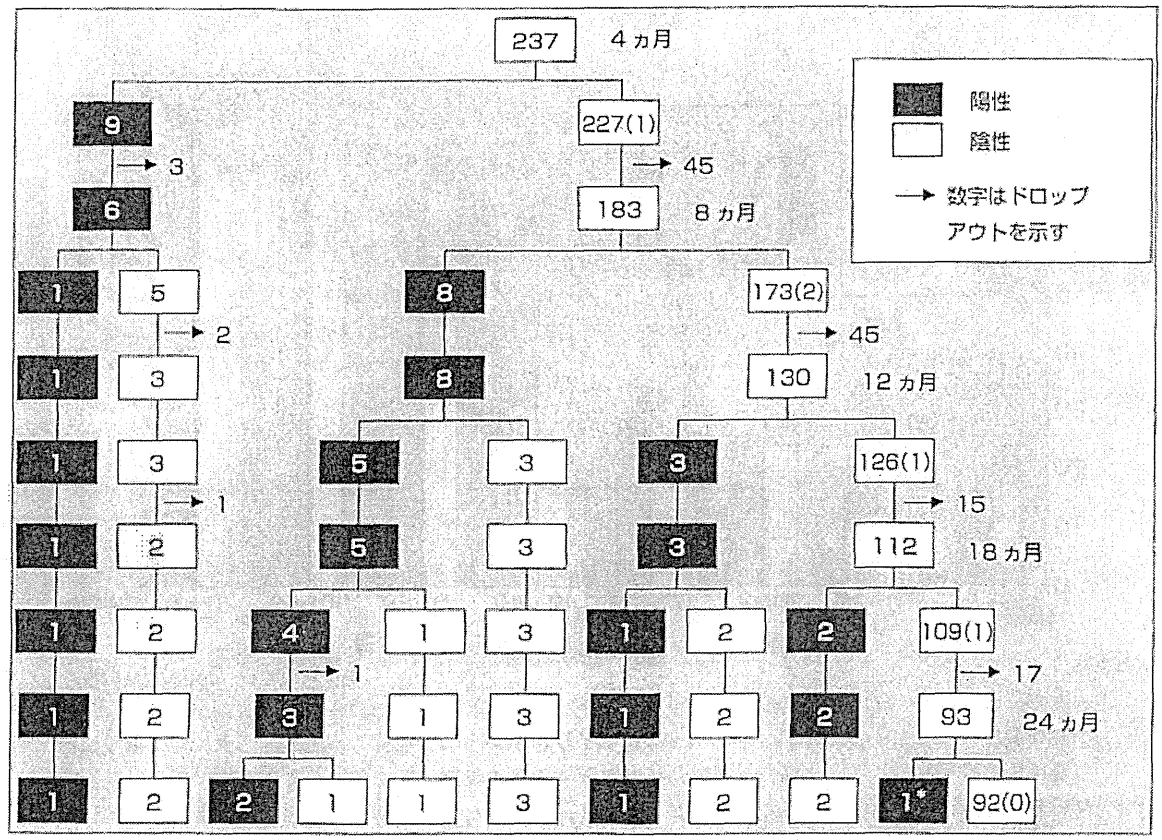

図❸ 生後 4〜24 カ月までの便中抗原測定経過

＊：後に陰性

(Okuda M *et al*, 2007[2]より引用)

後期のほうで高くなっている．筆者が勤務する篠山市の0〜9 歳の小児で 2010 年に調査した便中抗原陽性率は約 2%であった．赤松ら[3]は長野県の高校 2 年生（16〜17 歳）の尿中抗体（ラビラン®）陽性率を検討し，2007 年 3.4%（14/409），2008 年 7.6%（28/370），2009 年 4.9%（22/445），2010 年 4.8%（23/478）で全体では 5.1%（87/1702）であった．小児の *H. pylori* 感染率には地域差があるが，いずれの地域でも顕著に低下してきている．小児・青年期の *H. pylori* 感染率は地域によって若干差はあるものの 2〜5%（高い地域では 10%）であると推定できる．

若年者の感染率であるが，Konno ら[4]は 1995〜1999 年に調査した妊婦 350 名の抗 *H. pylori* 抗体保有率は 19.7%であったと報告しており，約 15 年前であるが若年者の感染率は低下してきていることが明らかである．われわれは H 医科大学学生（主として 5 年生）の *H. pylori* 感染率を検討したが，2001〜2006 年までの抗体保有率は 11.7%(61/520)，2009〜2011 年は尿素呼気試験(UB
でおこない 9.7%（23/238）であった．

2．わが国における *H. pylori* 感染時期

感染時期を知ることは感染経路の特定と除菌時期を
定するうえで重要である．すなわち，乳児から幼児期
期であれば家族内感染が，幼児期後期や学童期であれ
家族外感染が疑われる．感染診断や除菌治療は新たな
染リスクがなくなる時期におこなう必要がある．

感染の多くは小児期に成立すると報告されている．
きに示した兵庫県のデータ[1]からもわかるように，抗
保有率はいずれの年齢層でも低下してきており，右側
のシフトが認められ，成人での新たな感染の頻度はき
めて低いことがわかる．

わが国で便中抗原を用いて乳児から幼児期の感染時
を前向きに検討した二つの報告がある．Konno ら[4]が，

表❶ 生後4ヵ月～6歳までの便中抗原経過

	4ヵ月	8ヵ月	12ヵ月	18ヵ月	24ヵ月	30ヵ月	3歳	4歳	5歳	6歳
検査総数	237	189	142	126	108	80	61	40	33	21
陽性数	9	9	9	8	5	3	1	2	1	2
陽性率	3.8	4.8	6.3	6.3	4.1	3.8	1.6	5.0	3.0	9.5
陽転	9	8	3	2	1	1	0	1	0	1
陽転率	3.8	4.4	2.3	1.7	1.0	1.3	0	2.6	0	5.0
陽転率/月	0.95	1.1	0.58	0.28	0.17	0.22	0	0.22	0	0.42
感染成立	1	2	1	0	0	1	0	0	0	1

幌市で抗 *H. pylori* 抗体陽性の母親から生まれた44名の便中 *H. pylori* 抗原を5年間追跡調査した研究では，5名の感染を確認し，感染時期は1歳4名，4歳1名であった．われわれ[5]は，和歌山市で2001年2月～2002年4月に出生した乳児237名の感染時期を前方視調査した（図❸）．この検討はポリクロナール抗体のHpSAを用いた検討であるが，陽性になっても陰転する症例がまれではなかった．1ヵ月あたりの陽転率は生後4～8ヵ月において最も高く1.1%，ついで生後4ヵ月までの0.95%，生後8～12ヵ月の0.58%で，その後陽転率は低くなった（表❶）．便中抗原陽性が持続し，最終的に感染成立と判断した小児の感染時期は生後4ヵ月1名，8ヵ月2名，1歳，2歳，6歳がそれぞれ1名であった．これらの研究で感染時期を確認できた11名のうち8名（73%）が2歳未満であり，わが国における感染時期は2歳までが高頻度であることが示唆された．われわれは，和歌山市と篠山市において0～9歳の小児約500名を1年以上の間隔で便中抗原で追跡検査したが，陽転児を見出せなかった．このことからも多くの感染は乳児期あるいは幼児期早期に成立していると考えられる．

3．感染経路

家族内感染，とくに母-子感染が重要であることはこれまでも多くの国からの報告があり主要な感染経路のひとつである．一方，途上国では家族外感染がメインというものや，水からの感染が重要であるという報告も多い．Konno ら[4]の報告では感染がある母親の子どもを5歳まで観察したときの感染率は11.3%であった．このことから，感染リスクが一番高い小児でも感染は約1/10となるが，図❶からもわかるようにわが国で少なくとも30～40年間は高い感染率を維持してきたことは何らかの環境因子や水系感染があったと推測され，現在に至っては感染経路や感染様式が変化してきていると考えられる．さらに，小児をとりまく成人の感染率の低下は小児の感染率の急速な低下の要因となっている．

1）家族内感染

家族内はおもな感染経路である．Konno ら[6]によると，*H. pylori* 感染が確認された子どもの家族の検討では *H. pylori* DNA パターンは約7割が母親と一致し，家族と一致しなかったのは約2割であった．篠山市における検討では，小児の感染状況は父母ともに同率であった．この地域では共働きが多いためか，父親が子どもの病院受診に付き添う場面が多く，育児への貢献度が感染経路に関与していると考えられた．

2）家族外感染

家族外として，保育施設や障害児（者）施設での感染があげられる．重症心身障害児施設に入園1年後の抗体陽転率がきわめて高い[7]ことが報告されており，施設内感染が重要であることが示されている．胃チューブの挿入者が多く，吸引を頻回におこない，胃・食道逆流，嘔吐の頻度も高いため感染の機会が相当に高い環境であることは推測できる．

4．感染様式・感染に関与する要因

H. pylori が経口感染であることは一致した見解であるが，感染を媒介するものについては十分解明されておら

ず，具体的に感染予防策を講じることは困難である．

唾液や扁桃，歯垢などからPCR法で*H. pylori*が分離された報告が多くあり，口-口感染経路は重要と考えられている．母の悪心・嘔吐が頻繁であると子の感染率が高くなる[8]というものや家族の胃腸炎症状はとくに2歳未満の乳幼児の感染リスクとなる[9]という報告がある．嘔吐物や下痢便から*H. pylori*が検出されるかどうかの検討でも下剤，催吐剤投与前後の便，唾液，嘔吐物の*H. pylori*培養をおこなったところ，催吐剤で嘔吐後の唾液や下剤投与後の下痢便で培養が可能であった[10]と報告されている．感染者が嘔吐・下痢を伴う病態では通常より感染源になりやすいと考えられる．飲用水については，小児期に飲用した井戸水が同じであると感染菌株のパターンが同一で，井戸水からの感染が示唆された[11]という報告があるが，水からの*H. pylori*検出は困難であり，先進国の主たる感染経路ではないと考えられる．産道感染については，新生時期に便中抗原あるいはPCR法で*H. pylori*が検出される[12]報告があるが，いずれも追跡調査で自然消失し持続感染はなく否定的である．

5．胃癌予防のために小児科医がすべきこと

*H. pylori*は乳幼児期早期に成立した後は新たな感染はきわめて少ないと考えられる．まず，*H. pylori*感染の多くが家族内感染であり，親から子への感染が主であると考えられるが，感染様式は不明であり，感染予防をすることは困難である．したがって，感染源となる大人の除菌治療をおこなうことで感染予防ができるが，乳幼児期に感染するため親になる前の除菌が必要となるだろう．祖父母からの感染があるのかはこれからの検討課題である．すでに感染している小児については小児科医がさらに明らかにすべきことがある．再感染のリスクがなく，かつ胃粘膜変化が可逆的である最適な除菌の時期，また，クラリスロマイシン耐性率が高いことが報告されているため除菌レジメンの検討も必要である．

小児・青年期の*H. pylori*感染率は低下している．小児・青年期において胃癌予防のために*H. pylori*の感染診断・除菌治療をすることは現実的だと思われる．さらに，除菌治療は次世代への伝搬防止となり，いずれ*H. pylori*感染診断さえ必要なくなるであろう．

おわりに

わが国における小児・青年期の*H. pylori*感染率域差があるが2〜10%程度ときわめて低くなってお胃癌予防のための若年者に対する除菌治療も現実的のとなってきた．現在の小児が胃癌に苦しむことが未来をめざすとともに，*H. pylori*感染なしに成長すども達が将来罹患しやすくなる疾患をも考慮してい要があるだろう．

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＜消化管＞

Helicobacter pylori 感染症の診断と治療

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はじめに

胃内に細菌が認められることは19世紀末から観察されていたがその後，否定的な報告が多く，一過性の細菌を除き胃内は無菌の環境であると考えられてきた。しかし，1982年にオーストラリアのMarshallとWarrenによって初めてヒトの胃粘膜からグラム陰性のらせん状桿菌（*Helicobacter pylori*：*H. pylori*）が分離培養され，胃に存在する細菌が世に認められるようになった。

Ⅰ．*H. pylori* の生物学的特徴，感染率，感染時期と感染経路

1．生物学的特徴

H. pylori はグラム陰性のらせん菌で複数の鞭毛をもつ微好気性菌である。胃内の強力な酸から逃れるためによく発達した鞭毛を回転させ，酸度が中性になっている胃粘膜下層に侵入し，胃粘膜上皮細胞や細胞間隙あるいは粘液内に存在する。強いウレアーゼ活性を有し，尿素を二酸化炭素とアンモニアに分解し，このアンモニアが酸を中和し菌の周囲のpHを上昇させて棲息する環境をつくっている。

2．感染率

日本人の感染率は二相性で，60歳台以降は60%以上と非常に高率であるが，60歳未満では30～40%と低くなっている。感染の多くは小児期に成立し，高い感染層は第二次世界大戦による衛生環境が悪かった時代に成立したものと推測されている。便中抗原を用いた検討では小児の感染率は2009年に行った和歌山県の保育園・幼稚園児で4.3%（20/469），2010年に兵庫県篠山市で小学校3年生以下の小児を対象としたもので1.9%（13/689）であった。

3．感染時期と感染経路

乳幼児期は感染のリスクが最も高い時期と考えられている。急性感染の経過をとることはきわめてまれで，ほぼ無症状のうちに感染が成立する。日本で便中 *H. pylori* 抗原を用いて前方視的に感染時期を検討した報告[1,2]では，計11名の小児の感染時期（便中抗原陽転年齢）を同定し，0歳3名，1歳5名，2歳，4歳，6歳が各1名であり初感染は就学前の小児，とくに2歳以下に多いと考えられる。

感染経路は家族内が主であり，とくに母から子への感染が重要であると報告されている[1]が，子育てへの貢献度によるのか，父と子の感染が一致する場合もまれではない。

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表 1　生検組織を用いた診断法の感度・特異度（小児）

報告者	対象数	年　齢	検査法	感度（%）	特異度（%）
Roma-Giannikou E ら[8]（ギリシア）	1590 名	陽性平均 10.4 歳 陰性平均 7.3 歳	培養法 迅速ウレアーゼ 検鏡法	84.6 83.4 93.2	100 99 100
Guarner J ら[9]（Review）	Review	小児	培養法 迅速ウレアーゼ 検鏡法	55～96 75～100 66～100	100 84～100 94～100

Ⅲ．感染診断法

内視鏡による生検組織を必要とするものと必要としない診断法がある。診断法が複数であれば精度はさらに高くなる。それぞれの診断法には特徴があるため，理解したうえで選択する。

1．生検組織を必要とする診断法

生検組織を用いた診断法の感度，特異度（表 1）であるが，いずれの検査法も特異度は悪くないが感度はやや劣ることに注意が必要である。

1）培養法

唯一の直接的証明法であり，薬剤感受性試験もできる。感度がやや落ちるが特異性は 100%であり，陽性であれば感染ありと確定できる。専用培地が必要なため，外注検査となる医療機関が多い。組織を送付する際には *H. pylori* 用の保存輸送用培地が必要であり，検査前に取り寄せておく必要がある。

2）迅速ウレアーゼ試験

胃生検組織中に含まれる菌のウレアーゼ活性を検出することにより，間接的に *H. pylori* の存在を確認する。試薬は尿素と pH 指示薬を利用したもので，アンモニアが生じることによって pH が上昇し，pH の変化に伴う指示薬の変化で診断する。陰性を確認するための時間は 30 分から 3 時間である。薬物などで胃内 pH が上昇すると菌のウレアーゼ活性が低下し偽陰性となる可能性がある。

3）検鏡法

胃生検組織標本上で菌による組織変化と併せて形態学的にらせん状菌を検出し，同時に組織診断も可能であるが熟練が必要である。

2．生検組織を必要としない診断法

1）尿素呼気試験（UBT）（図）

内視鏡を使わない検査法のゴールドスタンダードとされ，*H. pylori* がもつ強いウレアーゼ活性を間接的に測定する方法である。呼気の採取と錠剤が飲めない場合は“うがい”が必要となり，乳児では検査が困難である。^{13}C 尿素製剤を服用し，胃内に *H. pylori* が存在すれば尿素はただちに胃内でアンモニアと $^{13}CO_2$ に分解され，$^{13}CO_2$ は呼気に排出される。服用前後の呼気を採取し，前に採取した呼気中の $^{13}CO_2$ を服用後と比較し増加率から存在を診断する。服用した ^{13}C 尿素がウレアーゼ活性を有する口腔内細菌と接触し，偽陽性の原因となるため，^{13}C 尿素の除去目的で“うがい”が必要である。ユービット錠®とピロニック錠®（いずれも 100 mg）が市販されているが，表面がフィルムコーティングされた錠剤（ユービット錠®）ではうがいの必要はない。錠剤を飲めない場合は約 100 mL の水で溶解する。投与量は 12 歳未満 75 mg，12 歳以上は 100 mg を大まかな目安としていたが，全年齢 100 mg としても構わない。服用後の呼気はユービット錠®では 20 分後に，ピロニック錠®では服用 10 分後（質量分析法）あるいは服用 15 分後（赤外分光法）に採取する。小児では体位変換は必要ない。日本人小児の多施設研究結果では，カットオフ値を 3.5‰とすると感度 97.8%，特異度 98.5%と報告されている[3]。しかし，成人ではカットオフ値 2.5‰が推奨されているので，われわれは 2.5～3.5‰は gray zone として他の診断法を追加している。抗菌薬や酸分泌抑制薬，とくにプロトンポンプ阻害薬などの内服で偽陰性になるため，最低 2 週間は休薬した後に検査する。

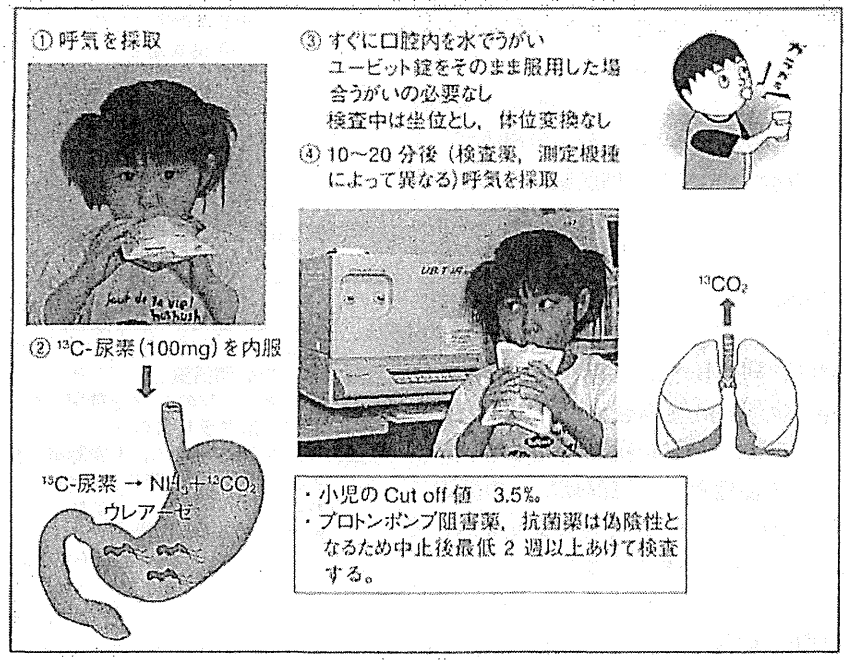

図　小児の UBT（奥田[10]，2012）

2）便中抗原測定法

便を採取するだけというきわめて非侵襲的，簡便な方法は乳幼児，重度の障害児も同様に検査ができる。小児においても成人と同じカットオフ値が用いられるが，抗菌薬の投与の影響については充分な検討はなく，UBT と同様に 2 週間程度の休薬後に検査することが望ましいと考えられる。現在販売されているものはいずれもモノクローナル抗体を用いたもので，小児において 90%以上の感度，特異度が報告されている。イムノクロマト法もあるが，ELISA 法（HpSA plus Meridian，テストメイトピロリ抗原 EIA）が推奨される。

3）抗 *H. pylori* 抗体測定

血清や尿を用いて測定できる。小児では抗原として用いられている菌株によってキット間で感度と特異度に差違がみられ，日本人から分離された菌株を使用したキットでは感度が良い[4,5]。乳児やγグロブリン投与後では受動抗体による偽陽性，除菌後は陰性となるまで長期間を要し偽陽性となる。また，感染の早期や年少児では偽陰性となるため注意が必要であり，診断法として単独では用いない。一方，抗菌薬の影響は受けず，特異度は良好であるため，これらの特性を知っていれば感染の目安となる。

3．その他の検査

H. pylori 感染児では非感染児と比較して血清ペプシノゲンⅠ，Ⅱ値，ガストリン値が上昇する。われわれの検討では血清抗体陽性の 20 歳以下の小児・青年 26 名のうち 8 名（31%）がガストリン 200 pg/mL 以上で，このうち 3 名が 800 pg/mL 以上（800 以上で定量なし）であった。ペプシノゲン，ガストリンが高値の場合，*H. pylori* 感染を疑う必要がある。

Ⅳ．*H. pylori* が関連する疾患，除菌治療が考慮される疾患

H. pylori 感染児の多くは無症状である。『小児期ヘリコバクター・ピロリ感染症の診断・治療，および管理指針[6]』に記載された以下の疾患について除菌治療が考慮される。

1．胃潰瘍，十二指腸潰瘍

日本の小児では，十二指腸潰瘍の約 80%，胃潰瘍の約 40%に *H. pylori* 感染が証明される[7]。

初発・再発を問わず，除菌療法が治療の第1選択である。除菌治療により維持療法なしに潰瘍再発が抑制されることは世界的にコンセンサスが得られている。活動性潰瘍では，除菌治療後プロトンポンプ阻害薬などの酸分泌抑制薬の投与を行うことが望ましい。

2．慢性胃炎

内視鏡検査と組織検査により診断する必要があり，1）症状改善を期待し本人および親が希望する，2）胃粘膜の萎縮が証明される，3）胃がんの家族歴を有する場合，除菌療法が考慮される。しかし，*H. pylori* 慢性胃炎と腹部症状との関連について確立した見解はなく，除菌により症状の消失ないし改善が得られる保証はない。

3．蛋白漏出性胃症

除菌治療により血清蛋白値や内視鏡・病理所見の正常化がみられることがある。*H. pylori* 感染以外に原因が見出されない場合に実施する。

4．鉄欠乏性貧血

小児では，*H. pylori* 感染と鉄欠乏性貧血との関連が多く報告されている。とくに，10歳以降の年長児の原因不明・再発をくり返す鉄欠乏性貧血には感染診断を行い，感染があれば除菌治療を考慮する。

5．血小板減少性紫斑病

成人（日本人）の *H. pylori* 陽性慢性 ITP 患者の約半数が除菌後に血小板増加を認められることが明らかとなってきた。成人では慢性 ITP の確定診断後早期に感染診断を実施し，*H. pylori* 陽性例に対しての first-line 治療として除菌治療をすることは，EBM として確立されてきている。小児の効果についてはさまざまな報告があるが，効果があったとする症例報告も散見され，治療抵抗性の症例あるいは無治療で経過観察中の症例（血小板数が正常化しない）における治療選択の一つと考えられる。

表2　小児の除菌療法に用いられる主な薬剤と一般的な用量

	用量 (mg/kg/日)	最大量 (mg/日)
プロトンポンプ阻害薬		
ランソプラゾール	1.5	60
オメプラゾール	1.0	40
抗菌薬		
アモキシシリン	50	1,500
クラリスロマイシン	10~20	800
メトロニダゾール	10~20	500

プロトンポンプ阻害薬はいずれか1剤，抗菌薬は1次除菌療法としてアモキシシリン，クラリスロマイシンの2剤を使用。ペニシリンアレルギーではクラリスロマイシン，メトロニダゾールの2剤を用いる。1次除菌が失敗した場合の2次除菌としてアモキシシリン，メトロニダゾールの2剤を用いる。いずれも分2投与とし，治療期間は原則7日間。

（加藤ら[6] 2005 を一部改変）

V．除菌治療法（表2）

1．一次除菌

まず選択される除菌薬剤は，プロトンポンプ阻害薬とアモキシシリン，クラリスロマイシンの3剤併用療法（PPI/AC）である。薬剤アレルギーに注意し，ペニシリンアレルギーがある場合はアモキシシリンをメトロニダゾールに変更する。投与期間は7日間が原則であるが，小児では14日間投与を推奨する意見もある[6]。副作用として下痢，味覚異常，悪心，発疹などがみられる。近年，除菌成功率は低下していると報告されており，主な原因はクラリスロマイシン耐性である。

2．二次除菌

一次除菌療法で除菌治療に失敗した場合，抗菌薬をクラリスロマイシンからメトロニダゾールに変更し，アモキシシリン・メトロニダゾール・プロトンポンプ阻害薬の3剤併用療法（PPI/AM）を7日間行う。

3．除菌判定法（表3）

除菌判定は治療終了後4週以降に実施する。判定時期を遅らせるほど診断精度は高くなる。除菌判定は，感染診断と同じ方法を用いるが，抗

表 3　小児の除菌判定

1）除菌判定は治療終了後 4 週以降に実施する。
2）判定時期を遅らせるほど診断精度は高くなる。
3）除菌判定は，生検組織を用いる診断法（培養法，迅速ウレアーゼ試験，鏡検法）ないし生検組織を用いない診断法（尿素呼気試験，便中抗原検査）で行う。
4）抗体測定法は除菌判定には用いない。
5）生検組織を用いた診断法では偽陰性に注意する。
6）尿素呼気試験では偽陽性が問題となるため，とくに低値の陽性ではただちに再除菌をせずに他の診断法の追加や追跡検査を行う。
7）最終的には検査を行ったすべての診断法が陰性の場合に除菌成功とする。

H. pylori 抗体測定は陰性化するまでに長期間を要するため除菌判定には用いない。複数の検査を併用することで感染診断の精度が高くなるため，2 法以上で除菌判定を行うことが望ましい。

Ⅵ. *H. pylori* 除菌治療の保険適用

（2012 年 4 月現在）

保険適用の対象疾患は *H. pylori* 感染がある胃潰瘍，十二指腸潰瘍，胃 MALT リンパ腫，特発性血小板減少性紫斑病，早期胃がんに対する内視鏡術後胃である。一次除菌治療としてプロトンポンプ阻害薬，アモキシシリン，クラリスロマイシンの 3 剤併用療法 7 日間，一次除菌治療に失敗した場合，二次除菌治療としてクラリスロマイシンをメトロニダゾールに変更した 3 剤併用療法 7 日間が適用となる。ただし，「小児に対する安全性は確立していない」と記載されていること，鉄欠乏性貧血や慢性胃炎などでは適用外であり，診療に際しては現時点の情報を本人と保護者に十分説明したうえで治療方針を決定することが重要である。

おわりに

小児の *H. pylori* 感染率の激減により胃十二指腸潰瘍は，小児期ではまれな疾患となってきた。一方，*H. pylori* 感染と胃がんとの関連が明らかになっており，胃がん予防として小児期の感染をどのようにコントロールするかは，今後の課題になると考える。

Key Points

❶ 小児の *H. pylori* 感染診断は 6 種の診断法からそれぞれの特徴を考慮して選択するが，複数であれば精度が高くなる。

❷ 小児の除菌治療は「小児に対する安全性は確立していない」と記載されており，適用外疾患も多く十分説明したうえで治療方針を決定することが重要である。

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EDITORIAL

Management of bleeding and artificial gastric ulcers associated with endoscopic submucosal dissection

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Abstract

Endoscopic submucosal dissection (ESD), an endoscopic procedure for the treatment of gastric epithelial neoplasia without lymph node metastases, spread rapidly, primarily in Japan, starting in the late 1990s. ESD enables en bloc resection of lesions that are difficult to resect using conventional endoscopic mucosal resection (EMR). However, in comparison to EMR, ESD requires a high level of endoscopic competence and a longer resection time. Thus, ESD is associated with a higher risk of adverse events, including intraoperative and postoperative bleeding and gastrointestinal perforation. In particular, because of a higher incidence of intraoperative bleeding with mucosal incision and submucosal dissection, which are distinctive endoscopic procedures in ESD, a strategy for endoscopic hemostasis, mainly by thermo-coagulation hemostasis using hemostatic forceps, is important. In addition, because of iatrogenic artificial ulcers that always form after ESD, endoscopic hemostasis and appropriate pharmacotherapy during the healing process are essential.

Key words: Artificial ulcer; Endoscopic hemostasis; Endoscopic submucosal dissection; Gastric epithelial neoplasia; Hemostatic forceps

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INTRODUCTION

Endoscopic submucosal dissection (ESD) is a novel endoscopic procedure developed in the 1990s[1,2], and is characterized by the use of electrosurgical knives for mucosal incision and submucosal dissection[3-15]. In ESD, the resected size and shape of tumors can be controlled, and even lesions difficult to resect by endoscopic mucosal resection (EMR) can be resected en bloc by ESD. As this technique permits en bloc resection of tumors, ESD has the advantages of enabling accurate pathological assessment and reducing the risk of local recurrence[2,16-19].

However, ESD requires a higher level of endoscopic competence than EMR. In addition, as a result of ESD being used to treat larger lesions and lesions with ulcerative findings, operation time is longer, with a higher risk

of adverse events such as bleeding and gastrointestinal perforation[20-29]. The incidence of procedure-related bleeding is higher with ESD than with EMR, and to permit safe completion of ESD, control of bleeding is very important. In this article, we discuss the characteristics of ESD-related bleeding (intraoperative and postoperative bleeding) and endoscopic hemostasis. Furthermore, to prevent postoperative bleeding, we also discuss the pharmacotherapy of artificial ulcers after ESD.

ENDOSCOPIC HEMOSTASIS USING HEMOSTATIC FORCEPS

Endoscopic hemostatic methods for peptic ulcers include various techniques, such as local injection of hypertonic saline-epinephrine (HSE) and ethanol, mechanical hemostasis using endoscopic hemoclips, and thermo-coagulation hemostasis[30,31]. Local injection of HSE alone is inferior to combination therapy with other hemostatic methods, but the clear superiority of any one method has not been definitively established[32]. Thermo-coagulation devices include contact thermal devices such as heater probes and hemostatic forceps, and non-contact thermal devices such as an argon plasma coagulator[33,34].

For hemostasis of ESD intraoperative bleeding, Enomoto *et al*[35] reported the usefulness of a method of thermo-coagulation hemostasis using monopolar hemostatic forceps in combination with an endoscope equipped with a water-jet system. Hemostatic technique in ESD, which differs from hemostasis for usual gastrointestinal bleeding, is often characterized by the need for repeated hemostasis during both mucosal incision and submucosal dissection. In addition, precise hemostatic maneuvers are required, in order not to interfere with the subsequent procedure after hemostatic treatment[36,37]. Therefore, hemostatic forceps, which enable reliable hemostasis when, with re-holding of the ruptured vessels permissible several times before coagulation, bleeding points can be accurately grasped, are useful for hemostasis in ESD-related bleeding[38,39] (Figure 1).

With wider use of ESD, hemostasis using hemostatic forceps has become routine at medical centers, and its usefulness for bleeding from exposed vessels at the base of peptic ulcers has also been reported[40,41]. Moreover, the usefulness not only of monopolar, but also of bipolar hemostatic forceps, has been reported[42].

MANAGEMENT OF BLEEDING DURING AND AFTER ESD

ESD-related bleeding includes intraoperative bleeding associated with procedures such as mucosal incision and submucosal dissection, and delayed bleeding, which occurs postoperatively from exposed vessels at ulcer bases. Appropriate management of each type of bleeding is required.

Endoscopic hemostasis for intraoperative bleeding

In ESD, the incidence of intraoperative bleeding, which is to some degree unavoidable given the nature of techniques such as incision and dissection, is as high as 22.6%[16]. In particular, with ESD for lesions in the upper third of the stomach, because of abundant vessels in the submucosa, the incidence of intraoperative bleeding is relatively high[43]. To predict intraoperative bleeding, identification of the submucosal vascular structure by preoperative endoscopic ultrasonography can be useful[44].

Of the series of techniques in ESD, bleeding is inevitable with submucosal local injection and mucosal incision because they are blind procedures in the vascular-rich submucosal tissue. To produce higher hemostatic ability, a small amount of epinephrine to a concentration of 0.0005% is added to the submucosal cushion (glyceol, Chugai Pharmaceutical Co., Tokyo Japan). On the other hand, during submucosal dissection, bleeding can be avoided at all sites by making every effort to visually identify vessels and not perform dissection blindly. Oyama *et al*[45] noted that identification of vessels prior to submucosal dissection and prophylactic thermo-coagulation are most important in preventing ESD intraoperative bleeding. Toyonaga *et al*[13,46] stated that knowing the correct layer of the submucosa containing fewer vessels and existing fibrous tissue, is important in reducing ESD intraoperative bleeding.

When bleeding occurs during ESD, by washing out the blood with the water-jet system and using a transparent attachment hood, a clear visual field can be maintained, and bleeding points can be rapidly identified[35]. For bleeding from vessels smaller than the electrosurgical knife tip or arm, hemostasis by thermo-coagulation with the knife is usually possible. For bleeding from vessels larger than the electrosurgical knife tip or arm, or bleeding for which hemostasis with the knife is difficult, hemostatic forceps are used (Figure 2). Fujishiro *et al*[47] reported that hemostatic forceps for vessels smaller than 2 mm in diameter, and hot biopsy forceps for vessels larger than 2 mm in diameter, are useful. When hemostasis by thermo-coagulation cannot be achieved, hemostasis using endoscopic hemoclips is necessary, so that subsequent procedures are not hindered.

Hemostasis for delayed bleeding

Delayed bleeding after ESD occurs in 0%-9% of cases[6,16,18,28,48-54] (Table 1). For resected lesions located in the middle and lower third of the stomach, the incidence is higher. Bleeding occurs when vessels at ulcer bases rupture due to physical stimulation by peristalsis or due to chemical stimulation, for example, by bile reflux[48]. Delayed bleeding often occurs within 24 h postoperatively and is related to lesion location, size, and ulcer-findings[48,55]. For delayed bleeding, in almost all cases, hemostasis is achieved with urgent endoscopic hemostasis[56]. However, cases requiring vascular embolization because endoscopic hemostasis could not be achieved[57], and cases complicated by disseminated intravascular coagulation the day after delayed bleeding[58] have been reported, so caution is necessary.

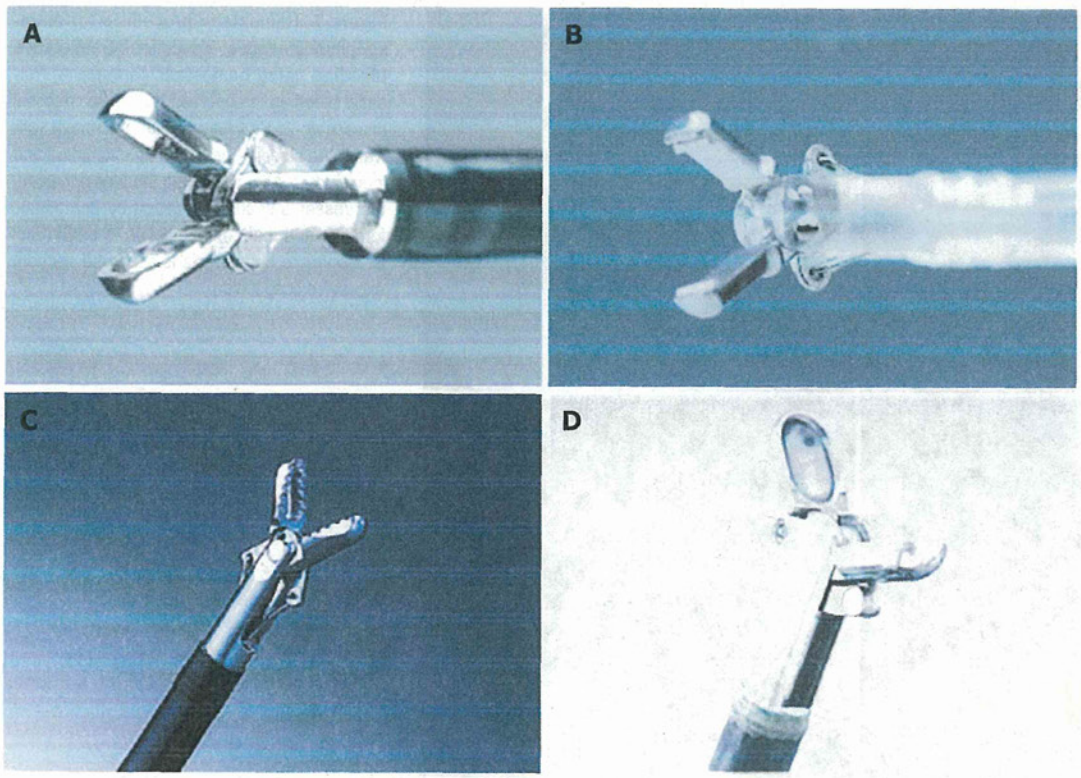

Figure 1 Hemostatic forceps tips. A: Monopolar hemostatic forceps (HDB2422W; Pentax, Tokyo, Japan); B: Bipolar hemostaticforceps (H-S2518; Pentax, Tokyo, Japan); C: Hemostatic forceps (Coagrasper: FD-410LR; Olympus, Tokyo, Japan); D: Hot biopsy forceps (FD-1L-1; Olympus, Tokyo, Japan).

Table 1 Delayed bleeding rate of endoscopic submucosal dissection for gastric epithelial neoplasia

Author	Year	Total cases	Delayed bleeding (%)	En bloc resection rate (%)
Oda *et al*[48]	2005	945	6	93
Kakushima *et al*[49]	2006	383	3.4	91
Imagawa *et al*[18]	2006	196	0	93
Onozato *et al*[50]	2006	171	7.6	94
Oka *et al*[16]	2006	195	6.2	83
Hirasaki *et al*[51]	2007	112	7.1	96
Ono *et al*[6]	2008	161	8.7	99
Hoteya *et al*[52]	2009	572	4.9	95
Isomoto *et al*[53]	2009	510	1.8	95
Tsuji *et al*[54]	2010	398	5.8	NA
Akasaka *et al*[28]	2011	1188	3.1	95

NA: Not analyzed.

To prevent delayed bleeding, prophylactic coagulation of exposed vessels at the bases of artificial ulcers that occur after ESD lesion resection is very useful. According to Takizawa *et al*[59], the cause of delayed bleeding is due more to insufficient prophylactic thermo-coagulation than insufficient primary hemostasis during ESD[60], because the site of delayed bleeding is not the site of endoscopic hemostasis during surgery. In addition, a study has been conducted on the prevention of delayed bleeding by evaluation of blood flow at ulcer bases using endoscopic Doppler ultrasound (US). Uedo *et al*[61], based on blood flow detected using Doppler US, reported that, by coagulation of vessels seen at artificial ulcer bases after ESD lesion resection, delayed bleeding is reduced, and unnecessary thermo-coagulation of vessels without blood flow can be avoided. On the other hand, Choi *et al*[62] reported that prophylactic closure of gastric EMR-induced ulcers with metal hemoclips prevent delayed bleeding.

In 2008, a survey of treatment methods for peptic and artificial ulcer bleeding was conducted at nine departments of high-volume center hospitals in Japan[63]. For endoscopic hemostasis of peptic ulcer bleeding, the number one method used was clipping (32.9%), followed by coagulation forceps (23.5%). In contrast, for artificial ulcer bleeding, coagulation forceps (77.8%) were used significantly more. In addition, the proportion of patients who underwent second-look endoscopy, compared to peptic ulcers, was significantly lower for artificial ulcers (86% and 71%, respectively).

The effectiveness of second-look endoscopy after hemostasis of peptic ulcer bleeding has previously been shown[64,65]. However, according to Goto *et al*[66], for artificial ulcers, no significant difference in the incidence of delayed bleeding before and after second-look endoscopy was found. This suggests that delayed bleeding after ESD, irrespective of whether second-look endoscopy is performed, may develop. However, for artificial ulcers located in the lower third of the stomach, compared to ulcers located in the upper and middle third of the stomach, because delayed bleeding occurs earlier, careful follow-up observation or early second-look endoscopy may be useful[54,66].

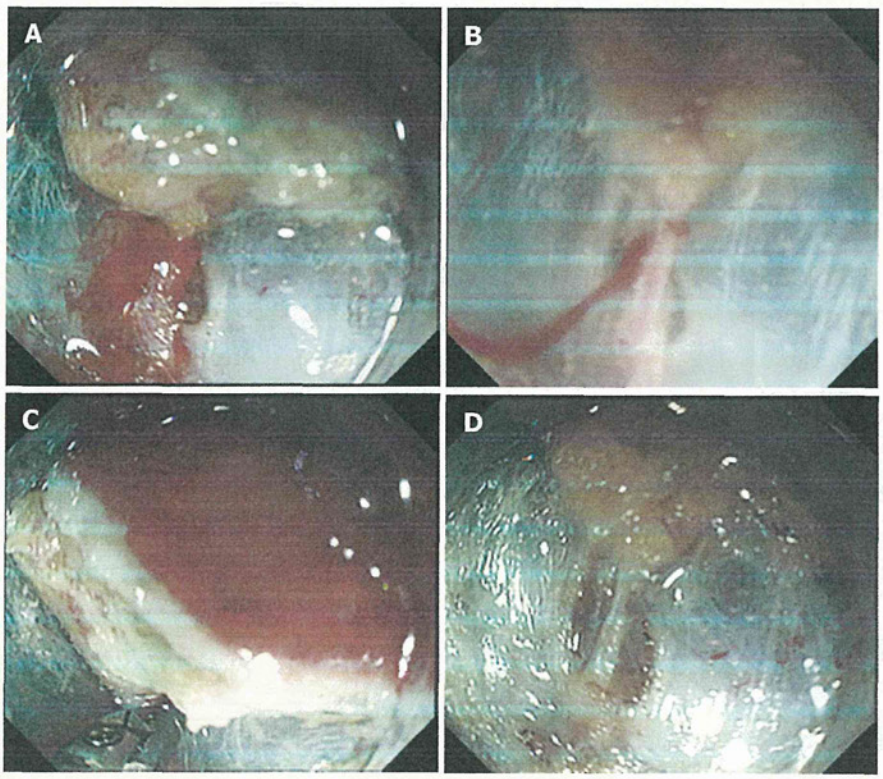

Figure 2 Hemostatic procedure for endoscopic submucosal dissectionintraoperative bleeding using hemostatic forceps. A: Pulsatile bleeding is observed during submucosal dissection; B: By filling the tip attachment with water, the bleeding point can be pinpointed and identified; C: After identifying the bleeding point, the vessel is securely grasped by hemostatic forceps, and thermo-coagulation is performed; D: Complete hemostasis is achieved, without excessive coagulation.

MANAGEMENT OF ARTIFICAL GASTRIC ULCERS AFTER ESD

Pharmacotherapy of artificial ulcers that develop after ESD lesion resection is also important to prevent delayed bleeding. However, management must take into account the differences in etiology between peptic ulcers and artificial ulcers after ESD.

Comparison of peptic ulcers and artificial ulcers

Currently, proton pump inhibitors (PPIs) are the drugs of first choice for treatment of peptic ulcers, and when a PPI cannot be used, an H2-receptor antagonist (H2RA) is selected. Treatment is generally for 8 wk. A meta-analysis of ulcer healing rates reported significantly higher ulcer healing rates with PPIs than with H2RAs[67,68]. In addition, in a meta-analysis of the efficacy of preventing recurrence of bleeding gastric ulcers, no differences in rebleeding rates, surgical intervention rates, or mortality rates between the two classes of drugs were reported[69].

The etiology of artificial ulcers after gastric ESD and peptic ulcers also differs greatly[70]. First, peptic ulcers develop, at least in part, due to hyperacidity, whereas artificial ulcers form in a hypoacidic environment in which there is severe mucosal atrophy. Second, peptic ulcers develop at sites where there is breakdown of gastric mucosal defense mechanisms, whereas artificial ulcers occur iatrogenically at sites where mucosal defense mechanisms are intact. Third, peptic ulcers include ulcers deeper than the submucosa, and inflammation spreads in the ulcer periphery, whereas artificial ulcers, because they basically occur due to submucosal dissection, are relatively shallow ulcers down to the submucosa, and the inflammation is localized. Despite these differences, treatment of an artificial ulcer after gastric ESD, based on treatment for a peptic ulcer, is empiric, with an anti-acid drug for 8 wk[63] (Table 2).

Anti-acid drugs for artificial ulcers

For artificial ulcers that develop after ESD for gastric mucosal lesions without preoperative ulcer findings, Kakushima *et al*[71] reported that healing occurred within 8 wk with PPI administration for 8 wk, irrespective of ulcer size or location. In addition, factors that influence artificial ulcer healing such as artificial ulcer size, location, *Helicobacter pylori* infection status, and extent of gastric mucosal atrophy had no effect. However, with fibrosis deeper than the submucosa of lesions prior to ESD, healing may be delayed[72,73]. According to Huang *et al*[74], although the recurrence rate of ESD artificial ulcers is lower than that of peptic ulcers, *Helicobacterpylori* infection and lesion ulcer findings are risk factors for recurrence. In contrast, Oh *et al*[75] reported that, because the extent of healing of artificial ulcers 4 wk after ESD is determined by the size of the ulcer initially formed, the duration of PPI treatment should be decided based on this parameter.

For artificial ulcers after EMR, Lee *et al*[76] compared PPIs in 1-wk and 4-wk treatment groups. They found that, after 4 wk, ulcer size, stage, subjective symptoms, and use of other mucosal-protective antiulcer drugs did not significantly differ between the groups. Niimi *et al*[77] reported that administration of PPI for 2-wk for artificial ulcers after ESD may be sufficient to help them heal. These results suggest that, for artificial ulcers, unlike peptic ulcers, the importance of acid secretion inhibition

Table 2 Healing process of gastric artificial ulcers after endoscopic submucosal dissection

Author	Year	Total cases	Drugs administration	Weeks	Ulcer healing rate (%)		Average ulcer size	
					4 wk	8 wk	Maximal diameter (mm)	Resected area (mm^2)
Kakushima *et al*[71]	2004	70	PPI + sucralfate	8	NA	100	34.7	NA
Lee *et al*[76]	2004	26	OPZ 20 mg	1	12	NA	NA	503
		34	OPZ 20 mg	4	15	NA	NA	575
Yamaguchi *et al*[78]	2005	29	OPZ 20 mg	8	NA	NA	27.8	NA
		28	Famotidine 40 mg	8	NA	NA	22.4	NA
Uedo *et al*[79]	2007	73	RPZ 20 mg	8	NA	83	41	NA
		70	Cimetidinde 800 mg	8	NA	89	40.5	NA
Asakuma *et al*[80]	2009	28	RPZ 20 mg + ES 3.0 g	8	40.7	96.3	NA	1306
		28	RPZ 20 mg	8	11.5	76.9	NA	1274
Kato *et al*[81]	2010	31	RPZ 10 mg + rebamipide 300 mg	4	68	NA	35	NA
		31	RPZ 10 mg	4	35	NA	31	NA
Fujiwara *et al*[82]	2011	30	RPZ 20 mg + rebamipide 300 mg	8	NA	86.7	41	1453
		31	RPZ 20 mg	8	NA	54.8	42.8	1521
Niimi *et al*[77]	2011	55	RPZ 10 mg	2	NA	80.0	32.7	NA

NA: Not analyzed; PPI: Proton pump inhibitor; OPZ: Omeprazole; RPZ: Rabeprazole; ES: Ecabet sodium.

in the ulcer healing process may be low.

Yamaguchi *et al*[78] compared PPI-treatment and H2RA-treatment groups in patients with artificial ulcers after EMR. They reported no differences in the incidence of delayed bleeding or ulcer size at 30 d and 60 d postoperatively. They did state that artificial ulcers healed more easily than peptic ulcers, and they concluded that, for artificial ulcers with severe bleeding within 24 h after surgery, treatment with H2RA drugs, whose onset of inhibition of gastric acid secretion is more rapid than that with PPIs, is appropriate.

Uedo *et al*[79] compared PPI-treatment and H2RA-treatment groups in patients with artificial ulcers after ESD. There were no differences in the incidence of delayed bleeding or ulcer healing rates between the groups. However, the cumulative non-bleeding rate using the Kaplan-Meier method was significantly higher in the PPI group. Moreover, on multivariate analysis, PPI treatment was an independent factor in reducing the rate of delayed bleeding. Their results suggested that PPIs are more effective than H2RAs for preventing ESD delayed bleeding.

For post-EMR ulcers and post-ESD ulcers, in terms of formation by endoscopic resection, with the exception of size, the pathophysiology is the same. However, in studies to date, with regard to ulcer healing and prevention of delayed bleeding when artificial ulcers are treated with acid secretion inhibitors, there is no agreement in the results. Regarding the need for and duration of treatment with acid secretion inhibitors for artificial ulcers, there is still room for debate.

Mucosal-protective antiulcer drugs in artificial ulcers

In the treatment of peptic ulcers, there is no evidence that combined therapy with a PPI and a mucosal-protective antiulcer drug is superior to a PPI alone. However, in artificial ulcers, an additive effect of mucosal-protective antiulcer drugs has been reported (Table 2). Asakuma *et al*[80] compared combined therapy with a PPI (rabeprazole 20 mg/d) and ecabet sodium (3.0 g/d) *vs* the PPI alone for artificial ulcers after ESD. At 4 wk and 8 wk, ulcer healing rates were significantly higher in the combined treatment group. In addition, Kato *et al*[81] compared combined therapy with a PPI (rabeprazole 10 mg/d) and rebamipide (300 mg/d) *vs* the PPI alone for artificial ulcers after ESD. At 4 wk, the ulcer scarring rate was significantly higher in the combined treatment group. Similarly, Fujiwara *et al*[82] compared combined therapy with a PPI (rabeprazole 20 mg/d) and rebamipide (300 mg/d) *vs* the PPI alone for artificial ulcers after ESD. At 8 wk, the ulcer scarring rate was significantly higher in the combined treatment group.

Thus, among the mucosal-protective antiulcer drugs, there are drugs that accelerate ulcer healing. This may be attributable to differences in the etiology between artificial ulcers and peptic ulcers, as previously mentioned, but further evidence must be accumulated.

CONCLUSION

With the increasing use of ESD for gastric epithelial neoplasia, management of ESD-related bleeding and artificial ulcers after lesion resection has become an important issue not only in Japan, but throughout the world. Therefore, more effective endoscopic hemostatic methods and appropriate pharmacotherapy of artificial ulcers, taking into account their etiology, are becoming increasingly important. Moreover, safer and more reliable ESD techniques must be developed.

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Image of the Month

Microcoil Slipping Out of the Gastric Varices

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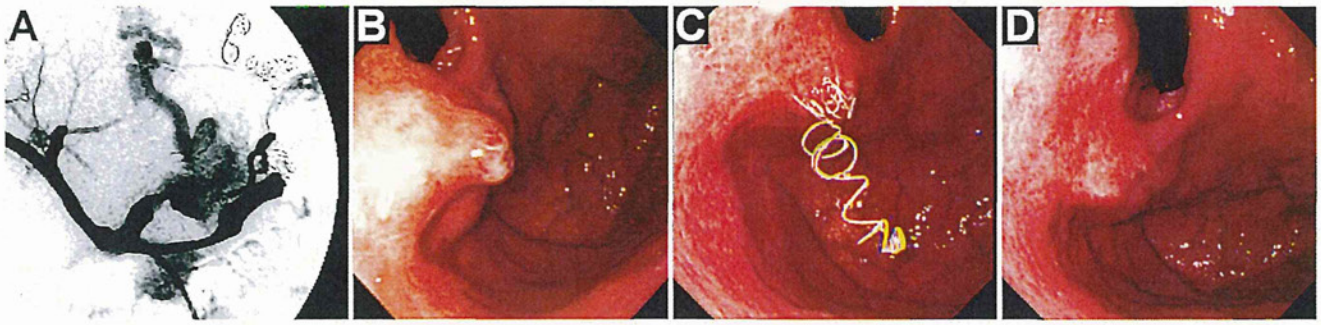

A 67-year-old man with alcoholic cirrhosis developed a gastric varix with a gastrorenal shunt. He underwent the interventional radiology of balloon-occluded retrograde transvenous obliteration and percutaneous transhepatic obliteration using ethanolamine oleate and microcoils (Figure *A*). Three years after the radiologic procedures, a part of the coil was found to be exposed at the apex of the gastric varix with ulceration (Figure *B*). Although ulceration was aggravated after 5 months, no sign of bleeding was observed. To evaluate blood flow to the varices, angiography was performed again. Negligible blood flow to the varices strongly indicated that the chance of massive bleeding was unlikely, therefore, the clinical course was carefully followed. After a follow-up period of 5 months, the exposed coil protruded in a spring pattern into the gastric lumen (Figure *C*). After an additional follow-up period of 10 months, the exposed coil completely migrated, passed per stomach wall, and the ulcer healed with a scar (Figure *D*). All through the clinical course, neither symptoms such as hematemesis or tarry stools, nor the progression of anemia was observed.

Hemorrhagic peptic ulcers and varices are treated by embolization with an embolic agent including coils using interventional radiology when their endoscopic treatment is difficult. In addition, there is an increase in cases treated by angiographic intervention, which is minimally invasive and helpful in patients with severe complications and a high risk for surgery. Investigators reported patients with hemorrhage gastroduodenal ulcer or aneurysms treated using coil embolization in whom a part of the coil was exposed to the gastrointestinal lumen after the procedure.[1,2]

We present a rare case of coil embolization for gastric varices, in which the clinical course from microcoil exposure to spontaneous migration into gastric lumen could be followed up. There is a possibility that microcoils, even after their placement in gastric varices, could become displaced and migrate into the gastrointestinal lumen, and, therefore, a careful follow-up evaluation of the coil in each case is necessary.

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Conflicts of interest

The authors disclose no conflicts.

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CASE REPORT

A case of chronic pancreatitis in which endoscopic ultrasonography was effective in the diagnosis of a pseudoaneurysm

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Abstract

Endoscopic ultrasonography (EUS) was performed on a patient being treated for chronic pancreatitis because a submucosal tumor was observed in the stomach during gastrointestinal endoscopy. As internal pulsatile blood flow on Doppler was present, the diagnosis of an aneurysm was made. The pseudoaneurysm of the left gastric artery was embolized with histoacryl and lipiodol and the splenic artery was embolized with coils at the location of the pseudoaneurysm to prevent hemorrhage. Follow up EUS confirmed the cessation of blood flow from the pseudoaneurysm. Clinicians encountering a gastric submucosal tumor-like protrusion in a patient with chronic pancreatitis should use EUS to investigate the possibility of a pseudoaneurysm, which must be treated as quickly as possible once identified.

INTRODUCTION

Pseudoaneurysms are a known complication of chronic pancreatitis. Untreated, pseudoaneurysms may rupture, and can be fatal.

We herein describe a patient with chronic pancreatitis who was diagnosed with a pseudoaneurysm of the left gastric artery while undergoing endoscopic ultrasonography (EUS) for a gastric submucosal tumor-like protrusion.

CASE REPORT

The patient, a 39-year-old male, presented with the primary complaints of chest tightness and upper abdominal pain. Previously, the patient had been repeatedly admit-

ted and discharged for alcoholic pancreatitis. An approximately 4 cm, left mediastinal, cystic lesion continuing from the tail of the pancreas was seen on multidetector row computed tomography (MDCT) at the time of presentation. An area of high density was observed within the cyst, and a severely atrophied pancreas with a calcified body was observed (Figure 1). As a pseudocyst complicating an acute exacerbation of chronic pancreatitis and hemorrhage in the pseudocyst was suspected, it was suggested that the patient be admitted for a detailed examination. However, the patient, refused to be admitted for a detailed examination as recommended, and returned home. Later, when his symptoms progressively worsened and his stool had been black for 1 wk, he was rushed to the hospital.

At the time of admission, his blood pressure was 105/60 mmHg, his pulse was regular at 90 bpm, and his temperature was 37.2 °C. The patient's abdomen was soft, flat, and slightly distended, with mild tenderness in the upper abdomen. The laboratory findings were as follows: marked anemia with hemoglobin of 7.2 g/dL, amylase of 262 IU/L, mildly elevated pancreatic enzymes with lipase of 109 IU/L, and an inflammatory response with C-reactive protein of 4.76 mg/dL. Following admission, 4 units of packed red blood cells were transfused to treat anemia. Endoscopic retrograde pancreatography (ERCP) was performed to further investigate and treat the pseudocyst. Pancreatography revealed stenosis of the principal pancreatic duct at the head, dilation of the duct at the tail, and a communication between the tail duct and the pseudocyst (Figure 2). Therefore, the pancreatic duct was stented (stent size, 7 Fr, 7 cm). Although no substantial bleeding in the upper gastrointestinal tract was seen during ERCP, upper gastrointestinal endoscopy was performed to investigate the marked anemia which was present on admission. Endoscopy revealed a 2 cm protrusion resembling a submucosal tumor in the lesser curvature of the middle of the body of the stomach (Figure 3). EUS using the GF-UE260-AL5 (Olympus, Tokyo, Japan) and Prosound α10 (Aloka, Tokyo, Japan) was performed for diagnosis. On EUS, a 1 cm submucosal anechoic region whose entire periphery was hypoechoic was seen. The pulsating anechoic mass with Doppler signal enhancement identified in the gastric submucosa was diagnosed as an aneurysm with hematomas around the periphery (Figure 4A). Angiography proceeded, and a 1 cm pseudoaneurysm of the left gastric artery and a large pseudoaneurysm of the splenic artery measuring 2 mm in diameter were detected. Hemorrhage was prevented with transluminal embolization using lipiodol and histoacryl because a small aneurysm was observed in the left gastric artery upon angiography. This was embolized with coils as a pseudoaneurysm measuring 2 mm was further observed in the splenic artery (Figure 5).

Cessation of blood flow to the pseudoaneurysm was confirmed on EUS performed 1 wk later (Figure 4B). Since there was no subsequent bleeding, follow-up MDCT was performed 1 mo later. The left mediastinal pseudocyst had shrunk markedly.

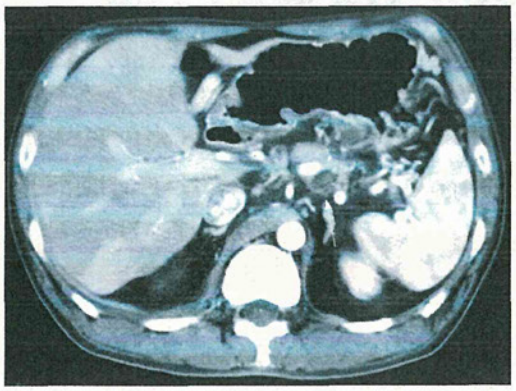

Figure 1 Abdominal computed tomographic findings. A severely atrophied pancreas with a calcified body was noted. The pseudocyst (arrow) ranged from the back of the pancreas to the left mediastinum and was adjacent to the splenic artery.

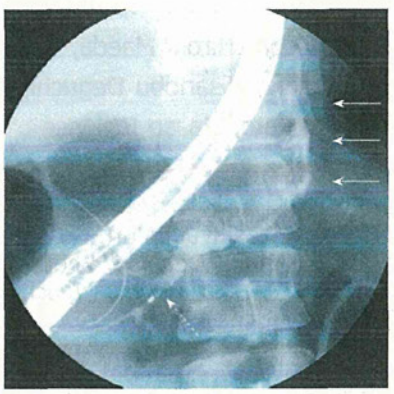

Figure 2 Endoscopic retrograde pancreatography findings. A: Endoscopic retrograde pancreatography showed stenosis of the principal pancreatic duct at the pancreatic head (dotted arrow) and a dilated tail duct communicating with the left mediastinal pseudocyst (solid arrows).

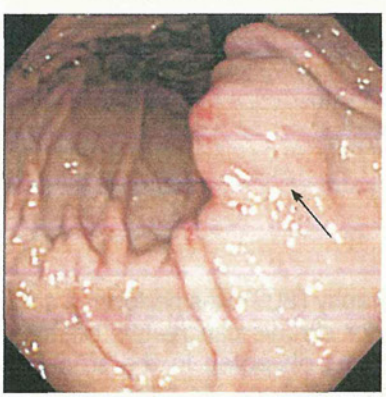

Figure 3 Upper gastrointestinal endoscopy findings. Upper gastrointestinal endoscopy showed a 2 cm, submucosal tumor-like protrusion with a red, eroded upper region located in the lesser curvature of the middle of the body of the stomach (arrow).

DISCUSSION

Hemorrhage in the pseudocyst was seen on MDCT at the time of presentation and ERCP performed after ad-