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DORI SABABLI KELIB CHIQADIGAN TOKSIK GEPATIT: ZAMONAVIY QARASHLAR.

Olimova Madina, Muhammadiyeva Sitora,
Xidoyatova Madina
Toshkent tibbiyot akademiyasi

Izoh. Ushbu tadqiqotning maqsadi gepatotoksiklikka olib keladigan dorilarning yangilangan ro‘yxatini tayyorlash va ilmiy ma’lumotlarga ko‘ra, gepatotoksiklikka olib kelishi mumkin bo‘lgan dori-darmonlarni aniqlash. Gepatotoksik dorilarning ayrim jihatlari gepatotoksiklik, travma turi, gepatotoksiklik mexanizmlari, xavf omillari va klinik ko‘rinishlar kabilarda namoyon bo‘ldi. Gepatotoksiklik ehtimolini va lezyon turini baholash uchun uchta toifa belgilandi: aniq, ehtimoliy va mumkin bo‘lgan. Ro‘yxat gepatotoksikatsiyaga olib kelishi mumkin bo‘lgan 181 dori va 17 kombinatsiyalangan dozalash shakllari yoki terapevtik rejimlardan tuzilgan. Ulardan Metotreksat, Minotsiklin, Vankomitsin, Everolimus, Izoniazid va Tamoksifen ma’lum ehtimoliylar toifasiga kiritilgan. Xulosa: 180 dan ortiq gepatotoksik preparatlar aniqlandi, shulardan oltitasi ma’lum ehtimoliylar toifasiga, aksariyati mumkin bo‘lganlar toifasiga kiritilgan. Axborotni sarhisob qilsak, turli toifadagi dorilar jigar zaharlanishiga olib kelishi mumkin.

Аннотация. Целью этого исследования было подготовить обновленный список препаратов, вызывающих гепатотоксичность, и определить препараты, которые, согласно научным данным, с наибольшей вероятностью могут вызвать гепатотоксичность.. Некоторые аспекты гепатотоксических препаратов были как проявление гепатотоксичности, тип травмы, механизмы гепатотоксичности, факторы риска и клинические проявления. Для оценки вероятности гепатотоксичности и типа поражения были установлены три категории: определенная, вероятная и возможная. Список был составлен из 181 лекарственного средства и 17 комбинированных лекарственных форм или терапевтических схем, которые могут вызвать гепатотоксичность. Из них Метотрексат, Миноциклин, Ванкомицин, Эверолимус, Изониазид и Тамоксифен были отнесены к категории определенных вероятностей.

Выводы: более 180 гепатотоксичных лекарств были идентифицированы, из них шесть были отнесены к категории определенных вероятностей, а большинство - к категории возможностей. Обобщение информации показывает, что различные категории лекарств могут вызывать токсическое воздействие на печень.

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Abstract. The aim of this study was to prepare an updated list of drugs that cause hepatotoxicity and to identify drugs that, according to scientific data, are most likely to cause hepatotoxicity. Some aspects of hepatotoxic drugs were as manifestation of hepatotoxicity, type of injury, mechanisms of hepatotoxicity, risk factors and clinical manifestations. To assess the likelihood of hepatotoxicity and the type of injury, three categories were established: certain, probable and possible. The list was compiled from 181 drugs and 17 combined dosage forms or therapeutic regimens that can cause hepatotoxicity. Of these, Methotrexate, Minocycline, Vancomycin, Everolimus, Isoniazid and Tamoxifen were categorized as definite probabilities. Conclusions: More than 180 hepatotoxic drugs were identified, of which six were categorized as certain probabilities, and most were categorized as possibilities. Summarizing the information shows that different categories of drugs can cause liver toxicity.

Gepatotoksiklik — bu dori vositasi yoki farmakologik bo‘lmagan agent ta’siridan kelib chiqqan shikastlanish. Xavf omillari individual qabul qila olmaslik, yosh, jins, spirtli ichimlik iste’moli, chekish, boshqa dorilarni bir vaqtda qabul qilish, jigar kasalliklari, genetik va ekologik sabablarni o‘z ichiga oladi [1-3]. Jigar toksikligini keltirib chiqarishi mumkin bo‘lgan ko‘pchilik lipofilik preparatlar [4], eng ko‘p uchraydigan sabablari esa antibiotiklar, nosteroid yallig‘lanishga qarshi preparatlar (NYQP) va tutqanoqqa qarshi preparatlaridir [1,5-9]. Vena ichiga yuboriladigan dorilar orasida antibiotiklar va jigar toksikligi bilan bog‘liq bo‘lgan neoplaziya preparatlari mavjud [10].

Gepatotoksiklik ichki va idiosinkratik reaksiyalarga bo‘linishi mumkin. Birinchisi bashorat qilinadigan, dozaga bog‘liq va takrorlanuvchi, lekin ularning uchrashish chastotasi haqida ma’lumot cheklangan. Idiosinkratik reaksiyalar esa immunologik yoki metabolik bo‘lib, oldindan bashorat qilib bo‘lmaydi, dozaga bog‘liq emas va takrorlanmaydi, lekin ular faqat kichik bir qismiga ta’sir qiladi (1/1000 dan 1/100 mingtagacha) [11].

Ichki gepatotoksiklik idiosinkratik gepatotoksiklikdan kamroq uchraydi [12,18-20]. Jigar gistologiyasi jigar toksikligini aniqlash uchun ideal, lekin klinik amaliyotda ko‘pchilik gepatotoksik zararlanishlar biokimyoviy testlarga muvofiq tasniflanadi [21]. Xalqaro Tibbiyot Fanlari Tashkilotlari Kengashi (CIOMS)ning xalqaro konsensusiga ko‘ra, jigar zararlanishi mavjud bo‘lganda jigar fermentlari me’yorlar yuqori chegarasi (MYCH)dan ikki baravar ortiq bo‘lishi kerak. Boshqa tomondan, shikastlanish turlari quyidagicha tasniflanadi:

Gepatotsellyulyar shikastlanish alaninaminotransferaza (ALT) darajasining ikki martadan ortiq izolyatsiyalangan oshishi yoki ALT/ishqoriy fosfataza nisbatining besh martadan ortiq bo‘lishi sifatida aniqlanadi. Xi qonuni bu turdagi shikastlanishni ALT

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qiymatlarining yuqori normal chegaradan (VCH) uch martadan ortiq bo‘lishi sifatida aniqlaydi [24,25].

Xolestatik shikastlanish ishqoriy fosfataza darajasining yuqori normal chegaradan (VCH) ikki martadan ortiq oshishi yoki nisbatning ikki martadan kam bo‘lishi sifatida aniqlanadi.

Aralash shikastlanish ALT va ishqoriy fosfataza darajalarining yuqori normal chegaradan ikki martadan ortiq oshishi hamda nisbatning ikki martadan ortiq, lekin besh martadan kam bo‘lishi sifatida aniqlanadi.

Gepatotoksiklik mitoxondriyalarning disfunksiyasi, hujayra nafas olishini ingibirlaydi yoki yog‘ kislotalarining β-oksidlanishining o‘zgarishi bilan bog‘liq [6,27]. Bu apoptoz, nekroz, autofagiya va, natijada, hujayraning o‘limiga olib keladi [28,29].

Gepatotoksiklikning asosiy klinik-patologik belgilari va uning gistologik ma’lumotlari:

a. O‘tkir gepatit (parenxima yallig‘lanishi, Kupfer hujayralari va sinusoidalarda nekroz bilan tavsiflanadi).

b. Surunkali gepatit (fibroz).

c. Fulminant gepatit (nekroz va yallig‘lanish),

d. Xolestatik gepatit (yallig‘lanish va jigar shikastlanishi).

e. Xolestaz (3-zonada safro to‘siqlari).

f. Yo‘qolayotgan safro kanali sindromi (safro kanali shikastlanishi, xolestaz va yallig‘lanish).

g. Granulematoz gepatit (vorotli yo‘laklarda yoki parenximada granulemalar).

h. Makrovezikulyar steatoz (gepatotsitlarning sitoplazmasida lipid tomchilari).

i. Mikrovezikulyar steatoz (gepatotsitlarning sitoplazmasida kichik lipid tomchilari).

j. Steatogepatit (steatoz, lobulyar yallig‘lanish, gepatotsitlarning to‘planishi va perisellyulyar fibroz) [12,29-31].

Bu belgilar noaniq alomatlar va quyidagi simptomlar bilan birga kechadi: isitma, charchoq, qusish, og‘riq, saraton, peshobning to‘qlashishi, qichishish, assit, ensefalopatiya va transaminazlar darajasining oshishi [16,32,46].

Gepatotoksiklik bilan bog‘liq bo‘lmagan tabiiy mahsulotlarga kiritilmagan taxminan 1100 dori vositasi [19] mavjud bo‘lsa-da, ushbu nojo‘ya hodisani aniqlash murakkab vazifadir.

Shuning uchun har qanday moddaning aniqlanishi va jigar kasalligining boshqa sabablarini istisno qilishga qaratilgan batafsil tekshiruv o‘tkazish zarur [3,8,33]. Bundan tashqari, jigar biopsiyasi gepatotoksiklikni aniqlash uchun asosiy ahamiyatga ega [34]. Shubhali moddaning ta’siri va gepatotoksik reaksiya o‘rtasidagi xronologik

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o‘zaro bog‘liqlik muhim ahamiyatga ega. Dori vositasining gepatotoksiklik bilan bog‘liq ekanligini aniqlash uchun klinik shkalalar, masalan, Russell-Uklaf (RUCAM) sabab-oqibat munosabatlarini baholash usuli va Maria va Victorino (M&V) klinik shkalasi qo‘llaniladi [13-15]. RUCAM shkalasining tarkibi va kriteriylarining amal qilishi uni eng mos keladigan usul deb hisoblashga olib keladi va u gepatotoksiklik bo‘yicha tibbiy xulosa va ekspert xulosasi bilan mos keladigan natijalarni ishlab chiqaradi. Shunga qaramay, dastur narxining yuqoriligi sababli uning klinik amaliyotdagi foydasi cheklangan [35-37].

Maxsus farmakoterapiya mavjud emasligida, gepatotoksiklikni davolash shubhali dori vositasini olib tashlash, simptomlarni davolash va keyingi laboratoriya oldindan testlar o‘tkazishga asoslanadi [38].

Yangilangan gepatotoksik dorilar va bog‘liq omillar ro‘yxati aniqlashni optimallashtirishga va ushbu nojo‘ya hodisaning oldini olishga yordam berishi mumkin. Shunday qilib, ushbu tadqiqotning maqsadi gepatotoksiklik bilan bog‘liq bo‘lgan dorilar ro‘yxatini yangilashdan iborat bo‘ldi.

PubMed/Medlineda qidiruv “jigar kasalligi” (dorilarning ta’siri, shikastlanish, patologiya) va “dori bilan bog‘liq jigar shikastlanishi” MESH terminlari yordamida amalga oshirildi. Qidiruv 2020-yil dekabrigacha ingliz, ispan va fransuz tillarida to‘liq matni mavjud bo‘lgan sarlavha yoki referatda kalit so‘zlar bilan chop etilgan maqolalar bo‘yicha filtrlandi. Maqolalar holat hisobotlari, sharhlar, sistematik sharhlar, klinik sinovlar, nazorat ostidagi sinovlar, randomizatsiyalangan klinik sinovlar va metatahlillar sifatida tasniflangan. Faqat dorilarni qabul qilish sababli gepatotoksiklik bo‘yicha dalillarga ega maqolalar va mavzu bilan bog‘liq deb hisoblangan maqolalar tahlil qilingan.

Gepatotoksiklik mexanizmlari, xavf omillari, klinik ko‘rinishlar, boshqarish, natijalar, jigar fermentlari va dorilarning dozalari — bularning barchasi ushbu tadqiqotni tayyorlashda inobatga olingan.

O‘rtacha qiymatlar va standart og‘ishlar sonli qiymatlar uchun hisoblangan. Nazariy ma’lumotlar, masalan, jigar fermentlari (aspartat aminotransferaza, ALT, FA va umumiy bilirubin) qiymatlari va kiritiladigan preparatning dozalaridir.

Qidiruv 610 ta maqolani aniqladi, ulardan 402 tasi qabul qilish mezonlariga mos kelgan va tanlangan, 208 tasi esa qabul qilish mezonlariga javob bermagan. Ko‘rib chiqish uchun tegishli deb hisoblangan 46 ta boshqa maqola kiritildi.

Gepatotoksiklikni keltirib chiqarishi mumkin bo‘lgan 181 dori va 17 ta kombinatsiyalangan farmakologik dori shakllari yoki terapevtik sxemalar ro‘yxati shakllantirildi. Ushbu dorilardan 6 tasi (Metotreksat, Minosiklin, Vankomitsin, Everolimus, Izoniazid va Tamoksifen) aniq dorilar sifatida tasniflandi, 5 ta kombinatsiyalangan dori shakli yoki terapevtik sxema ehtimollik sifatida tasniflandi,

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119 dori va 11 ta kombinatsiyalangan dori shakli esa mumkin bo‘lganlar sifatida tasniflandi [22, 23, 26].

Har bir dori tomonidan keltirilgan shikastlanish turi aniqlangan bo‘lib, gepatotsellyulyar shikastlanish xolestatik yoki aralash shikastlanishdan ko‘ra ko‘proq uchraydi. Har bir dori uchun aniq ehtimollik bilan ma’lumotlar to‘plangan bo‘lib, ular jadvalga kiritilgan: gepatotoksiklik turi, shikastlanish turi, tashqi ko‘rinishi, gepatotoksiklik mexanizmi, xavf omillari, klinik ko‘rinishlar va natijalar.

Antigipertenziv vositalar, masalan, Enalapril, jigar fermentlari darajasini oshiradi va sariqlik paydo bo‘lishiga olib keladi, jigar tuzilishidagi o‘zgarishlar esa transplantatsiya va o‘limga olib kelgan bo‘lib, bu biopsiya bilan tasdiqlangan [48].

Metildopa (ehtimoliy) uchun jigarning idiosinkratik toksikligi bo‘yicha 9 ta holat qayd etilgan [17]. Ularda, ayniqsa, sariqlik, anoreksiya va ko‘ngil aynishi bilan kasallangan ayollarda gepatotsellyulyar shikastlanish namunasi bor edi. Bundan tashqari, jigar biopsiyasida nekrozlar va yallig‘lanish infiltratlari aniqlangan [49,50].

Gepatotsellyulyar shikastlanishlar, jigar fermentlari darajasining oshishi, sariqlik, isitma va asteniya bilan birga atorvastatin va ezetimib bilan bog‘liq bo‘lgan [51,52].

Propiltiouratsil 1 nafar bemorning o‘limiga sabab bo‘lgan, undan jabr ko‘rganlar ayol va qiz bolalar bo‘lgan. Dori sariqlik, teri qichishi va ozish kabi simptomlarni keltirib chiqargan; nekroz, fibroz, yallig‘lanish infiltrati jigar biopsiyasida aniqlangan.

Metilprednizolonni qabul qilgan bemorlarda jigar fermenti darajasining oshishi, zaiflik va sariqlikning 4 ta holati aniqlangan. Dori qabul qilinishini to‘xtatgandan so‘ng simptomlar yo‘qolgan [54].

Antibiotiklar orasida, ayniqsa, teskari transkriptaza ingibitorlari bilan birga vankomitsin bilan bog‘liq idiosinkratik reaksiya aniqlangan [55]. Nukleozid analoglari va proteaza ingibitorlari doza bilan bog‘liq gepatotoksiklikni keltirib chiqarishi mumkin. Efavirens va nevirapin qabul qilgan bemorlarda transaminazlar darajasining oshishi va kasallanish 1% dan 14% gacha bo‘lgan holatlar haqida xabar berilgan [9]. Gepatit B yoki gepatit C viruslari bilan koinfeksiya antiretrovirusli davolash bilan bog‘liq gepatotoksiklik darajasini oshirishi mumkin.

Kimyoviy terapiya umr davomiyligini oshirishi mumkin, lekin bu jigar shikastlanishiga, steatozdan steatogepatit va jigarning serroziga olib kelishi mumkin. Tamoksifen, Everolimus va Metotreksatdan gepatotoksiklik ehtimoli yuqori darajada [41–44].

Flutamid, Etopozid, Imatinib, Ipilimumab, Oksaliplatin, Temozolomid, Tioguanin, Glatiramer, Azatioprin va Infliksimab gepatotoksiklikning ehtimoliy sabablariga tasniflangan.

Minoisiklinomat bilan shikastlangan ayollar 16 dan 57 yoshgacha bo‘lib, ularga autoimmun gepatit tashxisi qo‘yilgan. Rifampitsin gepatotsellyulyar shikastlanishlarni

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keltirib chiqargan va bundan ayniqsa ayollar ko‘proq shikastlanadi [57, 58]. Quyidagi antibiotiklar gepatotoksiklikning ehtimoliy sabablariga tasniflangan: nitrofurantoin (holatlarning 12% ida, idiosinkratik reaksiya) [59, 60], flukloxatsillin (11 holat, idiosinkratik reaksiya) [61], telitromitsin (oshgan transaminaza darajasi va isitma bilan gepatotsellyulyar shikastlanish) [62], Siprofloksatsin va Trofloksatsin (sotuvdan olib tashlangan).

Itrakonazol, Flukonazol va Ketokonazol bilan bog‘liq jigar shikastlanishi dori suspenziyasi yordamida yaxshilanadi [63].

NYQP (nosteroid yallig‘lanishga qarshi dorilar) jigar shikastlanishiga olib kelishi mumkin bo‘lgan muhim guruh sifatida aniqlangan, asosan, idiosinkratik holatlar, suiiste’mol yoki ortiqcha dozada qabul qilish salbiy oqibatlarni keltirib chiqaradi.

Ushbu ko‘rib chiqishga kiritilgan xavf omillari quyidagilarni o‘z ichiga oladi: yosh, ayollarda, surunkali alkogol iste’moli, birgalikda qabul qilinadigan dorilar, asosiy kasalliklar, semizlik, 2-toifa qandli diabet va insult. Sababchi dorilar qatoriga diklofenak, lumirakoksib va nimesulid kiradi. Asetaminofen jigar nekroziga olib keladigan metabolitlar tufayli keng tarqalgan gepatotoksik modda sifatida tan olingan.

Ba’zi bemorlarda N-asetilsistein va Prednizolon qabul qilganda holat yaxshilangan.

Galotan jigar toksikligini keltirib chiqarishi mumkin bo‘lgan umumiy anestetik edi.

Gepatotoksiklik jigar fermentlari darajasining oshishi, qorin og‘rig‘i, saraton, asteniya, qusish va nekroz bilan namoyon bo‘ladi va jigar biopsiyasi bilan tasdiqlanadi. Kombinatsiyalangan farmatsevtik dori shakllari, masalan, trimetoprim/sulfametoksazol va amoksitsillin/kalavulan kislotasi uchun gepatotoksiklik holatlari idiosinkratik sifatida aniqlangan va ehtimoliy sifatida tasniflangan [57]. Gepatotoksiklik asosan erkaklarda kuzatilgan bo‘lib, bu klinik jihatdan sariqlik va qichishish shaklida namoyon bo‘lgan.

Xavf omili sifatida qariyalik kiritilgan. Ayollarda jigar shikastlanishi, jumladan, gepatosellyulyar shikastlanish, jigar fermentlarining ko‘tarilishi, nekroz, isitma, sariqlik va charchoq kabi holatlar ko‘proq uchraydi.

Tutqanoqqa qarshi dorilar orasida eng muhim ahamiyatga ega bo‘lgan valproy kislota bo‘lib, uning gepatotoksiklik holatlari (gepatosellyulyar tur) oshgan transaminazlar, saraton va anoreksiya bilan namoyon bo‘ladi. Bundan tashqari, mikrovezikulyar va makrovezikulyar steatoz, nekroz va yallig‘lanish infiltratlari jigar biopsiyasida aniqlangan. Ushbu dori 30 yoshgacha bo‘lgan insonlarda jigar shikastlanishiga olib kelishi mumkin.

K. Matik [46] o‘z tadqiqotida bir nechta dorivor-induksiyalangan toksik gepatitlarni tahlil qilib, dorilar jigarga ta’sir ko‘rsatib, sitokinlar, ya’ni

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yallig‘lanishning asosiy vositachilari ishlab chiqarilishiga ta’sir qiladi, degan xulosaga keldi. Kvetiapin ta’sir mexanizmi dopamin (D2) va 5-gidroksitriptamin-2 (5HT2) retseptorlariga antogonizmda yotadi, shu bilan birga, uning metaboliti, N-dezalkilketiapin, noradrenalin transportchisining blokirovkasini amalga oshiradi. Kvetiapin, shuningdek, 5HT2C, 5HT3 va 5HT7 serottonin retseptorlariga ham yaqinlik ko‘rsatadi. U sitoxrom P450 3A4 izofermenti orqali metabolizmga uchraydi. Kvetiapin zaif gepatotoksik dori hisoblanadi va jigar transaminazlari darajasining faqat oz miqdorda, asimptomatik oshishiga olib keladi [47,53, 55, 56].

D. Stefan [60] o‘z tadqiqotida ba’zi dorilarning toksik gepatit jarayoniga ta’sirini o‘rganib, dorilarning katta qismi yog‘da eruvchan ekanligini, jigar tomonidan metabolizmga uchrayotganini va safro yoki siydik bilan chiqarilishini xulosaladi. Dorilarning metabolizmining birinchi bosqichi I faza reaksiyasi sifatida tanilgan bo‘lib, u jigarning sitoxrom p450 tizimi fermentlari tomonidan amalga oshiriladi. Ushbu bosqichda hosil bo‘lgan o‘rta biofaol mahsulotlar turli hujayra organellalari (masalan, mitoxondriyalarga) ta’sir ko‘rsatishi mumkin, bu esa gepatotsitlarning disfunksiyasiga va hujayralarning o‘lishiga olib keladi. Ushbu potentsial toksik o‘rta mahsulotlar keyinchalik II faza reaksiyalarida glukuronokonyugatsiya, glutatiyon-konyugatsiya yoki sulfat-konyugatsiya orqali inaktivatsiya qilinadi [64, 65]. Gepatotoksiklikni cheklash uchun I faza mahsulotlarining hosil bo‘lish tezligi jigar tomonidan ularni inaktivatsiya qilish qobiliyatidan oshmasligi kerak. Faza II kon’yugatsiya reaksiyalariga mas’ul bo‘lgan birikmalarning tugashi yoki yetishmasligi toksik metabolitlarning to‘planishiga olib kelishi mumkin. Bu alohida holat alkogolni suiiste’mol qiladigan va paratsetamol qabul qiladigan bemorlar bilan bog‘liq. Ushbu misolda, hatto past dozali paratsetamol jigarni jiddiy zararlanishiga olib kelishi mumkin.

Abstract. The aim of this study was to prepare an updated list of drugs that cause hepatotoxicity and to identify drugs that, according to scientific data, are most likely to cause hepatotoxicity. Some aspects of hepatotoxic drugs were as manifestation of hepatotoxicity, type of injury, mechanisms of hepatotoxicity, risk factors and clinical manifestations. To assess the likelihood of hepatotoxicity and the type of injury, three categories were established: certain, probable and possible. The list was compiled from 181 drugs and 17 combined dosage forms or therapeutic regimens that can cause hepatotoxicity. Of these, Methotrexate, Minocycline, Vancomycin, Everolimus, Isoniazid and Tamoxifen were categorized as definite probabilities. Conclusions: More than 180 hepatotoxic drugs were identified, of which six were categorized as certain probabilities, and most were categorized as possibilities. Summarizing the information shows that different categories of drugs can cause liver toxicity.

Xulosa.

1. Biz 180 dan ortiq jigar toksikligini keltirib chiqaradigan dori-darmonlarni aniqladik. Ularning oltitasi aniq ehtimolliklarga ega, aksariyati esa mumkin bo‘lgan ehtimolliklarga ega. E’tiborga molik jihati shundaki, topilgan dori-darmonlarning 50% dan ko‘prog‘i idiosinkratik jigar toksikligi bilan bog‘liq bo‘lib, ayol jinsi asosiy xavf omili hisoblanadi. Kasallikka chalingan odamlarning yosh oralig‘i keng.

2. Bundan tashqari, jigar fermentlarining oshishi, sariqlik va isitma — eng ko‘p uchraydigan simptomlardir. Ular jigar hujayralarining zararlanishiga va keyinchalik jigarning nekroziga olib kelishi mumkin. Ko‘p hollarda bemorlarda zararlovchi omil aniqlangandan so‘ng uning ta’sirini to‘xtatganda yaxshilanish yuz beradi.

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