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Antibiotics in acute calculous cholecystitis : do Tokyo guidelines influence the surgeons' practices?

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ORIGINAL ARTICLE

Antibiotics in acute calculous cholecystitis — do Tokyo guidelines influence the surgeons' practices?

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Abstract

Objective: To observe changes in surgeons' practice of antibiotic usage in patients with acute cholecystitis before and after the implementation of Tokyo Guidelines.

Methods: This retrospective, descriptive study was conducted at the Aga Khan University Hospital, Karachi, and comprised the medical records of all patients with the diagnosis of acute calculus cholecystitis who presented in 2009 and those who presented in 2014 after the implementation of Tokyo Guidelines. The major variables included patients' demographics, antibiotics used and surgical outcomes. SPSS 19 was used for data analysis.

Results: Of the 356 patients, 96(27%) were treated in 2009 and 260(73%) in 2014. The overall mean age was 48.9±14 years. There were 185(52%) females and 171(48%) males. Comparison of the data from 2 years showed no difference in gender, American Society of Anaesthesiologists level, grade of acute cholecystitis and frequency of use of empiric antibiotics (p>0.05 each). However, there was significantly less use of combination therapy (p=0.00) and metronidazole (p=0.00) in 2014than in 2009. Interval cholecystectomy was significantly less practised in 2014 (p=0.03) resulting in shorter hospital stay (p=0.00). Despite improvement in antibiotic usage practices, post-operative infection rates remained the same in both the groups (p=0.58).

Conclusion: Implementation of Tokyo Guidelines not only greatly influenced but also standardised the choice of antibiotics in patients without compromising the infective and surgical outcomes.

Keywords: Acute cholecystitis, Antibiotics, Tokyo Guidelines, Outcomes. (JPMA 67: 670; 2017)

Introduction

Acute cholecystitis (AC) is a common complication of gallstone disease and accounts for 3%to9% of all hospital admissions for acute abdominal pain.[1,2] In a systematic review, acute cholecystitis was seen in 6 to 11 percent of patients with symptomatic gallstones over a median follow-up of 7 to 11 years.[3] The patients with acute cholecystitis may present with varying degree of disease severity, usually dictated by the duration of obstruction by gallstones and the presence of secondary infection.[4] Associated co-morbid conditions may also influence the clinical presentation, for example, diabetic patients are more prone to develop acute gangrenous cholecystitis, as compared to non-diabetic patients.[5]

The usual treatment plan for patients with acute cholecystitis consists of antibiotics followed by surgical intervention. The choice and duration of antibiotics usually remain a contentious issue in this situation. Updated Tokyo Guidelines classified the patients with acute cholecystitis into three broad groups on the basis of severity of infection and provide recommendations for the antibiotic regimen and duration of therapy in each category.[6] Regarding surgical treatment, early laparoscopic cholecystectomy is the operation of choice for mild and moderate acute cholecystitis. For severe cholecystitis, Tokyo Guidelines recommend draining the gall bladder initially, and plan delayed cholecystectomy.[7]

The current study was conducted at a tertiary care university hospital which was trying to follow and implement Tokyo Guidelines for the last few years. The current study was planned to observe changes in surgeons' practices of antibiotic usage in patients with acute cholecystitis, before and after the implementation of the guidelines.

Patients and Methods

This retrospective, descriptive study was conducted at the Department of Surgery of Aga Khan University Hospital (AKUH), Karachi, and comprised medical records of all patients with the diagnosis of acute calculus cholecystitis who presented in 2009 and those who presented in 2014 after the implementation of Tokyo Guidelines. Exemption was obtained from the institutional ethics review committee. All adult patients who presented to our hospital with symptoms of right upper quadrant pain and diagnosed to have acute calculus cholecystitis on the basis of clinical and radiological signs and underwent cholecystectomy were included. Acute calculus cholecystitis was finally confirmed on the basis of

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histopathology. Patients with incomplete data and a calculus cholecystitis were excluded. Education regarding Tokyo Guidelines and its implementation was started in 2010 in our hospital. Tokyo Guidelines were last updated in 2013, so to assess the accurate outcomes and change in our practices we selected patients before implementation of Tokyo Guidelines (year 2009) in our set-up and compared them with the patients after the implementation and upgrading of Tokyo Guidelines (year 2014). During this period, the general surgery faculty members and residents at our hospital were repeatedly educated in evidence-based and core curriculum sessions, morbidity and mortality meetings and grand round presentations regarding Tokyo Guidelines and its implications.

A detailed proforma was developed to record information on patient's demographics, clinical features, haematological and radiological investigations, empiric antibiotics used (monotherapy — single antibiotic, combination therapy — more than one antibiotic) and sensitivity of organisms found in bile or gallbladder tissue cultures. Patients were classified into grade I, II and III according to Tokyo Guidelines on the basis of severity of disease (Table-1), and our practices of antibiotic usage were compared. Post-operative 30-day infective morbidity (surgical site infection, intra-abdominal abscess, and urinary tract and chest infections) was also recorded. Data regarding type of surgical intervention (laparoscopic or open cholecystectomy) and time of surgical intervention (early or delayed cholecystectomy) was also collected. With increasing experience in laparoscopy, the same admission laparoscopic cholecystectomy was offered for all grades of acute cholecystitis in our centre, and only a few patients underwent delayed cholecystectomy (i.e. after 6 weeks of conservative management and very a small number of them were managed with cholecystostomy tube). A four-port laparoscopic cholecystectomy was attempted in all patients in the year 2014 and a majority of patients in the year 2009 except for a few (in whom open cholecystectomy was preferred due to increase body mass index (BMI) or previous surgery or surgeon's preference). Unclear anatomy of Calot's triangle and dense adhesions were the major factors for conversion from laparoscopic to open cholecystectomy in our set-up.

SPSS 19 was used for data analysis. Quantitative variables were reported as means ±standard deviations or median ±interquartile range (IQR), depending upon distribution of data. Qualitative variables were reported as proportions and percentages. Association of qualitative variables was analysed using chi-square test, whereas association of quantitative variables was analysed by t-test. For more than two quantitative variables, one-way analysis of variance (ANOVA) test was used. $P<0.05$ was considered significant.

Results

Of the 356 patients admitted during these 2 non-consecutive years, 185(52%) were females and 171(48%) were males. The overall mean age was 48.9±14.1 years. As per Tokyo Guidelines, 142(40%) patients were classified as having grade I, 185(52%) as grade II and 29(8%) as grade

Table-1: Descriptive data.

Severity Grading for Acute Cholecystitis, According to Tokyo Guidelines	
Grade I (mild)	Does not meet the criteria of ''Grade III'' or ''Grade II'' acute cholecystitis. Grade I can also be defined as acute cholecystitis in a healthy patient with no organ dysfunction and mild inflammatory changes in the gallbladder, making cholecystectomy a safe and low-risk operative procedure
Grade II (moderate)	Associated with any one of the following conditions: 1. Elevated white blood cell count (> 18,000 cells per cubic millimetre) 2. Palpable tender mass in the right upper abdominal quadrant 3. Duration of complaints > 72 hours 4. Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis)
Grade III (severe)	Associated with dysfunction of any one of the following organs/systems: 1. Cardiovascular dysfunction Hypotension requiring treatment with dopamine $\geq$ 5 µg/kg per min, or any dose of norepinephrine 2. Neurological dysfunction Decreased level of consciousness 3. Respiratory dysfunction PaO_2/FiO_2 ratio < 300 4. Renal dysfunction Oliguria, creatinine> 2.0 mg/dl 5. Hepatic dysfunction PT-INR >1.5 6. Haematological dysfunction Platelet count < 100,000/mm^3

PT-INR: Prothrombin time - international normalised ratio.

Table-2: Descriptive data.

Variable	Grade I N=142 n (%)	Grade II N=185 n (%)	Grade III N=29 n (%)	p value
Age, mean (SD), y	46.7 ± 14.8	49.7 ± 13.8	55.1 ± 14.2	0.193
Gender				
Male	63 (44)	93 (50.3)	15 (51.7)	0.524
Female	79 (56)	92 (49.7)	14 (48.3)	
Co-morbids	56 (39.4)	97 (52.4)	19 (65.5)	0.010
DM II	21 (14.8)	54 (29.2)	14 (48.3)	
Hypertension	43 (30.3)	67 (36.2)	15 (51.7)	
Ischaemic Heart Disease	7 (4.9)	14 (7.6)	1 (3.4)	
ASA Level				
II or less	130 (91.5)	144 (77.8)	17 (58.6)	0.000
> II	12 (8.5)	41 (22.2)	12 (41.4)	
Hospital Stay				**0.000**
48 hours or less	108 (76.1)	102 (55.1)	7 (24.1)	
> 48 hours	34 (23.9)	83 (44.9)	22 (75.9)	

SD: Standard deviation
DM: Diabetes mellitus
ASA: American Society of Anaesthesiologists.

Table-3: Use of antibiotics.

Variable	Grade I N=142 n (%)	Grade II N=185 n (%)	Grade III N=29 n (%)	p value
Empiric Antibiotic Used				
Yes	136 (95.8)	184 (99.5)	29 (100)	0.043
No	6 (4.2)	1 (0.5)	0 (0)	
Combination Therapy	52 (36.6)	105 (56.8)	25 (86.2)	0.000
Monotherapy	84 (59.2)	79 (42.7)	4 (13.8)	0.000
Combination Therapy				
Ceftriaxone + Meronidazole	23 (16.2)	63 (34.1)	13 (44.8)	
Ceftriaxone + Meronidazole + Ampicillin	20 (14.1)	24 (12.9)	4 (13.8)	
Others	9 (6.3)	18 (9.8)	8 (27.6)	
Monotherapy or No antibiotic	90 (63.4)	80 (43.2)	4 (13.8)	
Monotherapy				
Ceftriaxone	35 (24.6)	51 (27.6)	4 (13.8)	
Cefazolin	49 (34.5)	25 (13.5)	0 (0)	
Ciprofloxacin	0 (0)	2 (1.1)	0 (0)	
Combination therapy or No antibiotic	58 (40.9)	107 (57.8)	25 (86.2)	
Use of Metronidazole	49 (34.5)	95 (51.4)	18 (62.1)	0.002
Antibiotic on discharge	55 (38.7)	122 (65.9)	24 (82.8)	0.000

For categorical variables chi-square test was used.

III cholecystitis. Of patients with severe acute cholecystitis (i.e. > grade II), 12(41.4%) had American Society of Anaesthesiologists (ASA) level of more than 2, compared to 12(8.5%) and 41(22.2%) of patients in mild (grade I) and moderate (grade II) acute cholecystitis, respectively (Table-2).

Empiric antibiotics were used in 349(97%) patients, including combination therapy in 182(52.1%) patients and monotherapy in 167(47.9%) patients. Most of the patients with severe acute cholecystitis received combination therapy, while monotherapy was more frequently used in patients with mild and moderate acute cholecystitis. Besides, 201(56.5%) patients also received antibiotics on discharge, including 55(38.7%) in grade I, 122(65.9%) in grade II and 24(82.8%) in grade III (Table-3).

Laparoscopic cholecystectomy was performed on 137(96.5%), 162(87.6%) and 19(65.5%) patients in grade I, II and III, respectively. Overall, 319(89.6%) patients

Table-4: Surgical data.

Variable	Grade I N=142 n (%)	Grade II N=185 n (%)	Grade III N=29 n (%)	p value
Type of Cholecystectomy				0.000
Laparoscopic Cholecystectomy	137 (96.5)	162 (87.6)	19 (65.5)	
Lap. converted to Open Cholecystectomy	4 (2.8)	19 (10.3)	9 (31)	
Open Cholecystectomy	1 (0.7)	4 (2.2)	1 (3.4)	
Time of Cholecystectomy				0.010
Same admission/early Cholecystectomy	135 (95.1)	161 (87)	23 (79.3)	
Interval Cholecystectomy	7 (4.9)	24 (13)	6 (20.7)	
Postoperative morbidity				0.046
Wound infection	4 (2.8%)	8 (4.3%)	2 (6.9%)	
Intra-abdominal abscess	0	2 (1.1%)	1 (3.4%)	
Chest infection	0	0	1 (3.4%)	

For categorical variables chi - square test was used.

Table-5: Comparison of two years (2009 vs. 2014).

Variable	2014 N=260 n (%)	2009 N=96 n (%)	p value
Age, mean (SD), y	48.0 ± 14.0	51.4 ± 14.4	0.03
Gender			
Male	119 (45.8)	52 (54.2)	0.18
Female	141 (54.2)	44 (45.8)	
ASA Level			
II or less	218 (83.8)	74 (77.1)	0.16
> II	42 (16.2)	22 (22.9)	
Grade of Acute Cholecystitis			
Mild	102 (39.2)	40 (41.7)	0.38
Moderate	135 (52)	50 (52)	0.53
Severe	23 (8.8)	6 (6.3)	0.51
Empiric Antibiotic Used			
Yes	256 (98.5)	93 (96.9)	0.28
No	4 (1.6)	3 (3.1)	
Combination Therapy	114 (43.8)	67 (69.8)	0.00
Monotherapy	142 (54.6)	26 (27.1)	0.00
Use of Metronidazole	98 (37.7)	64 (66.7)	0.00
Antibiotic on discharge	142 (54.6)	59 (61.5)	0.27

SD: Standard deviation
ASA: American Society of Anaesthesiologists.

Table-6: Comparison of two years — Operative outcomes.

Variable	2014 N=260 n (%)	2009 N=96 n (%)	p value
Type of Cholecystectomy			
Laparoscopic Cholecystectomy	241 (92.7)	77 (80.2)	0.00
Lap. converted to Open Cholecystectomy	19 (7.3)	13 (13.5)	0.09
Open Cholecystectomy	0 (0)	6 (6.3)	0.00
Time of Cholecystectomy			
Same admission/early Cholecystectomy	239 (91.9)	80 (83.3)	0.03
Interval Cholecystectomy	21 (8.1)	16 (16.7)	0.03
Hospital Stay			
48 hours or less	178 (68.5)	39 (40.6)	0.00
> 48 hours	82 (31.5)	57 (59.4)	0.00
Post-operative morbidity	12 (4.6%)	6 (6.3%)	0.58
Wound infection	9 (3.5%)	5 (5.2%)	0.53

For categorical variables chi-square test was used.

underwent cholecystectomy in the same admission while interval cholecystectomy was performed in 37(10.4%)patients, being highest in grade III acute cholecystitis, i.e. 6(20.7%). Conversion rate from laparoscopic to open cholecystectomy was 32(9%), being highest 9(31%) in grade III and lowest 4(2.8%) in grade I acute cholecystitis. Overall, 30-day post-operative infective complications were seen in 18(5%) patients; surgical site infection was most common at 14(3.9%) (Table-4).

Year-wise analysis showed that the total number of patients with acute cholecystitis was 96(27%) in the year 2009 and 260(73%) in the year 2014. The comparison of the data from 2 years showed no significant difference in gender, ASA level, grade of acute cholecystitis, use of empiric antibiotics in hospital and percentage of patients receiving antibiotics on discharge in 2 groups. However, there was a significant difference in the use of combination therapy (114(43.8%) in 2014 vs. 67(69.8%) in 2009, p=0.00), monotherapy (142(54.6%) in 2014 vs. 26(27.1%) in 2009, p=0.00) and metronidazole (98(37.7%) in 2014 vs. 64(66.7%) in 2009, p=0.00) (Table-5).

On comparing surgical outcomes between these two years, significantly more patients underwent laparoscopic cholecystectomy in 2014 (241(92.7%) in 2014 vs. 77(80.2%) in 2009, p=0.00), while conversion from laparoscopic to open cholecystectomy was comparatively less in 2014 (19(7.3%) in 2014 vs. 13(13.5%) in 2009,

p=0.09). Interval cholecystectomy was significantly less practised in 2014 (21(8.1%) in 2014 vs. 16(16.7%) in 2009, p=0.03). A significantly shorter hospital stay was noticed in 2014 (178(68.5%) in 2014 had a hospital stay of less than 48 hours vs. 39(40.6%) in 2009, p=0.00). Post-operative infective complications rate was not different between these two years (12(4.6%) in 2014 vs. 6(6.3%) in 2009, p=0.58) (Table-6).

Bile or gall bladder cultures were sent in 166(46.6 %) patients and 78(46.9 %) were positive for bacterial growth. The most common bacteria found were Escherichia coli 45(57.7%), Streptococcus 13(16.6%), Klebsiella 7(9%) and Enterococci 5(6.5%).

Discussion

After implementing Tokyo Guidelines, overall use of combination therapy has significantly reduced (from 69.8% in 2009 to 43.8% in 2014, p=0.00). In 2009, 62.5% patients with grade I acute cholecystitis received a combination of two or three antibiotics, whereas in 2014 the use of combination therapy for same grade of acute cholecystitis significantly dropped to 26.5%. Similarly in grade II acute cholecystitis, the use of monotherapy was becoming more frequent and combination therapy dropped from 74% to 49.6%.

Ceftriaxone (53.9%) was the most common antibiotic used as monotherapy, followed by cefazolin (44.3%). According to updated Tokyo Guidelines, ceftriaxone and cefazolin can be used as montherapy for grade I and II acute cholecystitis. In grade III acute cholecystitis, more than 80% patients received combination therapy in both years, with no significant difference. However, the difference was in the choice of antibiotics used. In 2009, most common combination therapy included three drugs (ceftriaxone, ampicillin andmetronidazole) with rationale of covering gram-negative, gram-positive and anaerobic organisms. However, after following Tokyo Guidelines, ceftriaxone + metronidazole (56.5%) was the most common combination, followed by piperacillin/tazobactam + metronidazole (17.4%) and imipenem + metronidazole (4.3%).

As per Tokyo Guidelines, piperacillin/tazobactam is the first antibiotic of choice for grade III acute cholecystitis. Alternate recommendations are cefepime, ceftazidime or cefozopran with or without metronidazole. In our study, the practice of using ceftriaxone in grade III acute cholecystitis can be partly attributed to the high cost of other alternative drugs. The most common dosage of ceftriaxone used in our set-up is 2 grams quaquedie (QD) (approximately 5.25 dollars), whereas the dosage of piperacillin/tazobactam is 4.5 grams ter in die (TID) (approximately 23.7 dollars). Also on the basis of our culture and sensitivity data, the overall sensitivity of ceftriaxone against Escherichia coli was 77.8%. However, on further analysis it was noticed that its sensitivity dropped from almost 88.9% in 2009 to nearly 70.4% in 2014. The final draft of the updated Tokyo Guidelines (TG13) recommendations for grade III acute cholecystitis are based on the concept that in severe acute cholecystitis, polymicrobial gram-negative and anaerobes or multi-drugs resistant microorganisms are present, including Pseudomonas. In our population, Pseudomonades were not isolated from any cultures of patients with grade III cholecystitis.

According to Tokyo Guidelines, metronidazole should be used only in patients who have biliary-enteric anastomosis or if the other antibiotic has poor anaerobic coverage.[8] In our study, metronidazole was used empirically not only in grade III (62.1%) but also in grade I (34.5%) and grade II (51.4%) acute cholecystitis. After implementation of TG13, the use of metronidazole dropped significantly in grade I (from 62.5% in 2009 to 23.5% in 2014) and grade II acute cholecystitis (from 70% in 2009 to 44.4% in 2014).

For definitive surgical options, TG13 clearly recommends early laparoscopic cholecystectomy for grade I and II acute cholecystitis.[7] In this study, early cholecystectomy was performed successfully in 95.1% and 87% patients with grade I and II cholecystitis.

For grade III acute cholecystitis, TG13 recommends delayed cholecystectomy, once the local and systemic inflammation is in control. Gall bladder drainage should be done for control of local inflammation. In our experience, almost 79.3% patients with grade III acute cholecystitis underwent early cholecystectomy. However, conversion rate from laparoscopic to open cholecystectomy was pretty high (31%) in grade III as compared to grade I and II combined (7%). A number of recently published studies and trials have proved the safety and efficacy of early cholecystectomy in patients with grade III acute cholecystitis or in critically ill patients.[9-12] Similarly, a recent review found no evidence to support the recommendation of percutaneous drainage rather than straight early emergency cholecystectomy, even in critically ill patients. This is based on the data that suggests the mortality rate after percutaneous cholecystostomy tube drainage (15.4%) is significantly higher than reported after early cholecystectomy (4.5%).[13] With experience, early cholecystectomy increased significantly in all grades in our set-up (from 83.3% in 2009 to 91.9% in 2014, p=0.03).

Regarding duration of antibiotic treatment, TG13 recommends that for grade I acute cholecystitis antimicrobial therapy can be discontinued within 24 hours after cholecystectomy is performed. For grade II and III acute cholecystitis, recommendation is to give antibiotics for 4-7 days, once source of infection is controlled. In our study it was observed that almost 38.7 % patients with grade I acute cholecystitis received antibiotics, after cholecystectomy. A significant drop was observed in this trend after implementation of TG13 (from 57.5% in 2009 to 31.4% in 2014). Nearly 65.9% and 82.8% patients of grade II and III cholecystitis, respectively, received antibiotics after cholecystectomy.

Although significant reduction was noticed in the use of combination therapy, no change in infective morbidity rate was noticed over the years (from 6.3% in 2009 to 4.6% in 2014, p=0.58). This suggests that antibiotics may have a limited role in preventing post-operative surgical site or distant site infection. There are multiple trials[14-17] showing that peri-operative use of antibiotics in grade I and grade II acute cholecystitis does not have any role in preventing surgical site or systemic infections. However, Tokyo Guidelines still recommend the use of antibiotics in these patients. At the same time there are reports in current literature which show the limitations of TG13 with respect to the grading of severity of acute cholecystitis on the basis of which antibiotics are recommended. For example, a study from Germany suggests that Tokyo Guidelines might underestimate the level of gallbladder inflammation in patients with grade I acute cholecystitis.[18]

In general, inappropriate use of antibiotics not only increases the risk of bacterial resistance, but it has a detrimental effect on the cost as well.[19,20] If patients with mild and moderate acute cholecystitis can undergo surgery without peri-operative antibiotics, it will reduce the chances of microbial resistance, lessen the hospital charges[21,22] and also decrease the incidence of allergic or worse reactions caused by antibiotics.[23] However, to ascertain that peri-operative antibiotics in mild and moderate acute cholecystitis do not affect the rate of surgical site infection or distant infection, a randomised study is required in our set-up.

It will also be interesting to look for the chances of infective complications in patients, who had intra-operative bile spillage, as nearly 50% of bile or tissue cultures sent in this study and reported in other population were positive for bacterial growth.[24] Also, the antibiotic practice may be influenced in critically ill patients (ASA III/IV) in whom recent studies suggests that they are at increased risk for extensive gallbladder inflammation with higher chances of morbidity and mortality as compared to otherwise healthy patients (ASAI/II).[25]

Conclusion

Implementation of Tokyo Guidelines effectively changed the surgeons' practices. It improved and simplified the selection of empirical antibiotic in patients with acute calculous cholecystitis, without compromising the surgical outcomes or post-operative infective morbidity. There is a need to explore further strategies to reduce the cost and antibiotic resistance.

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