1. 抗菌薬
Antimicrobial therapy (0330_Record)

抗菌薬班

2017 年 3 月 1 日

会議での班長案発表の内容

1. 旧 CQ1-2 は、2010 年から現在までの文献検索で関連性のある論文はほぼなし。
   Background question で、同様の内容を継続予定。

*G7 伊勢志摩サミットで、抗菌薬耐性 AMR への対応が取り上げらえており、それも記載し、抗菌薬適正使用の推進を Introduction/Background で記載予定

2. 旧 CQ3 は、新 CQ2 と統合

3. 新 CQ1(胆管炎の抗菌薬の治療期間)
   新 CQ2（胆嚢炎の抗菌薬の治療期間）は、systematic review で、少数の RCT, cohort study あり、まとめている。

   新 CQ1
   血流感染のある胆管炎ではグラム陰性菌 7-10 日間投与も可能か
   経口薬への変更タイミングは６日間静脈注射､その後経口薬 （RCT１つ）

   新 CQ2 Grade I, II の場合、抗菌薬投与は術後 24 時間以内
   Grade III はエビデンスなし

4. TG 13 の適切な抗菌薬の一覧
   アンピシリン・スルバクタムの使用に関する記述
   日本国内、世界各地で、施設ごと、地域ごとの感受性パターンが大きく異なるため、耐性率が 20%を超える場合、その抗菌薬の使用は推奨しない。

5. TG 13 の抗菌薬の投与期間の推奨まとめ
   新 CQ1, 2 でエビデンスのまとめ

6. 待機的 ERCP の際の抗菌薬予防投与
   ほかのガイドラインを確認　　し、テキストを修正、Table は削除しテキストのみにするか、Cochrane review 2010 は胆管炎、血流感染、膵炎の予防が評価されている。

<u>会議でのご指摘事項</u>

1. 抗菌薬フローチャートで、矢印をつけるか、チェックリストとするか
   →フローチャートして Figure として提示
   　フローチャートのセクションにも統合をお願いする

2. 待機的 ERCP での抗菌薬予防投与について　調べて確認
   記載事項を改訂する可能性あり

3. TG 13 抗菌薬推奨は国内事情に合っていない点がありとの指摘があり、改定時には考慮する
   →各施設、各地域、各国で antibiogram（感受性パターン）は異なるため、使用に適切な抗菌薬リストから、選んでもらう形
   耐性率のモニターを推奨

新 CQ1

新CQ1: What is the optimal duration and route of antimicrobial therapy for patients with acute cholangitis?

Key words: (acute cholangitis* OR acute biliary tract infections*) AND (antimicrobial therapy* OR antibiotics*) AND duration of therapy＊

*は、Mesh (類似語)すべてを検索のため。

文献検索およびRCT、前向き観察研究、良質エビデンスのスクリーニング結果

Cochrane CCT 16件

Cochrane CDSR　1件

PubMed 151件

ガイドライン案

（文献検索結果のサマリ）

Literature was searched using PubMed and Cochrane library using the key words of (acute cholangitis* OR acute biliary tract infections*) AND (antimicrobial therapy* OR antibiotics*) AND duration of therapy.＊ Mesh was also used for each word.

There were a total of 151 articles by PubMed, 16 by Cochrane CCT, and 1 by Cochrane CDSR. Among them, selection criteria were either randomized studies or observational studies. The articles met the selection criteria were screened initially by title first, then if it was difficult to judge it, the abstract was also reviewed. As a result, there were four relevant articles found.

（記載内容のサマリ）

Unoら（2016）によると、グラム陰性桿菌血流感染を伴う胆管炎の治療で、14日間治療と10日間治療が単施設後ろ向き観察研究で比較された。この研究では、30日死亡率および3か月以内での胆管炎の再発率は相違なかったが、入院期間が17.5日 vs. 14日と有意に差があった（p<0.01）。またvan Lentら(2002)によると、単施設において、胆道系ドレナージが成功後に何日間の治療が必要かを後ろ向き観察研究で比較されたが、3日以下（n=41）と5日以上(n=20)で、胆管炎の再発率は差がなかった。さらにKogureら（2011）らは、胆道系ドレナー

ジが成功後に何日間の治療が必要かを、発熱の有無をもとに前向き観察研究で報告した。この研究では、抗菌薬終了後3日目以内の急性胆管炎の再発率、18名の患者が解析されたが、再発患者はいなかった。Parkら（2012）はn=29, 30で、シプロフロキサシン感受性の腸内細菌の血流感染を伴う胆管炎の患者で、胆道系ドレナージが成功後に、6日間の静脈注射薬での治療後、早期の経口薬への変更群と静脈注射による継続治療群を比較した。このスタディでは、急性胆管炎の再発率および30日死亡率では両群で差が認められなかった。

（推奨内容）
現時点では、急性胆管炎で血流感染を伴う場合には後ろ向き、前向き観察研究、ランダム化研究が少数存在するのみで、どのくらいの期間の治療が最適かを推奨することが困難である。現時点でのエビデンスでは、グラム陰性桿菌血流感染を伴う胆管炎で、十分な胆道ドレナージがされている場合には10日間治療でもよい可能性がある。また、グラム陰性桿菌血流感染を伴う急性胆管炎の場合には、早期の経口薬へも安全に変更ができる可能性があるが、現時点ではエビデンスが乏しい。

一般に患者の希望に関しては、早期退院のため、静脈注射の期間は短く、経口薬への早期変更が望ましい。医療安全面から死亡率、急性胆管炎の再発率が問題となる。医療経済面では、静脈注射薬での治療期間が短いほうが入院期間が短縮され、医療経済効率では利点が大きい。医療経済面でのエビデンスや報告は乏しく評価が困難である。

グラム陰性桿菌血流感染を伴う急性胆管炎の抗菌薬治療期間は、胆道系ドレナージが成功後、10日間も可能である（弱い推奨、エビデンスレベル c）

そのほかの場合のエビデンスはないため、最適な治療期間はさらなる研究対象である。

ガイドラインへのエビデンスの引用文献

1. Park TY, Choi JS, Song TJ, Do JH, Choi SH, Oh HC. Early oral antibiotic switch compared with conventional intravenous antibiotic therapy for acute cholangitis with bacteremia. Dig Dis Sci. 2014 Nov;59(11):2790-6. doi: 10.1007/s10620-014-3233-0. PMID:24898101
2. Kogure H, Tsujino T, Yamamoto K, Mizuno S, Yashima Y, Yagioka H, Kawakubo K, Sasaki T, Nakai Y, Hirano K, Sasahira N, Isayama H, Tada M, Kawabe T, Omata M, Harada S, Ota Y, Koike K. Fever-based antibiotic therapy for acute cholangitis following successful endoscopic biliary drainage. J Gastroenterol. 2011 Dec;46(12):1411-7. doi: 10.1007/s00535-011-0451-5. PMID: 21842232
3. van Lent AU, Bartelsman JF, Tytgat GN, Speelman P, Prins JM. Duration of antibiotic therapy for cholangitis after successful endoscopic drainage of the biliary tract. van Lent AU, Bartelsman JF, Tytgat GN, Speelman P, Prins JM. Gastrointest Endosc. 2002 Apr;55(4):518-22. PMID:11923764
4. Uno S, Hase R, Kobayashi M, Shiratori T, Nakaji S, Hirata N, Hosokawa N. Short-course antimicrobial treatment for acute cholangitis with Gram-negative bacillary bacteremia. Int J Infect Dis. 2016 Dec 24;55:81-85. doi: 10.1016/j.ijid.2016.12.018. PMID:28027992

【4-5 評価シート 介入研究】新CQ1

診療ガイドライン	
対象	
介入	
対照	

＊各項目の評価は"高(-2)"、"中/疑い(-1)"、"低(0)"の3段階
まとめは"高(-2)"、"中(-1)"、"低(0)"の3段階でエビデンス総体に反映させる

各アウトカムごとに別紙にまとめる

アウトカム	Recurrence of cholangtiis
個別研究	バイアスリスク*

		選択バイアス		実行バイアス	検出バイアス	症例減少バイアス		その他				非直接性*					リスク人数(アウトカム率)								
研究コード	研究デザイン	ランダム化	コンシールメント	盲検化	盲検化	ITT	アウトカム不完全報告	選択的アウトカム報告	早期試験中止	その他のバイアス	まとめ	対象	介入	対照	アウトカム	まとめ	対照群分母	対照群分子	(%)	介入群分母	介入群分子	(%)	効果指標(種類)	効果指標(値)	信頼区間
Park 2014	RCT	0	-1	-1	-1		-1	-1	0		-1	-1	0	-1	-1	-1	30	0	0	29	1	3.4			p 0.50

コメント(該当するセルに記入)

【4-5 評価シート 介入研究】新CQ1

診療ガイドライン	
対象	
介入	
対照	

＊各項目の評価は"高(-2)"、"中/疑い(-1)"、"低(0)"の3段階
まとめは"高(-2)"、"中(-1)"、"低(0)"の3段階でエビデンス総体に反映させる

各アウトカムごとに別紙にまとめる

アウトカム		30 day mortality																						
個別研究		バイアスリスク*										非直接性*					リスク人数(アウトカム率)								
		選択バイアス		実行バイアス	検出バイアス	症例減少バイアス		その他																
研究コード	研究デザイン	ランダム化	コンシールメント	盲検化	盲検化	ITT	アウトカム不完全報告	選択的アウトカム報告	早期試験中止	その他のバイアス	まとめ	対象	介入	対照	アウトカム	まとめ	対照群分母	対照群分子	(%)	介入群分母	介入群分子	(%)	効果指標(種類)	効果指標(値)	信頼区間
Park 2014	RCT	0	-1	-1	-1		-1	-1	0		-1	-1	0	-1	-1	-1	30	0	0	29	0	0			No stats

コメント(該当するセルに記入)

【4-5 評価シート 介入研究】新CQ1

診療ガイドライン	
対象	
介入	
対照	

＊各項目の評価は"高(-2)"、"中/疑い(-1)"、"低(0)"の3段階
まとめは"高(-2)"、"中(-1)"、"低(0)"の3段階でエビデンス総体に反映させる

各アウトカムごとに別紙にまとめる

アウトカム	Length of hospital stay (LOS)
個別研究	バイアスリスク*

		バイアスリスク*										非直接性*					リスク人数(アウトカム率)								
		選択バイアス		実行バイアス	検出バイアス	症例減少バイアス		その他																	
研究コード	研究デザイン	ランダム化	コンシールメント	盲検化	盲検化	ITT	アウトカム不完全報告	選択的アウトカム報告	早期試験中止	その他のバイアス	まとめ	対象	介入	対照	アウトカム	まとめ	対照群分母	対照群分子	(%)	介入群分母	介入群分子	(%)	効果指標(種類)	効果指標(値)	信頼区間
Park 2014	RCT	0	-1	-1	-1		-1	-1	0		-1	-1	0	-1	-1	-1	30		12.3 SD 5.7	29		10.8 SD 3.8	LOS		No stats

コメント(該当するセルに記入)

Park 2014																								6 days IV with oral vs. 10 day IV Abx

【4-6 評価シート 観察研究】新CQ1

診療ガイドライン	
対象	
介入	
対照	

*バイアスリスク、非直接性
　各ドメインの評価は"高(-2)"、"中/疑い(-1)"、"低(0)"の3段階
　まとめは"高(-2)"、"中(-1)"、"低(0)"の3段階でエビデンス総体に反映させる
** 上昇要因
　各項目の評価は"高(+2)"、"中(+1)"、"低(0)"の3段階
　まとめは"高(+2)"、"中(+1)"、"低(0)"の3段階でエビデンス総体に反映させる
各アウトカムごとに別紙にまとめる

アウトカム		Length of stay (LOS)																							
個別研究		バイアスリスク*							上昇要因**				非直接性*					リスク人数(アウトカム率)								
		選択バイアス	実行バイアス	検出バイアス	症例現象バイアス	その他																				
研究コード	研究デザイン	背景因子の差	ケアの差	不適切なアウトカム測定	不完全なフォローアップ	不十分な交絡の調整	その他のバイアス	まとめ	量反応関係	効果減弱交絡	効果の大きさ	まとめ	対象	介入	対照	アウトカム	まとめ	対照群分母	対照群分子	(%)	介入群分母	介入群分子	(%)	効果指標(種類)	効果指標(値)	信頼区間
Uno 2016	コホート研究	-2	-1	0	-1	0	-1	-1	0	0	0	0	0	0	0	0	0	40		17.5 days	52		10.0 days			<0.001

コメント(該当するセルに記入)

Uno	single center retrospective																									short course (10 vs. 14 days) 30 day mortality

【4-6 評価シート 観察研究】新CQ1

診療ガイドライン	
対象	
介入	
対照	

*バイアスリスク、非直接性
　各ドメインの評価は"高(-2)"、"中/疑い(-1)"、"低(0)"の3段階
　まとめは"高(-2)"、"中(-1)"、"低(0)"の3段階でエビデンス総体に反映させる
** 上昇要因
　各項目の評価は"高(+2)"、"中(+1)"、"低(0)"の3段階
　まとめは"高(+2)"、"中(+1)"、"低(0)"の3段階でエビデンス総体に反映させる
各アウトカムごとに別紙にまとめる

アウトカム	Recurrence of cholangitis

個別研究		バイアスリスク*							上昇要因**				非直接性*					リスク人数(アウトカム率)								
		選択バイアス	実行バイアス	検出バイアス	症例現象バイアス	その他																				
研究コード	研究デザイン	背景因子の差	ケアの差	不適切なアウトカム測定	不完全なフォローアップ	不十分な交絡の調整	その他のバイアス	まとめ	量反応関係	効果減弱交絡	効果の大きさ	まとめ	対象	介入	対照	アウトカム	まとめ	対照群分母	対照群分子	(%)	介入群分母	介入群分子	(%)	効果指標(種類)	効果指標(値)	信頼区間
Uno 2016	コホート研究	-2	-1	0	-1	0	-1	-1	0	0	0	0	0	0	0	0	0	30	4	13.3	37	0	0			0.036
Kosuge 2011	コホート研究	-2	-1	0	-1	-1	-1	-1	0	0	0	0	0	0	0	0	0	NA	NA		18	0	0			NA
van Lent AU2002	コホート研究	-2	-1	0	-1	-1	-1	-1	0	0	0	0	-1	-1	0	0	-1	20	4	20	41	11	24			0.8

コメント(該当するセルに記入)

Uno	single center retrospective																								short course (10 vs. 14 days) recurrence rate within 3 months
Kosuge																									recurrence within 3 days after Abx discontinued
van Len AU 2002																									After drainage, < 3 days vs. > 5 days

【4-6 評価シート 観察研究】新CQ1

診療ガイドライン	
対象	
介入	
対照	

*バイアスリスク、非直接性
各ドメインの評価は"高(-2)"、"中/疑い(-1)"、"低(0)"の3段階
まとめは"高(-2)"、"中(-1)"、"低(0)"の3段階でエビデンス総体に反映させる
** 上昇要因
各項目の評価は"高(+2)"、"中(+1)"、"低(0)"の3段階
まとめは"高(+2)"、"中(+1)"、"低(0)"の3段階でエビデンス総体に反映させる
各アウトカムごとに別紙にまとめる

アウトカム		mortality or 30 day mortality																							
個別研究		バイアスリスク*							上昇要因**				非直接性*					リスク人数(アウトカム率)								
		選択バイアス	実行バイアス	検出バイアス	症例現象バイアス	その他																				
研究コード	研究デザイン	背景因子の差	ケアの差	不適切なアウトカム測定	不完全なフォローアップ	不十分な交絡の調整	その他のバイアス	まとめ	量反応関係	効果減弱交絡	効果の大きさ	まとめ	対象	介入	対照	アウトカム	まとめ	対照群分母	対照群分子	(%)	介入群分母	介入群分子	(%)	効果指標(種類)	効果指標(値)	信頼区間
Uno 2016	コホート研究	-2	-1	0	-1	0	-1	-1	0	0	0	0	0	0	0	0	0	35	2	5.7	47	0	0			0.179
van Lent AU2002	コホート研究	-2	-1	0	-1	-1	-1	-1	0	0	0	0	-1	-1	0	0	-1	20	1	5	41	6	15			NA

コメント(該当するセルに記入)

Uno	single center retrospective																									short course (10 vs. 14 days) 30 day mortality
van Len AU 2002	single center retrospective																									After drainage, < 3 days vs. > 5 days

【5-1 推奨文章案】新CQ1

1. CQ

2. 推奨草案

新CQ1: What is the optimal duration and route of antimicrobial therapy for patients with acute cholangitis?
要点　血流感染を伴う胆管炎において、従来の14日間治療と比べ、10日間静脈注射薬での治療も安全に行える可能性がある。(recommendation 2, エビデンスC) また6日間のみの静脈注射薬投与後、経口薬へ変更するにはさらなる前向きランダム化多施設研究が必要である。

3. 作成グループにおける、推奨に関連する価値観や好み(検討した各アウトカム別に、一連の価値観を想定する)

4. CQに対するエビデンスの総括(重大なアウトカム全般に関する全体的なエビデンスの強さ)

☐ A(強)　☐ B(中)　☑ C(弱)　☐ D(非常に弱い)

5. 推奨の強さを決定するための評価項目(下記の項目について総合して判定する)

推奨の強さの決定に影響する要因	**判定**	**説明**
アウトカム全般に関する全体的なエビデンスが強い ・全体的なエビデンスが強いほど推奨度は「強い」とされる可能性が高くなる。 ・逆に全体的なエビデンスが弱いほど、推奨度は「弱い」とされる可能性が高くなる。	☐ はい ☑ いいえ	
益と害のバランスが確実(コストは含まず) ・望ましい効果と望ましくない効果の差が大きければ大きいほど、推奨度が強くなる可能性が高い。 ・正味の益が小さければ小さいほど、有害事象が大きいほど、益の確実性が減じられ、推奨度が「弱い」とされる可能性が高くなる。	☐ はい ☑ いいえ	

推奨の強さに考慮すべき要因
患者の価値観や好み、負担の確実さ(あるいは相違)
正味の利益がコストや資源に十分に見合ったものかどうかなど

明らかに判定当てはまる場合「はい」とし、それ以外は、どちらとも言えないを含め「いいえ」とする

新 CQ2

（解説文）

What is the optimal duration of antimicrobial therapy for patients with acute cholecystitis?

急性胆嚢炎に対する抗菌薬投与に関する論文として 3 編の RCT 及び 1 編の観察研究が検索された。その内、2 編の RCT(1, 2)では、早期胆嚢摘出を行った軽症・中等症の急性胆嚢炎(TG13 による GRADE I 及び II(1)、APACH-II で 6 以下(2))の患者に対して、術前に抗菌薬を一度だけ投与する群と、抗菌薬を術前及び術後に投与する群で比較した。この 2 編の RCT を統合した結果、術後感染症のリスク差（術後抗菌薬なし群−術後抗菌薬あり群）は 0.01(95%CI: -0.04 – 0.06)、再入院率のリスク差は 0(95%CI: -0.04 – 0.05)であった。これらの研究では、患者、治療者および評価者の盲検化が出来ていないことに事によるバイアスリスクを認め、また同等性の検定のためあらかじめ定められた同等性マージンをリスク差の 95%信頼区間がまたいでいる事より不正確性の問題が有り、エビデンスの強さは B（中）とした。抗菌薬の投与は、患者に副作用を引き起こし、耐性菌を増加させるため、使用をなるべく控える事が患者の益となる。当然コストも小さくなる。患者は特に抗菌薬の使用を望むとは考えられない。

重症急性胆嚢炎患者に対しては、抗菌薬の投与が推奨されているが、その投与期間についてのエビデンスは検索されなかった。

1 編の RCT(3)は、早期手術を行わなかった軽症急性胆嚢炎患者に対して、抗菌薬投与する群と抗菌薬投与しない群で、入院期間、疼痛の改善までの時間等、再入院率等を比較したが、これらで有意な差はみとめられなかった。

1. Regimbeau JM, Fuks D, Pautrat K, Mauvais F, Haccart V, Msika S, et al. Effect of postoperative antibiotic administration on postoperative infection following cholecystectomy for acute calculous cholecystitis: a randomized clinical trial. Jama. 2014;312(2):145-54.

2. Loozen CS, Kortram K, Kornmann VN, van Ramshorst B, Vlaminckx B, Knibbe CA, et al. Randomized clinical trial of extended versus single-dose perioperative antibiotic prophylaxis for acute calculous cholecystitis. Br J Surg. 2017;104(2):e151-e7.

3. Mazeh H, Mizrahi I, Dior U, Simanovsky N, Shapiro M, Freund HR, et al. Role of antibiotic therapy in mild acute calculus cholecystitis: a prospective randomized controlled trial. World J Surg. 2012;36(8):1750-9.

【4-5 評価シート 介入研究】新CQ2

診療ガイドライン	
対象	軽度、中等度急性胆嚢炎
介入	術後抗菌薬なし
対照	術後抗菌薬

＊各項目の評価は"高(-2)"、"中/疑い(-1)"、"低(0)"の3段階
まとめは"高(-2)"、"中(-1)"、"低(0)"の3段階でエビデンス総体に反映させる

各アウトカムごとに別紙にまとめる

アウトカム	all complications

個別研究		バイアスリスク*										非直接性*					リスク人数(アウトカム率)								
		選択バイアス		実行バイアス	検出バイアス	症例減少バイアス		その他																	
研究コード	研究デザイン	ランダム化	コンシールメント	盲検化	盲検化	ITT	アウトカム不完全報告	選択的アウトカム報告	早期試験中止	その他のバイアス	まとめ	対象	介入	対照	アウトカム	まとめ	対照群分母	対照群分子	(%)	介入群分母	介入群分子	(%)	効果指標(種類)	効果指標(値)	信頼区間
Loozen 2017	RCT	0	0	-1	-1	0	0	0	0		0	0	0	0	0	0	79	12		73	8				
Regimbeau 2014	RCT	0	-1	-1	0	0	-1	0	0		-1	0	0	0	0	0	207	59		207	52				

コメント(該当するセルに記入)

			neither	assessors																					
		unclear	the absen	assessors		27 vs 49 did											感染症を								

【4-5 評価シート 介入研究】postoperative infection

新CQ2

診療ガイドライン	
対象	軽度、中等度急性胆嚢炎
介入	術後抗菌薬なし
対照	術後抗菌薬

＊各項目の評価は"高(-2)"、"中/疑い(-1)"、"低(0)"の3段階
まとめは"高(-2)"、"中(-1)"、"低(0)"の3段階でエビデンス総体に反映させる

各アウトカムごとに別紙にまとめる

アウトカム	post operative infection

個別研究		**バイアスリスク***										**非直接性***					**リスク人数(アウトカム率)**								
		選択バイアス		**実行バイアス**	**検出バイアス**	**症例減少バイアス**		**その他**																	
研究コード	**研究デザイン**	**ランダム化**	**コンシールメント**	**盲検化**	**盲検化**	**ITT**	**アウトカム不完全報告**	**選択的アウトカム報告**	**早期試験中止**	**その他のバイアス**	**まとめ**	**対象**	**介入**	**対照**	**アウトカム**	**まとめ**	**対照群分母**	**対照群分子**	**(%)**	**介入群分母**	**介入群分子**	**(%)**	**効果指標(種類)**	**効果指標(値)**	**信頼区間**
Loozen 2017	RCT	0	0	-1	-1	0	0	0	0		0	0	0	0	0	0	79	3		73	3		RD	0	(-0.06 - 0.07)
Regimbeau 2014	RCT	0	-1	-1	0	0	-1	0	0		-1	0	0	0	0	0	207	31		207	35		RD	0.02	(-0.05 - 0.09)

コメント(該当するセルに記入)

			neither	assessors																					
		unclear	the absen	assessors		27 vs 49 did																			

【4-5 評価シート 介入研究】新CQ2

診療ガイドライン	
対象	軽度、中等度急性胆嚢炎
介入	術後抗菌薬なし
対照	術後抗菌薬

＊各項目の評価は"高(-2)"、"中/疑い(-1)"、"低(0)"の3段階
まとめは"高(-2)"、"中(-1)"、"低(0)"の3段階でエビデンス総体に反映させる

各アウトカムごとに別紙にまとめる

アウトカム	readmission
個別研究	

		バイアスリスク*										非直接性*					リスク人数(アウトカム率)								
		選択バイアス		実行バイアス	検出バイアス	症例減少バイアス		その他																	
研究コード	**研究デザイン**	**ランダム化**	**コンシールメント**	**盲検化**	**盲検化**	**ITT**	**アウトカム不完全報告**	**選択的アウトカム報告**	**早期試験中止**	**その他のバイアス**	**まとめ**	**対象**	**介入**	**対照**	**アウトカム**	**まとめ**	**対照群分母**	**対照群分子**	**(%)**	**介入群分母**	**介入群分子**	**(%)**	**効果指標(種類)**	**効果指標(値)**	**信頼区間**
Regimbeau 2014	RCT	0	-1	-1	0	0	-1	0	0		-1	0	0	0	0	0	207	11		207	12		RD	0	(-0.04 - 0.05)

コメント(該当するセルに記入)

			neither	assessors																					
		unclear	the absen	assessors		27 vs 49 did																			

【5-1 推奨文章案】新CQ2

1. CQ

What is the optimal duration of antimicrobial therapy for patients with acute cholecystitis?
急性胆嚢炎患者に対する適切な抗菌薬投与期間は？

2. 推奨草案

Grade I 及びIIの急性胆嚢炎に対しては、術前の抗菌薬投与を行い、術後の抗菌薬投与は必要としない。(推奨度1 エビデンスレベルB)
Grade III の急性胆嚢炎に対する抗菌薬の投与期間についての根拠となるエビデンスはない。

3. 作成グループにおける、推奨に関連する価値観や好み(検討した各アウトカム別に、一連の価値観を想定する)

4. CQに対するエビデンスの総括(重大なアウトカム全般に関する全体的なエビデンスの強さ)

☐ A(強)　☑ B(中)　☐ C(弱)　☐ D(非常に弱い)

5. 推奨の強さを決定するための評価項目(下記の項目について総合して判定する)

推奨の強さの決定に影響する要因	判定	説明
アウトカム全般に関する全体的なエビデンスが強い ・全体的なエビデンスが強いほど推奨度は「強い」とされる可能性が高くなる。 ・逆に全体的なエビデンスが弱いほど、推奨度は「弱い」とされる可能性が高くなる。	☑ はい ☐ いいえ	
益と害のバランスが確実(コストは含まず) ・望ましい効果と望ましくない効果の差が大きければ大きいほど、推奨度が強くなる可能性が高い。 ・正味の益が小さければ小さいほど、有害事象が大きいほど、益の確実性が減じられ、推奨度が「弱い」とされる可能性が高くなる。	☑ はい ☐ いいえ	

推奨の強さに考慮すべき要因
患者の価値観や好み、負担の確実さ(あるいは相違)
正味の利益がコストや資源に十分に見合ったものかどうかなど

抗菌薬の使用は、副作用や耐性菌の問題を引き起こすのでなるべく使用しないことが患者に益になる。コストは小さくなる。
抗菌薬使用を患者が好むとは考えにくい。

明らかに判定当てはまる場合「はい」とし、それ以外は、どちらとも言えないを含め「いいえ」とする

J Hepatobiliary Pancreat Sci
DOI 10.1007/s00534-012-0572-0

GUIDELINE

TG13: Updated Tokyo Guidelines for acute cholangitis and acute cholecystitis

TG13 antimicrobial therapy for acute cholangitis and cholecystitis

Harumi Gomi · Joseph S. Solomkin · Tadahiro Takada · Steven M. Strasberg · Henry A. Pitt · Masahiro Yoshida · Shinya Kusachi · Toshihiko Mayumi · Fumihiko Miura · Seiki Kiriyama · Masamichi Yokoe · Yasutoshi Kimura · Ryota Higuchi · John A. Windsor · Christos Dervenis · Kui-Hin Liau · Myung-Hwan Kim

Abstract Therapy with appropriate antimicrobial agents is an important component in the management of patients with acute cholangitis and/or acute cholecystitis. In the updated Tokyo Guidelines (TG13), we recommend antimicrobial agents that are suitable from a global perspective for management of these infections. These recommendations focus primarily on empirical therapy (presumptive therapy), provided before the infecting isolates are identified. Such therapy depends upon knowledge of both local microbial epidemiology and patient-specific factors that affect selection of appropriate agents. These patient-specific factors include prior contact with the health care system, and we separate community-acquired versus healthcare-associated infections because of the higher risk

H. Gomi (✉)
Center for Clinical Infectious Diseases, Jichi Medical University, 3311-1, Yakushiji, Shimotsuke, Tochigi 329-0431, Japan
e-mail: hgomi-oky@umin.ac.jp

J. S. Solomkin
Department of Surgery, University of Cincinnati College of Medicine, Cincinnati, OH, USA

T. Takada · F. Miura
Department of Surgery, Teikyo University School of Medicine, Tokyo, Japan

S. M. Strasberg
Section of Hepatobiliary and Pancreatic Surgery, Washington University in Saint Louis School of Medicine, Saint Louis, MO, USA

H. A. Pitt
Department of Surgery, Indiana University School of Medicine, Indianapolis, IN, USA

M. Yoshida
Clinical Research Center Kaken Hospital, International University of Health and Welfare, Ichikawa, Japan

S. Kusachi
Department of Surgery, Toho University Medical Center Ohashi Hospital, Tokyo, Japan

T. Mayumi
Department of Emergency and Critical Care Medicine, Ichinomiya Municipal Hospital, Ichinomiya, Japan

S. Kiriyama
Department of Gastroenterology, Ogaki Municipal Hospital, Ogaki, Japan

M. Yokoe
General Internal Medicine, Nagoya Daini Red Cross Hospital, Nagoya, Japan

Y. Kimura
Department of Surgical Oncology and Gastroenterological Surgery, Sapporo Medical University School of Medicine, Sapporo, Japan

R. Higuchi
Department of Surgery, Institute of Gastroenterology, Tokyo Women's Medical University, Tokyo, Japan

J. A. Windsor
Department of Surgery, The University of Auckland, Auckland, New Zealand

C. Dervenis
First Department of Surgery, Agia Olga Hospital, Athens, Greece

K.-H. Liau
Hepatobiliary and Pancreatic Surgery, Nexus Surgical Associates, Mount Elizabeth Hospital, Singapore, Singapore

M.-H. Kim
Department of Internal Medicine, Asan Medical Center, University of Ulsan, Seoul, Korea

Published online: 11 January 2013

of resistance in the latter. Selection of agents for community-acquired infections is also recommended on the basis of severity (grades I–III).

Free full-text articles and a mobile application of TG13 are available via http://www.jshbps.jp/en/guideline/tg13.html.

Keywords Acute cholangitis · Acute cholecystitis · Antimicrobial therapy · Treatment guidelines · Biliary tract infection

Introduction

Acute cholangitis and cholecystitis are common conditions that may result in progressively severe infection, particularly in debilitated hosts. Epidemiology and risk factors for acute cholangitis and cholecystitis are provided in a separated section of "TG13: Current terminology, etiology, and epidemiology of acute cholangitis and cholecystitis." The primary goal of antimicrobial therapy in acute cholangitis and cholecystitis is to limit both the systemic septic response and local inflammation, to prevent surgical site infections in the superficial wound, fascia, or organ space, and to prevent intrahepatic abscess formation [1].

In acute cholangitis, drainage of the obstructed biliary tree (termed source control) was recognized as the mainstay of therapy long before the introduction of antimicrobial agents [1]. An additional role of antimicrobial therapy, allowing delay in operation until patients are more physiologically stable, was initially defined by Boey and Way [2]. They retrospectively reviewed 99 consecutive patients with acute cholangitis, and reported that 53 % of their patients who responded well to antimicrobial therapy were therefore given elective instead of emergency operation [1, 2].

The role of antimicrobial therapy in the broad range of diseases subsumed under the term "acute cholecystitis" also varies with severity and pathology. In early and non-severe cases, it is not obvious that bacteria play a significant role in the pathology encountered. In these patients, antimicrobial therapy is at best prophylactic, preventing progression to infection. In other cases, with clinical findings of a systemic inflammatory response, antimicrobial therapy is therapeutic, and treatment may be required until the gallbladder is removed.

Rationale for changes in these guidelines

Five years have passed since the Tokyo Guidelines were published in 2007, and it is now referred to as TG07 [3, 4]. During the last five years, there have been several developments in the management of biliary tract infections. For antimicrobial therapy, other guideline sources for biliary tract infections have been revised. These include the Surviving Sepsis Campaign 2008 [5] and treatment guidelines for complicated intra-abdominal infections developed by the Surgical Infection Society of North America (SIS-NA) and the Infectious Diseases Society of America (IDSA) 2010 [6]. Additionally, new agents and dosing regimens have been approved, including higher dose regimens for piperacillin/tazobactam, meropenem, levofloxacin and doripenem. The issues of pharmacokinetics and pharmacodynamics of antimicrobial agents have been clarified [3, 4]. Since the release of TG07 [3, 4], the emergence of antimicrobial resistance among clinical isolates of Enterobacteriaceae from patients with community-acquired intra-abdominal infections has been more widely reported [7–14]; in particular, antimicrobial resistance in Gram-negative bacilli driven by the appearance of extended-spectrum β-lactamases (ESBL) and carbapenemases (i.e., metallo-β-lactamase and non-metallo-β-lactamase) [15–19]. Finally, in the updated Tokyo Guidelines (TG13), both the diagnostic and severity criteria for acute cholangitis and cholecystitis have been revised and recommendations for antimicrobial therapy are reconsidered against this new structure.

There are new topics dealt with in these guidelines. We now make specific recommendations for antimicrobial therapy of healthcare-associated biliary infections. This was prompted by recognition of the increasing number of elderly patients with multiple medical problems exposed to the health care system and thereby being at risk of acquiring resistant organisms [14]. In addition, there are several agents that are no longer recommended by the SIS-NA/IDSA 2010 guidelines [6]. We also clarify concerns regarding the importance (or lack thereof) of biliary penetration. We also now address prophylaxis for elective endoscopic retrograde cholangiopancreatography (ERCP).

Background

The bacteria commonly found in biliary tract infections are well known, and are presented in Tables 1 and 2 [3, 4, 20–31]. Antimicrobial therapy largely depends on local antimicrobial susceptibility data. In the international guidelines for acute cholangitis and cholecystitis (TG13), a framework for selecting antimicrobial agents will be provided, with class-based definitions of appropriate therapy. Listed agents in the guideline are appropriate for use, and recommendations for modification based upon the local microbiological findings, referred to as antibiogram, are made.

Decision process

A systematic literature review was performed using PubMed from January 1, 2005 to May 15, 2012. All references were searched with the keywords "Acute cholangitis" AND "Antibiotics OR Antimicrobial therapy," and "Acute

Table 1 Common microorganisms isolated from bile cultures among patients with acute biliary infections

Isolated microorganisms from bile cultures	Proportions of isolated organisms (%)
Gram-negative organisms	
Escherichia coli	31–44
Klebsiella spp.	9–20
Pseudomonas spp.	0.5–19
Enterobacter spp.	5–9
Acinetobacter spp.	–
Citrobacter spp.	–
Gram-positive organisms	
Enterococcus spp.	3–34
Streptococcus spp.	2–10
Staphylococcus spp.	0[a]
Anaerobes	4–20
Others	–

The data are from references [3, 20–27, 30]

[a] A recent study by Salvador et al. [27] reported none from bile cultures, while a study by Sung et al. [14] reported 3.6 % from blood cultures among community-acquired (2 %) and healthcare-associated (4 %) bacteremic acute biliary infections

Table 2 Common isolates from patients with bacteremic biliary tract infections

Isolated microorganisms from blood cultures	Proportions of isolates (%)	
	Community-acquired infections[a]	Healthcare-associated infections[b]
Gram-negative organisms		
Escherichia coli	35–62	23
Klebsiella spp.	12–28	16
Pseudomonas spp.	4–14	17
Enterobacter spp.	2–7	7
Acinetobacter spp.	3	7
Citrobacter spp.	2–6	5
Gram-positive organisms		
Enterococcus spp.	10–23	20
Streptococcus spp.	6–9	5
Staphylococcus spp.	2	4
Anaerobes	1	2
Others	17	11

[a] The data are from references [14, 28–30]

[b] The data are from reference [14]

cholecystitis" AND "Antibiotics OR Antimicrobial therapy" among human studies. Sixty-five and 122 articles were found, respectively. These references were further narrowed using keywords "Clinical trials" and "Randomized trials." Literature cited in the TG07 was also reviewed and integrated for revision. If there were few data and few new developments on clinical questions addressed since 2005, a consensus process was used by the members of the Tokyo Guidelines Revision Committee after consultations with internationally recognized experts.

The structure of recommendations for selecting antimicrobial agents has been revised. Antimicrobial agents appropriate for initial therapy (empirical therapy or presumptive therapy) for various grades of severity of biliary tract infections have been developed. Table 3 lists antimicrobial agents appropriate for use for the treatment of patients with both community-acquired and healthcare-associated cholangitis and cholecystitis.

Clinical questions

Clinically relevant questions are provided with brief answers and explanations below.

Q1. What specimen should be sent for culture to identify the causative organisms in acute cholangitis and cholecystitis?

- **Bile cultures should be obtained at the beginning of any procedure performed. Gallbladder bile should be sent for culture in all cases of acute cholecystitis excepting those with grade I severity (recommendation 1, level C).**
- **We suggest cultures of bile and tissue when perforation, emphysematous changes, or necrosis of gallbladder are noted during cholecystectomy (recommendation 2, level D).**
- **Blood cultures are not routinely recommended for grade I community-acquired acute cholecystitis (recommendation 2, level D).**

Identifying the causative organism(s) is an essential step in the management of acute biliary infections. Positive rates of bile cultures range from 59 to 93 % for acute cholangitis [3, 4, 20–27], and positive rates of either bile or gallbladder cultures range from 29 to 54 % for acute cholecystitis [3, 4, 20–27]. In a recent study which utilized the TG07 diagnostic classification, positive rates of bile cultures among patients with cholangitis were 67 % (66 of 98 patients) and 33 % (32 of 98) without [27]. Table 1 shows common microbial isolates from bile cultures among patients with acute biliary infections [3, 4, 20–27]. Common duct bile should be sent for culture in all cases of suspected cholangitis.

On the other hand, previous studies indicated that positive rates of blood cultures among patients with acute cholangitis ranged from 21 to 71 % [3]. For acute cholecystitis, the prevalence of positive blood cultures is less than acute cholangitis, and in the last two decades it has been reported

Table 3 Antimicrobial recommendations for acute biliary infections

	Community-acquired biliary infections				Healthcare-associated biliary infections[e]
Severity	Grade I		Grade II	Grade III[e]	
Antimicrobial agents	Cholangitis	Cholecystitis	Cholangitis and cholecystitis	Cholangitis and cholecystitis	Healthcare-associated cholangitis and cholecystitis
Penicillin-based therapy	Ampicillin/sulbactam[b] is not recommended without an aminoglycoside	Ampicillin/sulbactam[b] is not recommended without an aminoglycoside	Piperacillin/tazobactam	Piperacillin/tazobactam	Piperacillin/tazobactam
Cephalosporin-based therapy	Cefazolin[a], or cefotiam[a], or cefuroxime[a], or ceftriaxone, or cefotaxime ± metronidazole[d]	Cefazolin[a], or cefotiam[a], or cefuroxime[a], or ceftriaxone, or cefotaxime ± metronidazole[d]	Ceftriaxone, or cefotaxime, or cefepime, or cefozopran, or ceftazidime ± metronidazole[d]	Cefepime, or ceftazidime, or cefozopran ± metronidazole[d]	Cefepime, or ceftazidime, or cefozopran ± metronidazole[d]
	Cefmetazole,[a] Cefoxitin,[a] Flomoxef,[a] Cefoperazone/sulbactam	Cefmetazole,[a] Cefoxitin,[a] Flomoxef,[a] Cefoperazone/sulbactam	Cefoperazone/sulbactam		
Carbapenem-based therapy	Ertapenem	Ertapenem	Ertapenem	Imipenem/cilastatin, meropenem, doripenem, ertapenem	Imipenem/cilastatin, meropenem, doripenem, ertapenem
Monobactam-based therapy	–	–	–	Aztreonam ± metronidazole[c]	Aztreonam ± metronidazole[d]
Fluoroquinolone-based therapy[c]	Ciprofloxacin, or levofloxacin, or pazufloxacin ± metronidazole[d]	Ciprofloxacin, or levofloxacin, or pazufloxacin ± metronidazole[d]	Ciprofloxacin, or levofloxacin, or pazufloxacin ± metronidazole[c]	–	–
	Moxifloxacin	Moxifloxacin	Moxifloxacin		

[a] Local antimicrobial susceptibility patterns (antibiogram) should be considered for use

[b] Ampicillin/sulbactam has little activity left against *Escherichia coli*. It is removed from the North American guidelines [6]

[c] Fluoroquinolone use is recommended if the susceptibility of cultured isolates is known or for patients with β-lactam allergies. Many extended-spectrum β-lactamase (ESBL)-producing Gram-negative isolates are fluoroquinolone-resistant

[d] Anti-anaerobic therapy, including use of metronidazole, tinidazole, or clindamycin, is warranted if a biliary-enteric anastomosis is present. The carbapenems, piperacillin/tazobactam, ampicillin/sulbactam, cefmetazole, cefoxitin, flomoxef, and cefoperazone/sulbactam have sufficient anti-anerobic activity for this situation

[e] Vancomycin is recommended to cover *Enterococcus* spp. for grade III community-acquired acute cholangitis and cholecystitis, and healthcare-associated acute biliary infections. Linezolid or daptomycin is recommended if vancomycin-resistant *Enterococcus* (VRE) is known to be colonizing the patient, if previous treatment included vancomycin, and/or if the organism is common in the community

to range from 7.7 to 15.8 % [28, 31]. Table 2 shows the most recently reported microbial isolates from patients with bacteremic biliary tract infections [14, 28–30].

There is a lack of clinical trials examining the benefit of blood cultures in patients with acute biliary tract infections. Most of the bacteremic isolates reported (Table 2) are organisms that do not form vegetations on normal cardiac valves nor miliary abscesses. Their intravascular presence does not lead to an extension of therapy or selection of multidrug regimens. We therefore recommend such cultures be taken only in high-severity infections when such results might mandate changes in therapy [5]. Blood cultures are not routinely recommended for grade I community-acquired acute cholecystitis (level D).

The SIS-NA/IDSA 2010 guidelines recommended against routine blood cultures for community-acquired intra-abdominal infections, since the results do not change the management and outcomes [6]. This is in part driven by a study of the clinical impact of blood cultures taken in the emergency department [32]. In this retrospective study, 1,062 blood cultures were obtained during the study period, of which 92 (9 %) were positive. Of the positive blood cultures, 52 (5 %) were true positive, and only 18 (1.6 %) resulted in altered management.

Q2. What considerations should be taken when selecting antimicrobial agents for the treatment of acute cholangitis and cholecystitis?

- **When selecting antimicrobial agents, targeted organisms, pharmacokinetics and pharmacodynamics, local antibiogram, a history of antimicrobial usage, renal and hepatic function, and a history of allergies and other adverse events should be considered (recommendation 1, level D).**
- **We suggest anaerobic therapy if a biliary-enteric anastomosis is present (recommendation 2, level C).**

There are multiple factors to consider in selecting empiric antimicrobial agents. These include targeted organisms, local epidemiology and susceptibility data (antibiogram), alignment of in-vitro activity (or spectrum) of the agents with these local data, characteristics of the agents such as pharmacokinetics and pharmacodynamics, and toxicities, renal and hepatic function, and any history of allergies and other adverse events with antimicrobial agents [3, 4, 20–27]. A history of antimicrobial usage is important because recent (<6 months) antimicrobial therapy greatly increases the risk of resistance among isolated organisms.

Before dosing antimicrobial agents, renal function should be estimated with the commonly used equation: Serum creatinine = (140 − age) [optimum body weight (kg)]/72 × serum creatinine (mg/dl) [3, 4, 33]. Individual dosage adjustments for altered renal and hepatic function are available in several recent publications [34, 35]. Consultation with a clinical pharmacist is recommended if there are concerns.

Regarding the timing of therapy, it should be initiated as soon as the diagnosis of biliary infection is suspected. For patients in septic shock, antimicrobials should be administered within 1 h of recognition [5]. For other patients, as long as 4 h may be spent obtaining definitive diagnostic studies prior to beginning antimicrobial therapy. Antimicrobial therapy should definitely be started before any procedure, either percutaneous, endoscopic, or operative, is performed. In addition, anaerobic therapy is appropriate if a biliary-enteric anastomosis is present (level C) [6].

Selected newer agents

Moxifloxacin has been investigated for intra-abdominal infections in several randomized studies [36–39]. It was demonstrated that moxifloxacin is safe, well-tolerated, and non-inferior to the comparators, such as ceftriaxone plus metronidazole [37], or piperacillin/tazobactam followed by amoxicillin/clavulanic acid [39]. This study was conducted prior to the appearance of ESBL-mediated resistance [40]. There are few data specifically regarding the treatment of acute cholangitis or cholecystitis, and resistance rates of *E. coli* and other common Enterobacteriacae to fluoroquinolones have risen [7–14].

Tigecycline was under clinical trials for approval during preparation of the manuscript, and is now approved for clinical use in Japan. Tigecycline has in-vitro activity against a wide range of clinically significant Gram-positive and Gram-negative bacteria [41]. These include multidrug-resistant Gram-positive cocci such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* spp. For Gram-negative bacilli, ESBL-producing Enterobacteriaceae are susceptible, as are most anaerobes. Tigecycline has no activity against *Pseudomonas aeruginosa*. Tigecycline has been investigated for skin and soft tissue infections and complicated intra-abdominal infections [41]. Tigecycline causes nausea and vomiting in approximately 10–20 % of patients, and is dose-related. This limits the dose that can be routinely administered and suggests only a secondary role for this agent, in the event of unusual pathogens or allergy to other classes of antimicrobial agents. Recent meta-analyses have demonstrated an increased mortality rate and treatment failure rate in randomized trials with this agent [42].

Antimicrobial agents appropriate for use in the management of community-acquired acute cholangitis and cholecystitis

Table 3 summarizes antimicrobial recommendations. It should be kept in mind that in the treatment of cholangitis,

source control (i.e., drainage) is an essential part of management. The indications and timing for drainage are provided in the severity and flowchart of the management sections regarding acute cholangitis. Since 2005, there have been no randomized clinical trials of antimicrobial therapy for community-acquired acute cholangitis and/or acute cholecystitis. There have been multiple reports on clinical isolates with multiple drug resistance from intra-abdominal infections worldwide, and biliary infections in particular [7–14, 40].

Recommendations for antimicrobial therapy are based primarily upon extrapolations of microbiological efficacy and behavior of these agents against the more susceptible isolates treated in the clinical trials cited [36–39, 43–49]. Some concerns about this approach to defining efficacy against resistant isolates has been raised [50].

The use of severity of illness as a guide to antimicrobial agent selection has been questioned in the face of the increasing numbers of ESBL-producing *E. coli* and *Klebsiella* in the community. These organisms are not reliably susceptible to cephalosporins, penicillin derivatives, or fluoroquinolones. Previous guidelines have recommended that if more than 10–20 % of community isolates of *E. coli* are so resistant, then empiric coverage should be provided for these organisms until susceptibility data demonstrates sensitivity to narrower spectrum agents. Carbapenems, piperacillin/tazobactam, tigecycline, or amikacin may also be used to treat these isolates [6].

For grade III community-acquired acute cholangitis and cholecystitis, agents with anti-pseudomonal activities are recommended as initial therapy (empirical therapy) until causative organisms are identified. *Pseudomonas aeruginosa* is present in approximately 20 % of recent series [14, 27], and is a known virulent pathogen. Failure to empirically cover this organism in critically ill patients may result in excess mortality.

Enterococcus spp. is another important pathogen for consideration in patients with grade III community-acquired acute cholangitis and cholecystitis. Vancomycin is recommended to cover *Enterococcus* spp. for patients with grade III community-acquired acute cholangitis and/or cholecystitis, until the results of cultures are available. Ampicillin can be used if isolated strains of *Enterococcus* spp. are susceptible to ampicillin. Ampicillin covers most of the strains of *Enterococcus faecalis* from community-acquired infections in general. For *Enterococcus faecium*, vancomycin is the drug of choice for empirical therapy. However, in many hospitals, vancomycin-resistant *Enterococcus* spp., both *E. faecium* and *E. faecalis*, have emerged as important causes of infection. Treatment for these organisms requires either linezolid or daptomycin. Surgeons and other physicians making treatment decisions for patients with healthcare-associated infections should be aware of the frequency of these isolates in their hospital and unit. Then, regarding infrequently isolated anaerobes such as the *Bacteroides fragilis* group, we suggest to cover these organisms empirically when a biliary-enteric anastomosis is present (level C) [6].

For grade I and II community-acquired cholangitis and cholecystitis, Table 3 shows the agents appropriate for use. Of note, the intravenous formulation of metronidazole has not been approved in Japan. As a result, clindamycin is one of the alternatives where intravenous metronidazole is not available. Clindamycin resistance among *Bacteroides* spp. is significant and the use of clindamycin is no longer recommended in other intra-abdominal infections [6]. Cefoxitin, cefmetazole, flomoxef, and cefoperazone/sulbactam are the agents in cephalosporins that have activities against *Bacteroides* spp. Cefoxitin is no longer recommended by the SIS-NA/IDSA 2010 guidelines due to the high prevalence of resistance among *Bacteroides* spp. [6]. Local availability of agents as well as local susceptibility results are emphasized when choosing empirical therapy.

Table 4 summarizes antimicrobial agents with high prevalence of resistance among Enterobacteriaceae [7–14]. Ampicillin/sulbactam is one of the most frequently used agents for intra-abdominal infections. Nonetheless, the activity of ampicillin/sulbactam against *E. coli*, with or without ESBLs, has fallen to levels that prevent a recommendation for its use.

In the TG13, ampicillin/sulbactam alone is not recommended as empirical therapy if the local susceptibility is <80 %. It is reasonable to use ampicillin/sulbactam as definitive therapy when the susceptibility of this agent is proven. Ampicillin/sulbactam may be used if an aminoglycoside is combined until susceptibility testing results are available.

Table 4 Antimicrobial agents with high prevalence of resistance among Enterobacteriaceae

Antimicrobial class	Antimicrobial agents
Penicillin	Ampicillin/sulbactam
Cephalosporins	Cefazolin
	Cefuroxime
	Cefotiam
	Cefoxitin
	Cefmetazole
	Flomoxef
	Ceftriaxone[a] or cefotaxime[a]
Fluoroquinolones	Ciprofloxacin
	Levofloxacin
	Moxifloxacin

References [4–11]

[a] This resistance indicates the global spread of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae

Fluoroquinolone use is only recommended if the susceptibility of cultured isolates is known since antimicrobial resistance has been increasing significantly [7–14]. This agent can also be used as an alternative agent for patients with β-lactam allergies.

Antimicrobial agents appropriate for use in the management of healthcare-associated acute cholangitis and cholecystitis

There is no evidence to support any agent as optimal treatment of healthcare-associated acute cholangitis and cholecystitis. The principles of empirical therapy of healthcare-associated infections include using agents with antipseudomonal activity until definitive causative organisms are found. This paradigm is now expanded to include empirical coverage for ESBL-producing Gram-negative organisms based on local microbiological findings (local antibiogram). Table 3 shows empirical agents (presumptive therapy) for healthcare-associated acute cholangitis and cholecystitis. Vancomycin is recommended when patients are colonized with resistant Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* and/or *Enterococcus* spp. or when these multidrug-resistant Gram-positives are of concern. *Staphylococcus aureus* is not as common an isolate for acute biliary infections as *Enterococcus* spp. Vancomycin-resistant *Enterococcus* (VRE) should be covered empirically with linezolid or daptomycin if this organism is known to be colonizing the patient, if previous treatment included vancomycin, and/or if the organism is common in the community.

Regarding anaerobes such as the *Bacteroides fragilis* group, we suggest to cover these organisms empirically in the presence of a biliary-enteric anastomosis (level C) [6].

Is it necessary for agents used in acute biliary infections to be concentrated in bile?

Historically, biliary penetration of agents has been considered in the selection of antimicrobial agents. However, there is considerable laboratory and clinical evidence that as obstruction occurs, secretion of antimicrobial agents into bile stops [1]. Well-designed randomized clinical trials comparing agents with or without good biliary penetration are needed to determine the clinical relevance and significance of biliary penetration in treating acute biliary infections.

How should highly resistant causative organisms be managed in treating acute cholangitis and cholecystitis?

The major microbiological phenomenon of the last decade has been the emergence of novel β-lactamase-mediated resistance mechanisms in Enterobacteriaceae. These have been seen in intra-abdominal infections worldwide [7–19, 27]. These organisms have moved into many communities, and are now seen increasingly in community-acquired infections such as cholangitis and cholecystitis. The frequency of ESBL-producing *E. coli* and *Klebsiella* spp. has reached the point in some countries where decisions regarding empirical therapy must be guided by their prevalence. ESBL-producing *E. coli* is highly susceptible to carbapenems and to tigecycline. In some communities, highly resistant *Klebsiella* spp. and *E. coli* with carbapenemases are now seen [51–54]. The widely accepted rule for empirical therapy is that resistant organisms occurring in more than 10–20 % of patients should be treated. Colistin is the salvage agent for the above multidrug-resistant Gram-negative bacilli epidemic strains [40, 54]. This agent is toxic, dosing is uncertain, and its use should involve consultation with infectious disease specialists [40].

In the SIS-NA/IDSA 2010 guidelines [6], antimicrobial agents as empirical therapy for healthcare-associated intra-abdominal infections were given. In the guidelines, carbapenems, piperacillin/tazobactam, and ceftazidime or cefepime, each combined with metronidazole, have been recommended when the prevalence of resistant *Pseudomonas aeruginosa*, ESBL-producing Enterobacteriaceae, *Acinetobacter* or other multidrug-resistant Gram-negative bacilli is less than 20 %. For ESBL-producing Enterobacteriaceae, carbapenems, piperacillin/tazobactam, and aminoglycosides are recommended. For *Pseudomonas aeruginosa*, if the prevalence of resistance to ceftazidime is more than 20 %, carbapenems, piperacillin/tazobactam, and aminoglycosides are recommended. Even with this guide, selecting appropriate agents for antimicrobial stewardship is often difficult.

Q3. What are the special concerns for community-acquired acute cholecystitis in management with antimicrobial agents?

- **When cholecystectomy is performed, antimicrobial therapy can be stopped within 24 hours since the source of infection is controlled (recommendation 2, level C).**
- **Grade II or Grade III acute cholecystitis should be treated with antimicrobial therapy even after cholecystectomy is performed (recommendation 1, level D).**
- **In patients with pericholecystic abscesses or perforation of the gallbladder, treatment with an antimicrobial regimen as listed in Table 3 is recommended. Therapy should be continued until the patient is afebrile, with a normalized white count, and without abdominal findings (recommendation 1, level D).**

In most cases, cholecystectomy removes the infection, and little if any infected tissue remains. Under these circumstances, there is no benefit to extending antimicrobial therapy beyond 24 h.

Recent randomized clinical trials for antimicrobial therapy of acute cholecystitis are limited [43, 46–48]. In these randomized studies, comparisons were made such as ampicillin plus tobramycin versus piperacillin or cefoperazone, pefloxacin versus ampicillin and gentamicin, and cefepime versus mezlocillin plus gentamicin [4, 43, 46, 48]. There were no significant differences between the agents compared. In the TG13, the agents considered as appropriate therapy, and detailed in Table 3, have all been utilized in randomized controlled trials of intra-abdominal infections. These studies included patients with pathologically advanced cholecystitis (abscess or perforation). Table 3 is provided for both community-acquired and healthcare-associated acute cholecystitis.

Antimicrobial therapy after susceptibility testing results are available

Once susceptibility testing results of causative microorganisms are available, specific therapy (or definitive therapy) should be offered. This process is called de-escalation [5]. Agents in Table 4 can be used safely once the susceptibility is proven.

Duration of treatment of patients with clinical and laboratory success

The optimal duration of antimicrobial therapy for community-acquired and healthcare-associated acute cholangitis and cholecystitis has not been determined in well-designed randomized controlled studies. Whether the source of infection (i.e., biliary obstruction) is well controlled or not is critical in determining the duration of therapy. In addition, recent technological advances for biliary drainage have significantly affected the overall management strategies for at least the last two decades.

In the SIS-NA/IDSA 2010 guidelines, the recommended duration of antimicrobial therapy for complicated intra-abdominal infections is 4–7 days once the source of infection is controlled [6]. Since there are very few data available for the duration of either community-acquired or healthcare-associated acute cholangitis and cholecystitis, Table 5 was developed to guide the duration of antimicrobial therapy as expert opinion. When bacteremia with Gram-positive bacteria such as *Enterococcus* spp. and *Streptococcus* spp. is present, it is prudent to offer antimicrobial therapy for two weeks since these organisms are well known to cause infective endocarditis.

Conversion to oral antimicrobial agents

Patients with acute cholangitis and cholecystitis who can tolerate oral feeding may be treated with oral therapy [55]. Depending on the susceptibility patterns of the organisms identified, oral antimicrobial agents such as fluoroquinolones (ciprofloxacin, levofloxacin, or moxifloxacin), amoxicillin/clavulanic acid, or cephalosporins may also be used. Table 6 lists commonly used oral antimicrobial agents with good bioavailabilities.

What is the optimal prophylaxic agent before elective endoscopic retrograde cholangiopancreatography (ERCP)?

A Cochrane meta-analysis examining the benefits of antibiotic prophylaxis for elective ERCP has been performed, and found benefit to the practice [56]. The international guidelines on prophylaxis with endoscopy indicated that

Table 5 Recommended duration of antimicrobial therapy

	Community-acquired biliary infections				Healthcare-associated biliary infections
Severity	Grade I		Grade II	Grade III	
Diagnosis	Cholecystitis	Cholangitis	Cholangitis and cholecystitis	Cholangitis and cholecystitis	Healthcare-associated cholangitis and cholecystitis
Duration of therapy	Antimicrobial therapy can be discontinued within 24 h after cholecystectomy is performed	Once source of infection is controlled, duration of 4–7 days is recommended If bacteremia with Gram-positive cocci such as *Enterococcus* spp., *Streptococcus* spp. is present, minimum duration of 2 weeks is recommended			If bacteremia with Gram-positive cocci such as *Enterococcus* spp., *Streptococcus* spp. is present, minimum duration of 2 weeks is recommended
Specific conditions for extended therapy	If perforation, emphysematous changes, and necrosis of gallbladder are noted during cholecystectomy, duration of 4–7 days is recommended	If residual stones or obstruction of the bile tract are present, treatment should be continued until these anatomical problems are resolved			

Table 6 Representative oral antimicrobial agents for community-acquired and healthcare-associated acute cholangitis and cholecystitis with susceptible isolates

Antimicrobial class	Antimicrobial agents
Penicillins	Amoxicillin/clavulanic acid
Cephalosporins	Cephalexin ± metronidazole[a]
Fluoroquinolones	Ciprofloxacin or levofloxacin ± metronidazole[a]
	Moxifloxacin

[a] Anti-anaerobic therapy, including use of metronidazole, tinidazole, or clindamycin, is warranted if a biliary-enteric anastomosis is present

prophylaxis with ERCP is recommended [57]. As consensus statements, the guidelines [57] recommended the standard prophylaxis regimen to prevent infective endocarditis. The regimen includes amoxicillin or clindamycin orally, or ampicillin or cefazolin as intravenous agents, and vancomycin for patients with β-lactam allergies to prevent infective endocarditis. However, the regimens for preventing cholangitis and bacteremia due to obstructive biliary tract were not included.

Recent meta-analyses [56, 58] had conflicting conclusions regarding the effectiveness of prophylactic therapy before elective ERCP. Bai et al. concluded that prophylaxic agents cannot prevent cholangitis [58], while a Cochrane review indicated that prophylaxic antimicrobial therapy before elective ERCP reduces the incidence of bacteremia [relative risk (RR) 0.50], cholangitis (RR 0.54), and pancreatitis (RR 0.54) [56]. However, overall mortality was not reduced with prophylaxis before elective ERCP [RR 1.33, confidence interval (CI) 0.32–5.44]. In this review, the numbers needed to treat (NNT) to prevent bacteremia (NNT = 11) and cholangitis (NNT = 38) were also demonstrated. The Cochrane review concluded that further studies are needed, including randomized placebo-controlled studies, to investigate the effectiveness of prophylaxis for elective ERCP with low risk of bias, randomized comparison of the timing of administration of prophylaxis (before vs. during or after ERCP), and randomized head-to-head comparison of antimicrobial agents as prophylactic therapy with elective ERCP [56].

Antimicrobial agents investigated with elective ERCP include minocycline orally [59], piperacillin [60, 61], clindamycin plus gentamicin [62], cefuroxime [63], cefotaxime [64, 65], and ceftazidime [66].

In the TG13, antimicrobial prophylactic agents appropriate for use in preventing cholangitis or bacteremia due to biliary tract obstruction are provided on a consensus basis. Table 7 lists those agents. Cefazolin or other narrower-spectrum cephalosporins can be used as prophylactic agents. Cefazolin is one of the agents for preventing infective endocarditis with endoscopy and a convenient agent to be used to prevent both endocarditis and cholangitis. Piperacillin is one of the anti-pseudomonal agents that have been studied as a prophylactic agent for elective ERCP [60, 61]. Given the emergence of resistance among Gram-negative organisms worldwide, including ESBL-producing strains [7–14, 27], we recommend anti-pseudomonal agents such as piperacillin or piperacillin/sulbactam listed in Table 7.

Table 7 Antimicrobial prophylaxic agents for elective endoscopic retrograde pancreatocholangiography (ERCP)

Antimicrobial class	Antimicrobial agents
Cephalosporins	Cefazolin
	Cefoxitin
	Cefmetazole
	Flomoxef
Penicillins	Piperacillin[a]
	Piperacillin/tazobactam[a]

[a] Anti-pseudomonal agents

Use of antibiotic irrigation

There has been continuing interest in irrigation of surgical fields with antimicrobial agents, and the subject has recently been reviewed [67]. The authors concluded that topical antimicrobial agents are clearly effective in reducing wound infections and may be as effective as the use of systemic antimicrobial agents. The combined use of systemic and topical antimicrobial agents may have additive effects, but this is lessened if the same agent is used for both topical and systemic administration.

Conclusions

Antimicrobial agents should be used prudently while promoting antimicrobial stewardship in each institution, local area, and country. The recent global spread of antimicrobial resistance gives us warning in current practice. TG13 provides a practical guide for physicians and surgeons who are involved in the management of community-acquired and healthcare-associated acute biliary infections. There are still many areas of uncertainty in this subject. Continuous monitoring of local antimicrobial resistance and further studies on acute cholangitis and cholecystitis should be warranted.

Conflict of interest None.

References

1. van den Hazel SJ, Speelman P, Tytgat GNJ, Dankert J, van Leeuwen DJ. Role of antibiotics in the treatment and prevention of acute and recurrent cholangitis. Clin Infect Dis. 1994;19:279–86.

2. Beoy JH, Way LW. Acute cholangitis. Ann Surg. 1980;191: 264–70.
3. Tanaka A, Takada T, Kawarada Y, Nimura Y, Yoshida M, Miura F, et al. Antimicrobial therapy for acute cholangitis: Tokyo Guidelines. J Hepatobiliary Pancreat Surg. 2007;14:59–67 (Clinical practice guidelines: CPGs).
4. Yoshida M, Takada T, Kawarada Y, Tanaka A, Nimura Y, Gomi H, et al. Antimicrobial therapy for acute cholecystitis: Tokyo Guidelines. J Hepatobiliary Pancreat Surg. 2007;14:83–90 (CPGs).
5. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med. 2008;36:296–327 (CPGs).
6. Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJC, Baron EJ, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: Guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis. 2010;50:133–64 (CPGs).
7. Paterson DL, Rossi F, Baquero F, Hsueh P-R, Woods GL, Satishchandran V, et al. In vitro susceptibilities of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections worldwide: the 2003 Study for Monitoring Antimicrobial Resistance Trends (SMART). J Antimicrob Chemother. 2005;55:965–73.
8. Rossi F, Baquero F, Hsueh P-R, Paterson DL, Bochicchio GV, Snyder TA, et al. In vitro susceptibilities of aerobic and facultatively anaerobic Gram-negative bacilli isolated from patients with intra-abdominal infections worldwide: 2004 results from SMART (Study for Monitoring Antimicrobial Resistance Trends). J Antimicrob Chemother. 2006;58:205–10.
9. Yang Q, Wang H, Chen M, Ni Y, Yu Y, Hu B, et al. Surveillance of antimicrobial susceptibility of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections in China: the 2002–2009 Study for Monitoring Antimicrobial Resistance Trends (SMART). Int J Antimicrob Agents. 2010;36:507–12.
10. Hsueh P-R, Badal RE, Hawser SP, Hoban DJ, Bouchillon SK, Ni Y, et al. Epidemiology and antimicrobial susceptibility profiles of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections in the Asia-Pacific region: 2008 results from SMART (Study for Monitoring Antimicrobial Resistance Trends). Int J Antimicrob Agents. 2010;36: 408–14.
11. Chen Y-H, Hsueh P-R, Badal RE, Hawser SP, Hoban DJ, Bouchillon SK, et al. Antimicrobial susceptibility profiles of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections in the Asia-Pacific region according to currently established susceptibility interpretive criteria. J Infect. 2011;62:280–91.
12. Ishii Y, Tateda K, Yamaguchi K. Evaluation of antimicrobial susceptibility for β-lactams using the Etest method against clinical isolates from 100 medical centers in Japan (2006). Diagn Microbiol Infect Dis. 2008;60:177–83.
13. Ishii Y, Ueda C, Kouyama Y, Tateda K, Yamaguchi K. Evaluation of antimicrobial susceptibility for β-lactams against clinical isolates from 51 medical centers in Japan (2008). Diagn Microbiol Infect Dis. 2011;69:443–8.
14. Sung YK, Lee JK, Lee KH, Lee KT, Kang C-I. The clinical epidemiology and outcomes of bacteremic biliary tract infections caused by antimicrobial-resistant pathogens. Am J Gastroenterol. 2012;107:473–83.
15. Paterson DL. Resistance in gram-negative bacteria: Enterobacteriaceae. Am J Infect Control. 2006;34 (5, Supplement):S20–S8.
16. Choi SH, Lee J, Park S, Kim MN, Choo E, Kwak Y, et al. Prevalence, microbiology, and clinical characteristics of extended-spectrum; beta-lactamase-producing *Enterobacter* spp., *Serratia marcescens*, *Citrobacter freundii* and *Morganella morganii* in Korea. Eur J Clin Microb Infect Dis. 2007;26:557–61.
17. Kang CI, Cheong H, Chung D, Peck K, Song JH, Oh MD, et al. Clinical features and outcome of community-onset bloodstream infections caused by extended-spectrum β-lactamase-producing *Escherichia coli*. Eur J Clin Microb Infect Dis. 2008;27:85–8.
18. Kumarasamy KK, Toleman MA, Walsh TR, Bagaria J, Butt F, Balakrishnan R, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. Lancet Infect Dis. 2010;10:597–602.
19. Peirano G, van der Bij AK, Gregson DB, Pitout JDD. Molecular epidemiology over an 11-year period (2000 to 2010) of extended-spectrum β-lactamase-producing *Escherichia coli* causing bacteremia in a centralized Canadian region. J Clin Microbiol. 2012; 50:294–9.
20. Kune G, Schutz E. Bacteria in the biliary tract. A study of their frequency and type. Med J Aust. 1974;1:255–8.
21. Csendes A, Fernandez M, Uribe P. Bacteriology of the gallbladder bile in normal subjects. Am J Surg. 1975;129:629–31.
22. Csendes A, Becerra M, Burdiles P, Demian I, Bancalari K, Csendes P. Bacteriological studies of bile from the gallbladder in patients with carcinoma of the gallbladder, cholelithiasis, common bile duct stones and no gallstones disease. Eur J Surg. 1994;160:363–7.
23. Csendes A, Burdiles P, Maluenda F, Diaz J, Csendes P, Mitru N. Simultaneous bacteriologic assessment of bile from gallbladder and common bile duct in control subjects and patients with gallstones and common duct stones. Arch Surg. 1996;131:389–94.
24. Csendes A, Mitru N, Maluenda F, Diaz J, Burdiles P, Csendes P, Pinones E. Counts of bacteria and pyocites of choledochal bile in controls and in patients with gallstones or common bile duct stones with or without acute cholangitis. Hepatogastroenterology. 1996;43:800–6.
25. Maluenda F, Csendes A, Burdiles P, Diaz J. Bacteriological study of choledochal bile in patients with common bile duct stones, with or without acute suppurative cholangitis. Hepatogastroenterology. 1989;36:132–5.
26. Chang W, Lee K, Wang S, Chuang S, Kuo K, Chen J, Sheen P. Bacteriology and antimicrobial susceptibility in biliary tract disease: an audit of 10-year's experience. Kaohsiung J Med Sci. 2002; 18:221–8.
27. Salvador V, Lozada M, Consunji R. Microbiology and antibiotic susceptibility of organisms in bile cultures from patients with and without cholangitis at an Asian Academic Medical Center. Surg Infect. 2011;12:105–11.
28. Kuo CH CC, Chen JJ, Tai DI, Chiou SS, Lee CM. Septic acute cholecystitis. Scand J Gastroenterol. 1995;30:272–5
29. Melzer M, Toner R, Lacey S, Bettany E, Rait G. Biliary tract infection and bacteremia: presentation, structural abnormalities, causative organisms and clinical outcomes. Postgrad Med J. 2007;83:773–6.
30. Lee C–C, Chang IJ, Lai Y-C, Chen S-Y, Chen S-C. Epidemiology and prognostic determinants of patients with bacteremic cholecystitis or cholangitis. Am J Gastroenterol. 2007;102:563–9.
31. Baitello AL, Colleoni Neto R, Herani Filho B, Cordeiro JA, Machado AMO, Godoy MF, et al. Prevalência e fatores associados à bacteremia nos portadores de colecistite aguda litiásica. Revista da Associação Médica Brasileira. 2004;50:373–9.
32. Kelly AM. Clinical impact of blood cultures taken in the emergency department. J Accid Emerg Med. 1998;15:254–6.
33. Brunton LL, Chabner BA, Knollman BC, editors. Goodman and Gilman's the pharmacological basis of therapeutics, 12th edition. New York: The McGraw-Hill Companies; 2011.
34. Amsden G. Chapter 49, Tables of antimicrobial agent pharmacology. In: Mandell G, Bennett J, Dolin R, editors. Principles and practice of infectious diseases, 7th edition, Volume 1. Philadelphia: Churchill Livingston, Elsevier; 2010. p. 705–61.

35. McKenzie C. Antibiotic dosing in critical illness. J Antimicrob Chemother. 2011;66 (suppl 2):ii25–31.
36. Goldstein EJ, Solomkin JS, Citron DM, Alder JD. Clinical efficacy and correlation of clinical outcomes with in vitro susceptibility for anaerobic bacteria in patients with complicated intra-abdominal infections treated with moxifloxacin. Clin Infect Dis. 2011;53:1074–80.
37. Solomkin J, Zhao YP, Ma EL, Chen MJ, DRAGON Study Team. Moxifloxacin is non-inferior to combination therapy with ceftriaxone plus metronidazole in patients with community-origin complicated intra-abdominal infections. Int J Antimicrob Agents. 2009;34:439–45.
38. Weiss G, Reimnitz P, Hampel B, Muehlhofer E, AIDA Study Group. Moxifloxacin for the treatment of patients with complicated intra-abdominal infections (the AIDA Study). J Chemother. 2009;21:170–80.
39. Malangoni MA, Song J, Herrington J, Choudhri S, Pertel P. Randomized controlled trial of moxifloxacin compared with piperacillin-tazobactam and amoxicillin-clavulanate for the treatment of complicated intra-abdominal infections. Ann Surg. 2006;244:204–11.
40. Schultsz C, Geerlings S. Plasmid-mediated resistance in Enterobacteriaceae: changing landscape and implications for therapy. Drugs. 2012;72:1–16.
41. Doan TL, Fung HB, Mehta D, Riska PF. Tigecycline: a glycylcycline antimicrobial agent. Clin Ther. 2006;28:1079–106.
42. Prasad P, Sun J, Danner RL, Natanson C. Excess deaths associated with tigecycline after approval based on non-inferiority trials. Clin Infect Dis. 2012;54:1699–1709.
43. Muller E, Pitt HA, Thompson JE Jr, Doty J, Mann L, Manchester B. Antibiotics in infections of the biliary tract. Surg Gynecol Obstet. 1987;165:285–92.
44. Gerecht W, Henry N, Hoffman W, Muller S, LaRusso N, Rosenblatt J, Wilson W. Prospective randomized comparison of mezlocillin therapy alone with combined ampicillin and gentamicin therapy for patients with cholangitis. Arch Intern Med. 1989;149:1279–84.
45. Thompson JE Jr, Pitt HA, Doty J, Coleman J, Irving C. Broad spectrum penicillin as an adequate therapy for acute cholangitis. Surg Gynecol Obstet. 1990;171:275–82.
46. Chacon J, Criscuolo P, Kobata C, Ferraro J, Saad S, Reis C. Prospective randomized comparison of pefloxacin and ampicillin plus gentamicin in the treatment of bacteriologically proven biliary tract infections. J Antimicrob Chemother. 1990;26,Suppl B:167–72.
47. Thompson JE Jr, Bennion R, Roettger R, Lally K, Hopkins J, Wilson SE. Cefepime for infections of the biliary tract. Surg Gynecol Obstet. 1993;177 Suppl:30–4. discussion 35–40.
48. Yellin AE, Berne TV, Appleman MD, Heseltine PN, Gill MA, Okamoto MP, Baker FJ, Holcomb C. A randomized study of cefepime versus the combination of gentamicin and mezlocillin as an adjunct to surgical treatment in patients with acute cholecystitis. Surg Gynecol Obstet. 1993;177 Suppl:23–29; discussion 35–40.
49. Sung J, Lyon D, Suen R, Chung S, Co A, Cheng A, Leung J, et al. Intravenous ciprofloxacin as treatment for patients with acute suppurative cholangitis: a randomized, controlled clinical trial. J Antimicrob Chemother. 1995;35:855–64.
50. Powers JH. Editorial commentary: Asking the right questions: morbidity, mortality and measuring what's important in unbiased evaluations of antimicrobials. Clin Infect Dis. 2012;54:1710–1713.
51. Kumarasamy KK, Toleman MA, Walsh TR, Bagaria J, Butt F, Balakrishnan R, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. Lancet Infect Dis. 2010;10:597–602.
52. Won SY, Munoz-Price LS, Lolans K, Hota B, Weinstein RA. Centers for Disease Control and Prevention Epicenter Program. Emergence and rapid regional spread of *Klebsiella pneumoniae* carbapenemase-producing Enterobacteriaceae. Clin Infect Dis. 2011;53:532–40.
53. Di Carlo P, Pantuso G, Cusimano A, D'Arpa F, Giammanco A, Gulotta G, Latteri AM, Madonia S, Salamone G, Mammina C. Two cases of monomicrobial intraabdominal abscesses due to KPC–3 *Klebsiella pneumoniae* ST258 clone. BMC Gastroenterol. 2011;30(11):103.
54. Bogdanovich T, Adams-Haduch JM, Tian GB, Nguyen MH, Kwak EJ, Muto CA, et al. Colistin-resistant, *Klebsiella pneumoniae* carbapenemase (KPC)-producing *Klebsiella pneumoniae* belonging to the international epidemic clone ST258. Clin Infect Dis. 2011;53:373–6.
55. Solomkin JS, Dellinger EP, Bohnen JM, Rostein OD. The role of oral antimicrobias for the management of intra-abdominal infections. New Horiz. 1998;Suppl 2:S46–52.
56. Brand M, Bizs D, O'Farrell PJR. Antibiotic prophylaxis for patients undergoing elective endoscopic retrograde cholangiopancreatography (review). Cochrane Database Syst Rev. 2010 Oct 6;(10):CD007345.
57. Hirota WK, Petersen K, Baron TH, Goldstein JL, Jacobson BC, Leighton JA, et al. Guidelines for antibiotic prophylaxis for GI endoscopy. Gastrointest Endosc. 2003;58:475–82 (CPGs).
58. Bai Y, Gao F, Gao J, Zou DW, Li ZS. Prophylactic antibiotics cannot prevent endoscopic retrograde cholangiopancreatography-induced cholangitis: meta-analysis. Pancreas. 2009;38:126–30.
59. Branders JW, Scheffer B, Lorenz-Meyer H, Korst HA, Littmann KP. ERCP: complications and prophylaxis. A controlled study. Endoscopy. 1981;13:27–30.
60. Byl B, Deviere J, Struelens MJ, Roucloux I, De Coninck A, Thys JP, et al. Antibiotic prophylaxis of infectious complications after therapeutic endoscopic retrograde cholangiopancreatography: a randomized, double-blind, placebo-controlled study. Clin Infect Dis. 1995;20:1236–40.
61. Van den Hazel SJ, Speelman P, Dankert J, Huibregtse K, Tytgat GNJ, Van Leeuen DJ. Piperacillin to prevent cholangitis after endoscopic retrograde cholangiopancreatography. A randomized, controlled trial. Ann Intern Med. 1996;125:442–7.
62. Llach J, Bordas JM, Almela M, Pellise M, Mata A, Soria M, et al. Prospective assessment of the role of antibiotic prophylaxis in ERCP. Hepatogastroenterology. 2006;53:540–2.
63. Lorenz R, Lehn N, Born P, Hermann M, Neuhaus H. Antibiotic prophylaxis with cefuroxime in therapeutic endoscopy of the bile ducts. Dtsch Med Wochenschr. 1996;121:223–30.
64. Sauter G, Grabein B, Mannes GA, Reckdeschel G, Sauerbruch T. Antibiotic prophylaxis of infectious complications with endoscopic retrograde cholangiopancreatography. A randomized controlled study. Endoscopy. 1990;22:164–7.
65. Niederau C, Pohlmann U, Lubke H, Thomas L. Antibiotic prophylaxis during therapeutic or complicated diagnostic ERCP: results of a randomized controlled clinical study. Gastrointest Endosc. 1994;40:533–7.
66. Räty S, Sand J, Pulkkinen M, Matikainen M, Norback I. Post-ERCP pancreatitis: reduction by routine antibiotics. J Gastrointest Surg. 2001;5:339–45.
67. Alexander JW, Solomkin JS, Edwards MJ. Updated recommendations for control of surgical site infections. Ann Surg. 2011; 253:1082–93 (CPGs).