和临床缓解;小肠克罗恩病中分别有75%和66.7%的患者达到了临床应答和缓解[127]。尚无专门针对乌帕替尼治疗深部小肠克罗恩病疗效及以小肠内镜缓解作为终点的疗效评估相关数据。

临床问题12:小肠克罗恩病伴狭窄如何进行内镜治疗?

【陈述意见17】对于狭窄长度<5 cm的纤维性小肠狭窄克罗恩病患者,可考虑使用小肠镜下球囊扩张术或狭窄切开术治疗。(证据质量/推荐等级:高/A;共识水平:100.0%)

小肠克罗恩病可并发多节段的小肠纤维性狭窄,对于狭窄长度<5 cm的小肠纤维性狭窄,且狭窄周围无明显炎症、腹腔脓肿和内瘘、急性完全性梗阻和癌变证据,可选择内镜下治疗[128],包括内镜下球囊扩张术(endoscopic balloon dilation, EBD)和内镜下狭窄切开术(endoscopic stricturotomy, EST)(图5)。

EBD和EST进镜途径的选择需基于小肠狭窄的部位。单灶或多处狭窄但狭窄部位较为集中时可单侧进镜实现狭窄治疗;多处狭窄且单侧进镜无法实现所有目标狭窄治疗通常需要双侧进镜治疗。择期双侧进镜治疗通常首次选择经肛进镜治疗,再次治疗时经口进镜。治疗前应尽可能改善患者营养状态,低体质量可能是治疗不良结局的危险因素[129]。

EBD是内镜下治疗克罗恩病小肠狭窄的首选方法[130],EBD的疗效被认为与扩张直径正相关,但穿孔率和其他并发症发生率亦随扩张直径增大而增加。扩张时气囊直径的选择需根据狭窄处直径调整,建议最终目标直径为15~18 mm为宜,扩张持续时间为60~90 s[130-131]。长段狭窄与EBD治疗不良结局相关,小肠狭窄节段长度超过2 cm是内镜治疗后再次手术的危险因素[132]。因而,小肠狭窄EBD的最佳治疗

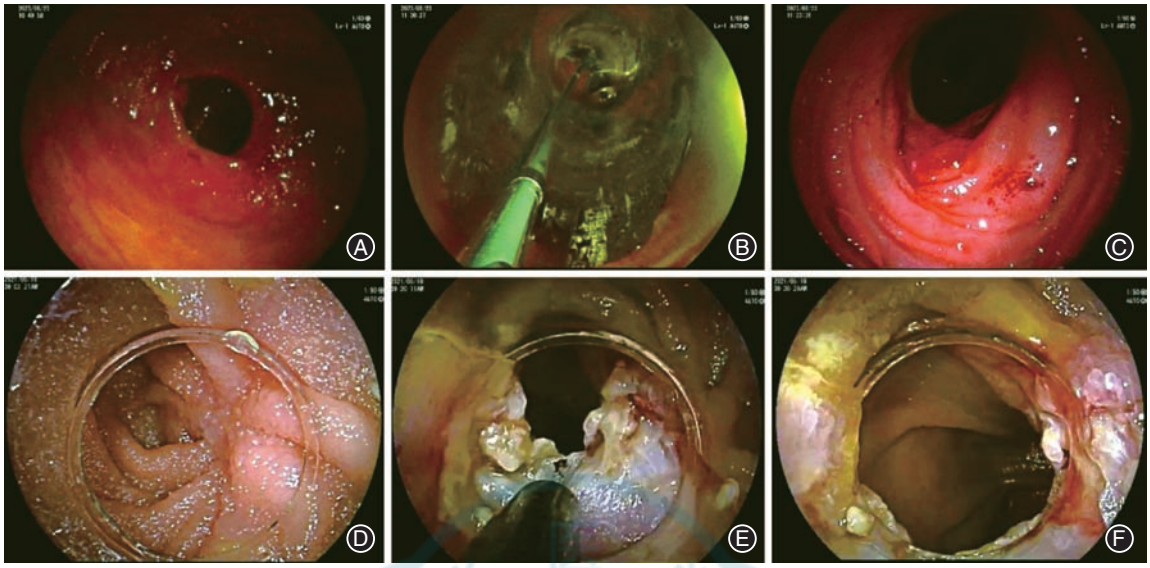


图5 内镜下球囊扩张术及内镜下狭窄切开术 A:回肠环形狭窄;B:小肠镜下球囊扩张治疗狭窄;C:扩张治疗后;D:回肠偏侧皱襞纠集形成纤维性狭窄;E:内镜下狭窄切开术治疗狭窄;F:治疗后狭窄缓解

指征包括短节段狭窄。长节段、成角狭窄以及狭窄附近有脓肿和瘘管的患者,需考虑其他内镜治疗方法或外科手术治疗[133]。小肠EBD的严重并发症包括需要手术治疗的肠穿孔和消化道大出血,发生率分别为3.2%和1.82%[79]。内镜治疗前的激素应用是已知的结肠镜下EBD穿孔的危险因素,但EBD在小肠狭窄治疗中的穿孔相关预测因素尚不明确。狭窄部位伴有活动性炎症与溃疡并非EBD治疗绝对禁忌,但EBD治疗的前提是局部无深溃疡和瘘管[130]。狭窄病变处炎症溃疡是否影响EBD治疗预后目前仍有争议[130, 134]。部分研究结果提示,合并炎症溃疡的小肠狭窄,EBD长期预后较黏膜已愈合的狭窄病变差[134],这可能是由于存在溃疡时,操作者倾向于选择更小的扩张直径,也不排除溃疡愈合过程中更易发生纤维性狭窄。

荟萃分析显示EBD治疗克罗恩病小肠狭窄的有效性和安全性较好[79],463例患者行1 189次EBD操作,技术成功率为95%(86.7%~98.1%),短期临床有效率为82.3%,长期疗效评估显示随访20个月的临床复发率约为48%(33.2%~63.7%);但仍有多达2/3的患者在首次小肠EBD治疗后随访中需要再次EBD或外科手术。一项日本305例克罗恩病小肠狭窄的多中心回顾性研究显示,EBD后1年、5年和10年的外科手术率分别为26.0%、45.6%和55.7%[132];在丹麦全国队列研究中EBD后中位随访5年期间,大多数患者无需进一步手术,其中49例原发小肠狭窄在EBD治疗后中位3.4年的随访期中,59%的患者无需再次介入治疗,73%的患者在首次扩张后无需进行小肠外科手术[135]。

小肠镜下EST是近年来新兴起的小肠狭窄治疗方式,较EBD的狭窄解除效果更好,但对内镜医师的操作要求更高。EST包括放射状切开、纵行切开、环形旋切并移除纤维疤痕组织等多种方式,可使用针刀、IT刀或Hook刀。在EST的基础上,对创面进行类似于外科肠狭窄成型术的方法以环腔方向横行缝合创面,称之为内镜下狭窄成形术(endoscopic stricturoplasty, ESTx)[136-137]。ESTx可能降低迟发出血及穿孔风险,有利于狭窄处创面愈合、塑型和管腔维持,因而可能降低狭窄复发风险或延后狭窄复发时间[136]。ESTx疗效已在病例报告、小样本单中心队列研究中进行了探讨,笔者经验认为EST适用于以纤维性狭窄为主的顽固性狭窄的治疗,其长期疗效可能优于EBD。EST与EBD相比,操作者可以主动控制切开纤维瘢痕的深度和位置,从而最大限度地提高治疗效果,对于难治性狭窄,EST可能优于EBD,其治疗后狭窄复发风险较小[128]。近期国内开展的一项多中心回顾性队列研究纳入了28例克罗恩病深部小肠狭窄行BAE-EST治疗58次,结果显示该技术成功率(92.9%)较高,治疗后8周临床症状改善率为71.4%,1年累积无手术率为74.8%,需要内镜或外科干预的严重不良事件发生率为3.4%[129]。对于营养状态较差的克罗恩病合并小肠狭窄者在营养状态改善前需谨慎选择EST。

由于纤维性狭窄具有持续进展和不可逆性,因此理论上预防性治疗狭窄可预防梗阻的发生,全球介入性IBD组织推荐,对偶然发现的内镜无法通过的肠道狭窄给予预防性EBD治疗[138]。针对克罗恩病结直肠吻合口狭窄的研究显示,有症状的狭窄患者比无症状的狭窄患者对EBD的反应更差,需要后续手术的风险更高,因此前置狭窄治疗时机可能更有效地减少外科手术需要[139]。“预防性”内镜下小肠狭窄治疗是否能改善预后是值得关注并研究的问题,当前,无症状小肠狭窄的内镜下治疗仍需在医患充分沟通后共同决策的前提下进行。

【陈述意见18】小肠镜下球囊扩张或狭窄切开术后,建议采用免疫抑制剂或生物制剂维持疗效、预防复发。(证据质量/推荐等级:中/A;共识水平:100.0%)

狭窄型小肠克罗恩病经内镜治疗后,仍需采用药物治

疗,预防复发。多项研究提示抗TNF-α单抗治疗联合EBD可有效预防狭窄复发及降低狭窄型小肠克罗恩病的外科手术率[140-142]。日本一项回顾性研究显示,抗TNF-α单抗治疗组小肠狭窄复发风险明显低于非治疗组(*HR* = 0.38)[142]。此外,降低狭窄复发风险程度亦与启动药物治疗的时机相关,以EBD同期(前后3 d)启动抗TNF-α单抗治疗为参照,EBD治疗前启动(*HR* = 0.34)或EBD后2周内启动抗TNF-α单抗治疗(*HR* = 0.25)有利于减少狭窄复发,而首次EBD治疗2周后启动抗TNF-α单抗治疗降低狭窄复发风险尤为显著(*HR* = 0.09)[142]。

临床问题13:小肠克罗恩病药物治疗后如何进行内镜下疗效评估?

【陈述意见19】小肠镜可用于小肠克罗恩病治疗后的疗效评估,尤其对黏膜愈合以及瘢痕性狭窄的判断有重要价值。(证据质量/推荐等级:中/A;共识水平:100.0%)

小肠克罗恩病患者的内镜下复发往往早于其临床表现[143],因此小肠镜可作为小肠克罗恩病治疗后疗效评估的重要手段之一,尤其在黏膜愈合(图6A)及瘢痕性狭窄(图6B)的观察中具有重要价值。内镜下黏膜愈合是小肠克罗恩病的关键治疗目标之一,同时与患者的预后结局相关[144]。一项回顾性研究共纳入116例在接受抗TNF-α单抗诱导治疗前和维持治疗期间均接受小肠镜检查的克罗恩病患者,结果显示小肠黏膜愈合的患者比例(36%)明显低于结肠黏膜愈合的患者比例(79%),且小肠黏膜愈合患者具有良好结局[119]。另一项研究收集了100例完成小肠镜检查的临床缓解期克罗恩病患者的随访资料,显示针对深部小肠黏膜的部分改良SES-CD是临床复发的独立预测因素[145]。狭窄是小肠克罗恩病最常见的并发症[146],小肠镜对于狭窄肠段的观察具有独特的优势。一项队列研究对165例有小肠狭窄表现的克罗恩病患者行CTE和小肠镜检查,结果显示小肠镜检出率为92.7%(153/165),CTE的检出率为85.5%(141/165)[76],小肠镜在监测克罗恩病狭窄中的作用较大。

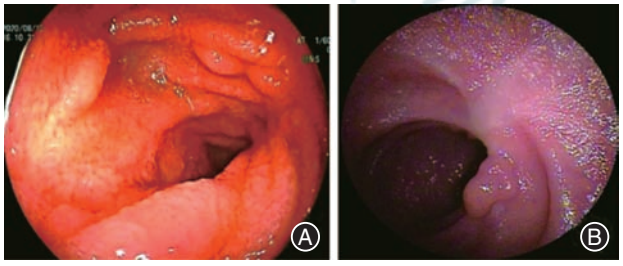


图6　小肠克罗恩病药物治疗后的小肠镜图　A:经抗TNF-α单抗治疗26周后复查小肠镜,可见纵行溃疡消失,达到黏膜愈合;B:纵行溃疡愈合伴环状纤维性狭窄形成

【陈述意见20】胶囊内镜可用于小肠克罗恩病治疗后的评估,但需评估其滞留风险。(证据质量/推荐等级:中/A;共识水平:100.0%)

胶囊内镜可用于小肠克罗恩病治疗后复查,利用CECDAI和Lewis评分均可对小肠克罗恩病患者是否达到黏膜愈合进行评判。由于小肠克罗恩病常伴有多发狭窄,确诊克罗恩病患者行胶囊内镜检查的内镜胶囊滞留率为2.6%~13%[61,147]。部分小肠克罗恩病患者在治疗后可能形成愈合相关的瘢痕及新增狭窄,即使治疗前曾行胶囊内镜检查未出现内镜胶囊滞留,治疗后也有一定的滞留风险。2005年,探路胶囊开始应用于胶囊内镜检查可能滞留的患者中[148],如小肠克罗恩病治疗后复查存在小肠镜或影像学检查禁忌而考虑行胶囊内镜者,可先行探路胶囊初判狭窄程度及胶囊内镜滞留风险。探路胶囊具有无需肠道准备、可降解的特点,可帮助判断消化道是否通畅。检查过程中探路胶囊解体或患者出现疼痛症状,则不建议进一步行胶囊内镜复查小肠克罗恩病。

临床问题14:胶囊内镜滞留时如何处理?

【陈述意见21】小肠克罗恩病发生胶囊内镜滞留时,首选小肠镜经口取出滞留的胶囊内镜,如经口无法取出,可尝试经肛小肠镜球囊扩张术后取出。(证据质量/推荐等级:中/A;共识水平:100.0%)

胶囊内镜自摄入后经影像学检查确认在小肠内停留时间超过2周,即可诊断为胶囊内镜滞留[149]。胶囊滞留是胶囊内镜的主要并发症,少数患者因胶囊内镜滞留导致小肠梗阻或穿孔[150]。可疑小肠克罗恩病患者胶囊内镜检查后滞留发生率约为0.5%[64]。小肠镜取出滞留胶囊成功率约为70%,成功与否与胶囊滞留部位、狭窄个数与狭窄程度有关[151]。因此,当胶囊内镜滞留时,结合患者意愿后首选小肠镜下取出滞留胶囊,少数需要采取外科手术[152]。小肠镜取胶囊路径通常根据影像学检查下初步判断的胶囊滞留位置进行选择,一般首选经口小肠镜用圈套器循胶囊内镜原路取出,如经口无法取出,可尝试经肛小肠镜球囊扩张术后取出(图7)。

【陈述意见22】小肠镜取出胶囊内镜失败时,可加用激素或生物制剂治疗,有助于促进滞留的胶囊内镜自行排出。(证据质量/推荐等级:中/A;共识水平:96.7%)

大约10%的胶囊内镜滞留经小肠镜无法取出,通过药物治疗后可自行排出[148]。克罗恩病狭窄致胶囊内镜滞留可使用硫唑嘌呤、抗TNF-α单抗等药物治疗,部分胶囊内镜可自行排出[153]。对于小肠克罗恩病来说,炎症是小肠肠腔狭窄的主要原因,使用激素药物治疗可使50%左右的滞留胶囊内镜自行排出体外[154]。药物治疗具有周期长、疗效不确定等特点,因此一般在小肠镜取出胶囊内镜失败后选择药物治疗。但需注意的是,药物治疗起效也可能导致小肠黏膜的瘢痕性愈合及瘢痕性狭窄,因此导致胶囊内镜滞留无法自行缓解,必要时可考虑EBD治疗取出胶囊内镜。如上述方法均无法取出或排出胶囊内镜,可酌情考虑外科手术。

临床问题15:小肠克罗恩病的外科手术指征包括哪些?

【陈述意见23】外科手术适应证包括严重的克罗恩病并发症、经内科治疗无效者需考虑手术治疗。(证据质量/推荐等级:高/A;共识水平:100.0%)

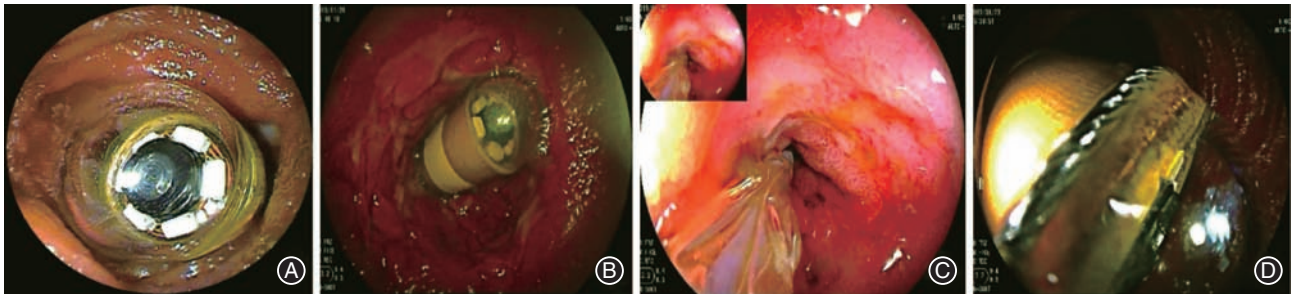


图7 小肠镜经口及经肛(狭窄扩张后)取出滞留的胶囊内镜 A:胶囊内镜滞留于空肠克罗恩病溃疡狭窄处;B:胶囊内镜滞留于回肠克罗恩病溃疡狭窄处;C:小肠镜下小肠克罗恩病狭窄扩张;D:小肠镜下取出滞留胶囊内镜

对小肠克罗恩病肠狭窄导致反复或慢性肠梗阻且药物及内镜治疗失败者,推荐择期手术治疗[155]。一项回顾性研究纳入56例症状性狭窄的小肠克罗恩病(定义为梗阻性症状或MRE下近端扩张)的儿童患者,结果显示64%的患者在狭窄诊断后4.8个月内需要手术治疗;狭窄诊断前的抗生素治疗、梗阻症状评分为重度和MRE小肠狭窄近端肠管扩张直径>28 mm与手术风险相关[156]。另一项回顾性研究评价小肠狭窄EBD治疗长期预后,结果显示内镜治疗3年后和5年后累积外科手术率分别为19.9%和26.5%,起病年龄<16岁是外科手术的危险因素[141]。回顾性分析小肠克罗恩病合并小肠狭窄患者,85例患者中26例在诊断狭窄后2年内进行了外科手术,影像结合Harvey-Bradshaw指数(Harvey-Bradshaw index, HBI)评分可以预测狭窄性小肠克罗恩病患者2年内手术风险[157]。

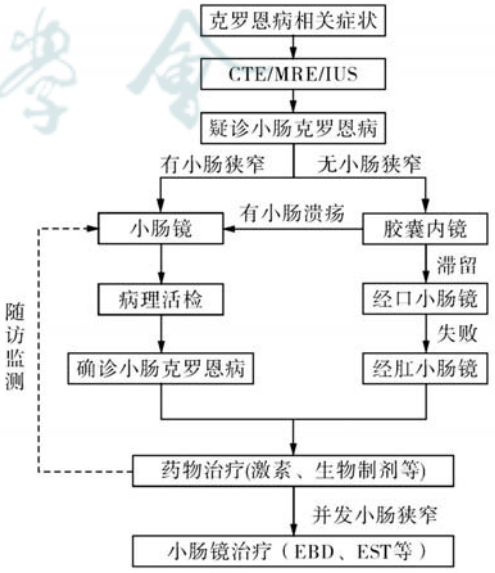
对局限性穿透型小肠克罗恩病反复发作或无法排除癌变者推荐手术治疗,穿透型小肠克罗恩病肠壁溃疡深大并可能伴有肠瘘等,不仅增加机体炎症负荷、药物治疗难度大,还常造成反复消化道出血、腹腔感染,并有一定的癌变风险。少部分患者保守治疗后瘘管暂时闭合但容易复发,形成腹腔脓肿者采用药物及其他非手术治疗通常无法完全解除上述并发症[158-159],因此建议在抗感染、充分引流及营养支持等治疗的同时考虑择期外科手术治疗[160]。小肠克罗恩病的择期手术通常需要多学科讨论通过且医患双方充分沟通[161-162],需兼顾病变清除和肠段保留,同时需充分考虑其他临床因素,术前需优化营养支持治疗、纠正贫血和尽可能清除腹腔内感染病灶,以减少术后吻合口相关并发症[163]。

小肠克罗恩病急性肠穿孔伴弥漫性腹膜炎时,应行急诊手术。急诊手术除清除腹腔污染外,通常需要切除穿孔肠段并根据肠道病变和腹腔感染情况决定是否实施肠造口术。克罗恩病伴急性消化道大出血发生率为0.9%~6.0%,小肠克罗恩病伴消化道大出血,若保守治疗无效时推荐手术治疗。合并急性消化道出血的小肠克罗恩病患者出血部位多在病变最严重处,数字减影血管造影(digital subtraction angiography, DSA)、CT血管造影(CT angiography, CTA)等影像学检查有助于出血部位的判断[164],由于肠系膜血管结构的特殊性,介入栓塞治疗容易造成肠缺血甚至坏死[165]。因此对于药物及小肠镜无法治疗的小肠克罗恩病合并危及生命的急性出血时,推荐急诊手术切除病灶以控制出血。有研究报道IFX可通过促使溃疡快速愈合治疗克罗恩病并发严重肠道出血,研究者通过1~2次的常规或强化剂量的IFX静脉注射治疗后成功止血[166-168]。

临床问题16:小肠克罗恩病的随访和监测如何实施?

【陈述意见24】建议对小肠克罗恩病定期复查肠道超声和(或)CTE和(或)MRE,必要时结合小肠镜复查。(证据质量/推荐等级:高/A;共识水平:100.0%)

对于确诊小肠克罗恩病患者,需监测疾病活动度,优化治疗策略(图8)。小肠克罗恩病复查时间节点应基于病情严重程度、治疗方案和患者的治疗反应等因素综合决定,在怀疑疾病进展或需要调整治疗方案时通常需参考超声、影像及内镜的病情评估结果[169-170],小肠镜复查推荐在治疗后6~12个月进行[171]。建议通过FC、肠道超声和(或)CTE和(或)MRE及小肠镜监测评估肠道炎症及并发症情况。小肠克罗恩病开始治疗后需通过内镜评估黏膜愈合情况、肠道超声和(或)CTE和(或)MRE评估透壁愈合情况[172-173]。考虑目前关于小肠克罗恩病治疗经验和检查可及性,建议在治疗开始后第12个月行小肠镜检查评估黏膜愈合[145, 174],适合胶囊内镜评估的患者可在治疗开始后12~24周行胶囊内镜检查



注:CTE指CT小肠成像;MRE指磁共振小肠成像;IUS指经腹肠道超声;EBD指内镜下球囊扩张术;EST指内镜下狭窄切开术

图8 小肠克罗恩病的诊治流程

评估内镜下缓解情况[175]。CTE和(或)MRE推荐在治疗开始后26周及52周进行,治疗效果不佳和(或)有并发症者可能需要提前或增加检查频率。

在内镜监测小肠克罗恩病疾病相对受限、影像学评估不宜频繁的情况下,肠道超声或FC可作为一线的疾病监测手段之一。

对于非狭窄型小肠克罗恩病,胶囊内镜可作为评估黏膜愈合的手段,其具有灵敏度高、评估范围广的优势[176-177]。需在回顾基线资料或既往胶囊内镜图片和报告的基础上给出病情对比及评估意见,实施前应评估是否存在肠道狭窄,从而降低胶囊内镜滞留风险。对于可能存在狭窄病变者,可选择BAE检查评估病情,相较于肠道超声/CTE/MRE,其对黏膜愈合、新发狭窄的灵敏度更高[178]。

荟萃分析显示,克罗恩病并发小肠癌的发病率为30/10万人年,克罗恩病患者小肠癌的发生率为正常人群的10倍[175]。克罗恩病相关小肠癌多为腺癌,多见于空肠下段和回肠,且与穿透和狭窄型疾病行为、既往手术史及病程相关。目前尚无明确证据支持对克罗恩病小肠癌风险进行常规筛查,但是如果患者存在病程长、难治性、肠道狭窄或相关症状,需注意是否合并小肠癌变。

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《中华炎性肠病杂志》2024年度优秀审稿专家名单

为了感谢广大审稿专家的辛勤工作,弘扬其严谨求实的工作作风、认真负责的工作态度,《中华炎性肠病杂志》根据2024年度各审稿专家的审稿数量、审稿质量和审稿时效评选出优秀审稿人10名。名单如下(按姓氏拼音字母顺序排列):

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《中华炎性肠病杂志》编辑部
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