5-Aminosalicylic Acid Chemoprevention in Inflammatory Bowel Diseases: Is It Necessary in the Age of Biologics and Small Molecules?

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Keywords

Inflammatory bowel disease · Chemoprevention · Ulcerative colitis · 5-Aminosalicylic acid · Colorectal cancer

Abstract

Background: Due to the increased incidence of colorectal cancer in inflammatory bowel diseases (IBDs), the value of chemoprevention for this patient group has been repeatedly debated in the past decade. This review describes available evidence and the current recommendations for chemoprevention in national and international guidelines IBD guidelines. **Summary:** 5-Aminosalicylic acid (5-ASA) compounds are the preferred therapeutic option for mild to moderate ulcerative colitis (UC). Aside from the known anti-inflammatory effects, their chemopreventive abilities have been described in vitro and in vivo. Pooling the increasing number of retrospective and population-based clinical studies over the last 15 years, 7 consecutive meta-analyses revealed partially conflicting results for the chemopreventive efficacy of 5-ASA, and thus, not all IBD guidelines currently recommend chemoprevention with mesalamine compounds. Accumulating evidence for decreasing the colorectal cancer (CRC) risk in support of thiopurines more recently shows a protective effect. This effect seems solely mediated

by control of intestinal inflammation since, for this drug class, another mechanistic interference in IBD-associated CRC pathogenesis is not known. The results regarding chemopreventive efficacy for ursodeoxycholic acid or folic acid are equivocal, and the use of these medications to prevent CRC is not firmly established. Like UC, the risk of CRC is also significantly increased in patients with Crohn's disease (CD), especially Crohn's colitis. However, no published studies exclusively assess the effects of surveillance on the early detection of cancer or CRC chemoprevention in CD patients. In meta-analyses, which predominantly included UC patients, 5-ASA or thiopurines were not beneficial in small CD subgroups. The level of evidence for anti-TNFα agents, anti-integrin (e.g., vedolizumab), or anti-IL-12/IL-23 agents (e.g., ustekinumab) and Janus kinase inhibitors is currently too low or nonexistent to use them solely for chemoprevention in UC or CD patients. **Key Message:** Intestinal inflammation is one of the main risk factors for developing CRC in IBD, and all drugs that induce and maintain mucosal healing most likely also decrease the IBD-associated CRC risk. Thus, a therapeutic strategy of adding a 5-ASA therapy to a successfully mucosal healing-inducing therapy, for example, with a biologic or a small molecule merely to prevent CRC appears to be obsolete.

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Introduction

The increased colorectal cancer (CRC) risk in patients with ulcerative colitis (UC) became apparent in the second half of the previous century. Eaden et al. [1] reported a CRC prevalence of 3.7% based on a meta-analysis, including 54,478 patients of 116 studies between 1966 and 1999. The CRC risk increased over time to cumulative probabilities to develop CRC of 2% by 10 years, 8% by 20 years, and 18% by 30 years. However, in the last 20 years, several epidemiologically well-performed studies, including a meta-analysis by Jess et al. [2], have shown a decreasing or lower CRC risk with estimations <1% at 10 years and from 1.1 to 5.3% at 20 years. A recently published large population-based study including 96,000 individuals with UC from Denmark and Sweden by Olen et al. [3] found a 1.7-fold increased risk for incident CRC and a 1.6-fold increased risk of death from CRC for a patient with UC. Based on this study, the incident CRC or death from CRC has been decreasing since the early 2000s, corresponding to 1 additional case of incident CRC per 1,058 UC patients and 1 additional death from CRC per 3,041 UC patients during the last 5 years of follow-up [3].

Patients with Crohn's disease (CD) are also at increased risk for developing CRC. In a meta-analysis of population-based studies in CD, Jess et al. [2] estimated in 2005 a pooled standard incidence ratio (SIR) for CRC of 1.9 (95 confidence interval [CI], 1.4–2.5) [4]. In another meta-analysis published 8 years later, Lutgens et al. [5] found an SIR of 1.7 (95% CI, 1.2–2.2) and identified patients with extensive colitis and a diagnosis before age 30 years at increased risk (SIR 6.4, 95% CI, 2.4–17.5 and 7.2, 95% CI, 2.9–17.8, respectively). PSC and a diagnosis before the age of 40 years present additive risk factors for CD patients [6]. Currently, inclusion in a screening and surveillance program is recommended for patients with Crohn's colitis with a somewhat arbitrary definition of an inflammatory involvement of more than one-third of the colon as determined endoscopically but not histologically [7–9].

Multiple factors additionally modify the risk for CRC in patients with inflammatory bowel diseases (IBD), as shown in Table 1 [10, 11]. Strictures, lead pipe colon, and pseudopolyps, which are the cumulative result of inflammation, are considered structural risk factors. However, pseudopolyps probably do not represent per se a risk factor for colonic neoplasia, including CRC, as shown recently in a large, international, retrospective cohort study as well as prospective surveillance cohort with 22 years of

follow-up [12, 13]. In both studies, pseudopolyps were not independently associated with the risk of neoplasia after correction for colonic inflammation. A recent systematic review and meta-analysis pooling 164 studies analyzed 31 potential risk factors for advanced colorectal neoplasia [14]. Evidence for each factor derived from the included studies was graded as strong, moderate, or weak according to the cumulative odds or hazard ratio, the statistical significance level of the pooled studies, and the heterogeneity and number of studies analyzing the factor. Thus, despite higher odds or hazard ratios, the quality of evidence for singular risk factors was often downgraded due to significant heterogeneity between the included studies or a smaller number of studies in the pooled analyses. Accordingly, the quality of evidence for extensive disease as a risk factor for CRC was classified as strong. In contrast, low-grade dysplasia, strictures, primary sclerosing cholangitis, postinflammatory polyps, family history of CRC, and UC versus CD were considered as moderate-quality evidence. Evidence for being a CRC risk factor was classified as weak for histologic inflammation, any dysplasia, colon segment resection, aneuploidy, male sex, and age.

Given the elevated risk of CRC in UC and CD with colonic involvement of >30%, the potential of medical CRC chemoprevention aside from regular surveillance colonoscopies has been debated in the past 3 decades [11]. The potential chemoprevention mechanisms by 5-ASA are reported in numerous in vitro and a few in vivo animal studies (reviewed in [15–17]). 5-ASA interferes with diverse biochemical pathways, including the arachidonic acid metabolism pathway and TNF α , TGF- β , NF- κ B, and WNT/ β -catenin pathways, all associated with the development of neoplasia [18]. 5-ASA also interferes with cell cycle progression on different levels, induces apoptosis in neoplastic cells, and acts as a scavenger of reactive nitrogen and oxygen metabolites [15, 16]. Interestingly just recently, a study comparing the chemopreventive efficacy of low-dose aspirin (100 mg/day) with 5-ASA (2 g/day) in high-risk familial adenomatous polyposis patients without previous colectomy showed in contrast to low-dose aspirin no preventive effect of 5-ASA for recurrent polyp formation >5 mm [19].

5-ASA and Chemopreventive Effects in IBD – Clinical Studies

Since 2005, 7 meta-analyses have been published, analyzing the potential chemopreventive effect of 5-ASA on the occurrence of CRC or colorectal dysplasia in patients

Table 1. Risk factors for CRC in IBD colitis (adapted from [11])

Disease-related factor	Patient-related factors
Extensive colitis	Prior history of dysplasia
Duration of disease	Family history of CRC in FDR, especially if <50 years old
Severity of inflammation	Primary sclerosing cholangitis
Cumulative inflammatory burden	Possible: earlier age of disease onset, male sex, and patient compliance with medication/follow-up
Structural alterations as a consequence of chronic inflammation	
Pseudopolyps*	
Stricture	
Shortened lead pipe colon	

IBD, inflammatory bowel diseases; CRC, colorectal cancer. * Newer studies indicate that pseudopolyps are not a risk factor [12, 13].

Table 2. Meta-analyses: use of 5-aminosalicylates and risk of colorectal neoplasia in patients with inflammatory bowel disease

Author meta-analysis	Studies, <i>n</i> Total (hospital-based/ population-based)	Total cases	CRC cases	Dysplasia cases	Colonic neoplasia risk and 5-ASA exposure and other findings
Velayos et al. [20]	9 (3/6) UC	474	334	140	CRC/Dys: OR = 0.51; 95% CI 0.37–0.69 <i>Significant reduction for CRC alone but not dysplasia</i>
Nguyen et al. [21]	13 (9/4)	1,259	Nr	Nr	CRC/Dys population based: OR = 0.95; 95% CI 0.66–1.38 CRC/Dys hospital based: OR = 0.58; 95% CI 0.45–0.75
Zhao et al. [22]	17 (9/8)	1,508	Nr	Nr	CRC/Dys: OR = 0.63; 95% CI 0.48–0.84 <i>Significant reduction in the hospital based but not in the population-based studies</i> <i>5-ASA dose effect >1.2 g/d and sulfasalazine ≥2 g/d</i>
O'Connor et al. [23]	8 (4/4)	867	724	143	CRC/Dys: OR = 0.6; 95% CI 0.4–0.9 <i>Significant reduction in the hospital based but not in the population-based studies</i> <i>No protective effect of sulfasalazine</i>
Qui et al. [25]	26 (17/9)	1,958	Nr	Nr	CRC/Dys: OR = 0.58; 95% CI 0.45–0.75 <i>Significant reduction in the hospital based but not in the population-based studies</i> <i>Significant reduction for CRC alone but not dysplasia</i> <i>5-ASA 1.2 g greater effect than ≤1.2 g, sulfasalazine not effective</i> <i>5-ASA effective in UC for CRC prevention but not for dysplasia and not for CD</i>
Bonovas et al. [24]	31 (19/12)	2,137	Nr	Nr	CRC/Dys: RR: 0.57, 95% CI 0.45–0.71 <i>Significant reduction in the hospital – and population-based studies</i> <i>Significant reduction for both CRC and dysplasia</i> <i>No effect of 5-ASA on CD CRC prevention</i> <i>5-ASA dose effect >1.2 g/d, sulfasalazine not effective</i>
Zeng et al. [26]	5 (5/0)	776	–	776	(This meta-analysis analyzed progression from LGD to HGD/CRC only). Progression to CRC/HGD: HR = 0.91, 95% CI 0.55–1.51 No significance by concomitant PSC status, study quality, sample size, or IBD type

Italics: additional significant findings. Nr, not reported; CRC, colorectal cancer; CD, Crohn's disease, Dys, dysplasia; HGD, high-grade dysplasia; UC, ulcerative colitis; CI, confidence interval; 5-ASA, 5-aminosalicylic acid; CD, Crohn's disease.

with IBD (Table 2) [20–26]. The number of studies included in the individual meta-analyses varied mainly due to the increasing number of original articles on this topic. In general, the studies included in the meta-analyses can be separated according to study setting in population-

based and clinical cohorts, which have a smaller sample size than population-based studies and are vulnerable to selection bias and have uncertain generalizability. Thus, it is interesting that in most meta-analyses, population-based studies show no or only a marginal CRC protective

Table 3. Meta-analyses: use of thiopurines and risk of colorectal neoplasia in patients with inflammatory bowel disease

Author meta-analysis	Studies, <i>n</i> Total (hospital-based/ population-based)	Total cases	CRC cases	Dysplasia cases	Colonic neoplasia risk
Gong et al. [32]	19	Nr	Nr	Nr	RR = 0.71, 95% CI 0.54–0.94, result significant for heterogeneity Analysis separated by case-control (RR = 0.46, 95% CI 0.29–0.74, result significant for heterogeneity) and cohort study (RR = 0.96, 95% CI 0.94–0.98)
Jess et al. [33]	15	1,574	1,344 230 CRC/ high- or low-grade Dys	Nr	OR = 0.87, 95% CI 0.59–1.29 (but significant heterogeneity) In subgroup analysis separation in clinical based (<i>n</i> = 13; [OR = 0.87, 95% CI 0.59–1.09]), case-control (<i>n</i> = 8; OR = 0.83, 95% CI 0.65–1.08, and cohort study (<i>n</i> = 7; OR = 0.93, 95% CI 0.67–1.28)
Lu et al. [34]	24	8,698	6,954 CRC 1,744 (CRC and/or high-grade Dys)	Nr	OR = 0.63, 95% CI 0.46–0.86 Colonic neoplasia risk decreases significant for UC (OR = 0.67, 95% CI 0.45–0.98), but not for CD patients (OR = 1.06, 95% CI 0.54–2.09) Decrease of risk significant for CRC (OR = 0.65, 95% CI 0.45–0.96) and advanced colorectal neoplasia (CRC and/or high-grade Dys) (OR = 0.62, 95% CI 0.44–0.89), but not dysplasia alone (OR = 0.90, 95% CI 0.37–2.21) Protective effect of thiopurines distinct in clinic based (OR = 0.59, 95% CI 0.42–0.82) and case-control studies (OR = 0.40, 95% CI 0.26–0.62), but not in population-based studies (OR = 0.95, 95% CI 0.55–1.62) and cohort studies (OR = 0.98, 95% CI 0.81–1.18)
Zhu et al. [35]	27	Nr	Nr	Nr	Analyses separated by case-control (OR = 0.49, 95% CI 0.34–0.70, result significant for heterogeneity) and cohort study (OR = 0.96, 95% CI 0.94–0.98) In subgroup analysis separation in hospital based (<i>n</i> = 12; OR = 0.37, 95% CI 0.26–0.52) and population based (<i>n</i> = 4; OR = 0.80, 95% CI 0.58–1.12), results significant for heterogeneity
Zeng et al. [26]	5(5/0)	776	–	776	(This meta-analysis analyzed progression from LGD to HGD/CRC only). Progression to CRC/HGD: HR = 0.64, 95% CI 0.23–1.79 No significance by concomitant PSC status, study quality, sample size, or IBD type

Nr, not reported; CRC, colorectal cancer, Dys, dysplasia; HGD, high-grade dysplasia; CI, confidence interval; IBD, inflammatory bowel disease; CD, Crohn's disease.

effect of 5-ASA in contrast to a robust effectiveness of clinical-based studies. This difference may reflect a selection bias of the clinically based studies favoring a higher risk patient group. Only the most recent and most comprehensive meta-analysis by Bonovas reports for the first time a CRC protective effect of 5-ASA for both the clinical-based (RR: 0.46, 95% CI 0.34–0.61) and population-based (RR: 0.70, 95% CI 0.52–0.94) studies. Bonovas et al. [24] included 17 studies with UC patients, 2 studies with CD only, and 12 studies included both UC and CD patients. The reduction of colorectal neoplasia with 5-ASA was only significant in patients with UC but not in patients with CD. Also, based on the available data, a dose effect of 5-ASA exists. 5-ASA doses >1.2 g/day have a more profound effect than <1.2 g/day [22, 24, 25]. There is some inconsistency regarding sulfasalazine, which even

at doses >2 g/day seemed to have no significant impact on CRC prevention [22–25]. However, one has to keep in mind that the recommended maintenance dose of sulfasalazine 2 g/day is equal to only 800 mg 5-ASA daily, which is below the effective dose of mesalamine of 1.2 g to prevent CRC [27]. Despite the overall consistent findings of the protective effects of 5-ASA in the meta-analyses, there are limitations for the interpretation of the results due to different design and methodology of the individual studies, the definitions of the length of 5-ASA exposure, and different degrees of control of confounding. Also, as Bonovas et al. [24] point out, a “small study effect” for the clinical-based studies may be present. A small study effect exists if smaller studies show larger treatment effects than large ones, which is clearly the case for the available 5-ASA studies. No study has yet shown

a beneficial chemopreventive effect of 5-ASA in combination, for example, with anti-TNF agents, which would combine both the anti-inflammatory effects of both agents with the additional benefits of the proposed molecular mechanisms for CRC prevention of 5-ASA. However, if one considers only clinical outcomes, 5-ASA seems to have no added benefit to anti-TNF therapy in patients with UC, but in the available studies, CRC incidences are not reported [28–30].

To ultimately define the role of 5-ASA for chemoprevention in patients with IBD, a prospective, double-blind placebo-controlled trial would be required. However, such a trial would pose several obstacles, making it very unlikely that it will ever occur. Assuming a 2% cumulative incidence of CRC, a minimum of 5,260 UC patients would be needed, with a follow-up time of 10 years [31]. Besides problems with compliance and dropouts, this trial would also be ethically rather challenging to implement if run as a 5-ASA monotherapy trial since a standard therapy for UC would be withheld in the placebo arm. In the setting of a 5-ASA or placebo add-on therapy trial, for example, in combination with biologics, it would be difficult to control for confounders.

Chemoprevention Biologics and Small Molecules (Thiopurines, JAK Inhibitors)

So far, no data are available for chemoprevention with biologics (anti-TNF, anti-IL-12/IL-23, or anti-integrin agents) or newer small-molecule therapies such as Janus kinase (JAK) inhibitors. For none of these agents, specific molecular mechanisms are known, which would interfere with carcinogenesis aside from controlling intestinal inflammation.

Five meta-analyses compiled the results of several studies investigating the chemopreventive effect of thiopurines (Table 3) [26, 32–35]. In contrast to 5-ASA, thiopurines have no known molecular mechanism to block tumorigenesis. The risk of CRC is most likely decreased solely by controlling chronic colonic inflammation, which, aside from genetic predisposition and coexisting PSC, appears to be one of the main drivers for CRC pathogenesis in IBD patients [36]. The initial meta-analyses for thiopurines and the risk of CRC were negative, but later meta-analyses did show a significant chemopreventive effect of thiopurines (Table 3). This change is most likely due to an increasing number of small clinical-based studies, which could indicate again to the aforementioned “small study effect.” All meta-analyses report significant

heterogeneity, impacting the overall interpretation of the results. Population-based studies for thiopurines are negative even if analyses were performed in subpopulations (e.g., those with longstanding colitis in the CESAME cohort) [37]. In contrast to 5-ASA studies, no dose-dependent chemopreventive effects for thiopurines have been reported since data about thiopurine dosing were unreliable and scarce.

Early data suggested a substantial chemoprevention benefit with ursodeoxycholic acid in patients with PSC [38, 39]. However, 2 meta-analyses show heterogeneity across studies and caution that the beneficial effect if at all was only associated with low-dose ursodeoxycholic acid (8–15 mg/kg bodyweight) [40, 41]. Also an overall protective effect for folic acid supplementation on CRC development in patients with IBD has been reported in a meta-analysis of 10 studies with 4,517 patients. The pooled hazard ratio was 0.58 (95% CI, 0.37–0.80), but there was a low-moderate heterogeneity among the studies.

What Are the Current Guideline Recommendations for Chemoprevention?

The current American, British, and European recommendations for chemoprevention in patients with UC are outlined in Table 4 [42–45]. A specific recommendation in regard to chemoprevention for CD patients does not exist. The recent British Society of Gastroenterology Consensus recommends the chemoprevention with 5-ASA [43]. The guideline does not recommend the use of thiopurines, despite a positive meta-analysis showing a protective effect of thiopurines in patients with UC (but not for CD) since “potential benefit in reducing CRC risk must be weighed against the increase in the risk of lymphoma (with thiopurine therapy), particularly in older patients” [34]. The British guidelines also point out the missing data for methotrexate, calcineurin inhibitors, anti-TNF, and anti-integrin agents. The European Crohn’s and Colitis Organization (ECCO) states that 5-ASA may reduce the incidence of CRC but does not give firm recommendations to stop or continue 5-ASA, for example, in the setting of concomitant therapies with biologics [42]. At the time of establishing this guideline, there was still insufficient evidence for the recommendation of thiopurines. The more recent American College of Gastroenterology (ACG) recommendations are embedded in a broader context [44]. In a so-defined key concept (key concepts or statements were based on the extrapolation

Table 4. Guideline recommendation for chemoprevention in IBD

Guideline/publication date	Recommendation
Magro et al. [42] ECCO 2017	"Chemoprevention with mesalamine compounds may reduce the incidence of colorectal cancer in ulcerative colitis. There is insufficient evidence to recommend for or against chemoprevention with thiopurines"
Rubin et al. [44] American College of Gastroenterology 2019	"No medical therapy has demonstrated sufficient prevention of dysplasia or CRC to avoid colonoscopic surveillance in UC." (Key concept statement)
Lamb et al. [43] British Society of Gastroenterology Consensus 2019	"We recommend that patients with ulcerative colitis or IBD-U with left-sided or more extensive disease should be advised to take mesalazine in doses of at least 2 g daily to reduce risk of colorectal cancer." We suggest that thiopurines may reduce the risk of colorectal cancer in patients with ulcerative colitis and IBD-U, but evidence for a chemopreventive role from methotrexate, calcineurin inhibitors, anti-TNF, and anti-integrin agents is lacking at present and they cannot be currently recommended solely for chemoprevention against colorectal cancer (GRADE: weak recommendation, low-quality evidence. Agreement: 93%)
Singh et al. [45] American Gastroenterology Association 2020	"In adult outpatients with moderate to severe UC, who have failed 5-ASAs, and have escalated to therapy with biologic agents, tofacitinib, and/or immunomodulators, there may be no benefit to continuing 5-ASAs over stopping 5-ASAs"
5-ASA, 5-aminosalicylic acid; IBD, inflammatory bowel disease.	

of evidence or an expert opinion and were not amenable to a defined Grading of Recommendations Assessment, Development, and Evaluation [GRADE] process, either because of the structure of the statement or because of the available evidence), Rubin et al. [46] state "Because the primary driver of cancer risk in UC seems to be inflammation, there may be a role for primary prevention (chemoprevention) of CRC by medical treatment of UC. Data from various case-control and cohort studies have demonstrated a protective effect of medical therapies for developing dysplasia in UC, including 5-ASA therapies [25] and azathioprine [35]. However, these results have been inconsistent across studies, and effect sizes are less when adjustments for all confounders, including the degree of inflammation, are included in the analyses [46]. Therefore, optimized medical therapy alone is not an appropriate prevention method for CRC in patients with UC and does not supplant colonoscopy. Using appropriate secondary prevention (screening and surveillance) is necessary at this time to prevent CRC in patients with long-standing UC." The latest 2020 American Gastroenterology Association (AGA) guideline for moderate to severe colitis focuses exclusively on medical treatment and not on chemoprevention [45]. But in the context of the question, if 5-ASA should be continued besides other therapies such as biologics or JAK inhibitors after 5-ASA failure, Singh et al. [45] discuss the following: "While large observational studies and meta-analyses have variably

suggested that UC patients treated with 5-ASA have a lower risk of developing colorectal cancer, recent evidence suggests that chronically active disease is a decisive risk factor for developing neoplasia, and sustained remission is a protective factor against colorectal cancer regardless of therapy used that achieves this outcome" [47].

5-ASA Chemoprophylaxis in IBD: Is It Necessary in the Age of Biologics and Small Molecules?

As stated by Ullman and Itzkowitz [36], colonic inflammation is most likely one of the main drivers of CRC in both UC and CD. If uncontrolled inflammation is the leading cause of CRC in patients with IBD, suppressing inflammation should lower the risk of colitis-associated cancer. This cause-effect relationship is suggested by the recent meta-analyses of thiopurines' effectiveness in UC, since thiopurines have no known direct inhibitory effect on the molecular CRC pathway but only downregulate inflammation-associated genes [34, 35]. Thus, most likely biologics or small molecules, which successfully treat colonic inflammation in UC or CD, are also protective for the development of CRC solely by blocking inflammatory pathways. Overall, given the current knowledge regarding the chemoprevention of CRC in IBD, the optimal therapy is the same as the recommended treatment goals to achieve clinical remission and resolution or improve-

ment of mucosal inflammation. The timing and possibility of achieving optimal outcomes vary across individual patients and therapies [48].

Overall, the current data suggest that in patients with 5-ASA monotherapy, 5-ASA continuation is mandatory to maintain clinical remission. There may be also a chemopreventive beneficial effect, but to separate this effect from the control of inflammation is difficult. If patients are on other more advanced therapies such as biologics or JAK inhibitors and achieve deep remission (clinical remission + mucosal healing), an addition of 5-ASA is according to the current state of knowledge not meaningful. An “extra” chemopreventive effect on top of the recommended endoscopic surveillance is most likely negligible. However, studies in the CRC/IBD high-risk groups with CRC family history or PSC would be interesting and could shed light on the question of an additional chemopreventive effect of such a 5-ASA combination therapy.

Conflict of Interest Statement

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Author Contributions

H.H. performed data collection, reviewed and analyzed the data, and drafted, revised, and approved the final manuscript. S.V. performed data collection, reviewed and analyzed the data, and revised and approved the final manuscript.

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