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# Susceptibility of Bile Cultures to Empiric Antibiotic Therapy and Impact on Clinical Outcomes in Patients with Acute Cholecystitis Undergoing Percutaneous Cholecystostomy

## Perkütan Kolesistostomi Uygulanan Akut Kolesistitli Hastalarda Safra Kültürlerinin Ampirik Antibiyotik Tedavisine Duyarlılığı ve Klinik Sonuçlar Üzerindeki Etkisi

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## Abstract

**Objective:** To characterize biliary microbiology, quantify empiric antibiotic-culture susceptibility concordance, and identify mortality-associated factors among acute cholecystitis (AC) patients undergoing percutaneous cholecystostomy (PC).

**Methods:** We conducted a retrospective single-center cohort (January 2019-June 2024) of adults with AC treated by PC (n=86). Diagnosis relied on clinical, laboratory, and imaging criteria; severity was graded per Tokyo Guidelines 2018 (grade II-III). Collected variables included demographics, comorbidities [Charlson comorbidity index (CCI), C-reactive protein (CRP)/procalcitonin (PCT)], empiric regimen, bile culture/susceptibility, and clinical outcomes. Concordance was defined as full coverage of all cultured organisms by the initial empiric regimen. Multivariable logistic regression assessed predictors of mortality.

**Results:** Mean age was 72.1±14.0 years; 48.8% were female. Tokyo grade II 85%, grade III 15%; CCI: 1.10±1.08. The predominant empiric regimen was 3rd-generation cephalosporin plus metronidazole (89.5%). Overall bile culture positivity was 68.6%; leading organisms were *Escherichia coli* (35%), *Enterococcus* spp. (22%), and *Klebsiella* spp. (18%). Empiric-culture concordance was 57.1%, with the most prominent discordance for *Enterococcus* (coverage 31.0%). Length of stay, drain removal time, and CCI did not differ between concordant versus discordant therapy. Overall mortality was 10.5%. In multivariable analysis, age independently predicted mortality [odds ratio (OR)=1.12, p=0.03]; higher Tokyo grade showed a non-significant upward trend (p=0.16). Concordance showed a protective trend for mortality (OR=0.23, p=0.12).

**Conclusion:** In AC managed with PC and timely source-control, empiric-culture concordance is moderate and appears to have limited impact on short-term mortality, which is primarily driven by age and disease severity. The frequency of *Enterococcus* underlies most discordance and should inform empiric choices. These findings support rapid de-escalation and short-course, targeted antibiotics following adequate drainage.

**Keywords:** Acute cholecystitis, percutaneous cholecystostomy, bile culture, empiric antibiotics, *Enterococcus*, mortality

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## Öz

**Amaç:** Akut kolesistit (AK) nedeniyle perkütan kolesistostomi (PK) uygulanan hastalarda mikrobiyolojik dağılımı, ampirik antibiyotik-kültür duyarlılık uyumunu ve mortalite ile ilişkili faktörleri değerlendirmek.

**Yöntem:** Ocak 2019-Haziran 2024 arasında tek merkezde yürütülen retrospektif kohortta PK yapılan erişkin AK hastaları incelendi (n=86). Tanı klinik, laboratuvar ve görüntüleme bulgularına; şiddet sınıflaması Tokyo Guidelines 2018 (grade II-III) ölçütlerine göre yapıldı. Kayıt edilen değişkenler: demografi, komorbiditeler [Charlson komordibite indeksi (CCI), C-reaktif protein (CRP)/prokalsitonin (PCT)], ampirik rejim, safra kültürü/antibiyogram ve klinik sonuçlar. Ampirik-kültür uyumu, kültürde üreyen tüm mikroorganizmaların başlanılan ampirik rejimle kapsanması olarak tanımlandı. Çok değişkenli lojistik regresyonla mortalite belirleyicileri analiz edildi.

**Bulgular:** Ortalama yaş 72,1±14,0 yıl; %48,8 kadın. Tokyo grade II %85, grade III %15; CCI: 1,10±1,08. Başlangıç ampirik tedavi çoğunlukla 3. kuşak sefalosporin+metronidazol (%89,5) idi. Safra kültürü pozitifliği %68,6; en sık etkenler *Escherichia coli* (%35), *Enterococcus* spp. (%22) ve *Klebsiella* spp. (%18). Ampirik-kültür uyumu %57,1 olup uyumsuzluk en belirgin *Enterococcus*'ta izlendi (kapsama %31,0). Uyumlu-uyumsuz gruplar arasında yatış süresi, dren çekilme süresi ve CCI açısından fark yoktu. Toplam mortalite %10,5 idi. Çok değişkenli analizde yaş mortalite ile bağımsız ilişkiliydi [olasılık oranı (OO)=1,12, p=0,03]; daha yüksek Tokyo derecesi anlamlı olmayan artış eğilimi gösterdi (p=0,16). Uyum, mortalite için koruyucu eğilimdeydi (OO=0,23, p=0,12).

**Sonuç:** PK ile etkin kaynak kontrolü sağlanan AK olgularında ampirik-kültür uyumu orta düzeyde olup kısa dönem mortalite üzerinde sınırlı etkiye sahiptir; mortalite daha çok yaş ve hastalık şiddeti ile ilişkilidir. *Enterococcus* sıklığı uyumsuzluğun başlıca nedenidir ve ampirik rejim seçimini etkiler. Sonuçlar, kültür sonrası hızlı daraltma ve kısa süreli, hedefe yönelik antibiyotik stratejilerini desteklemektedir.


**Anahtar Kelimeler:** Akut kolesistit, perkütan kolesistostomi, safra kültürü, ampirik antibiyotik, *Enterococcus*, mortalite

## Introduction

Acute cholecystitis (AC) is a common cause of acute abdomen, most commonly resulting from cystic duct obstruction and biliary stasis, and is associated with substantial morbidity. Contemporary guidelines emphasize severity grading [Tokyo Guidelines 2018, (TG18)] alongside clinical and laboratory findings for diagnosis and recommend rapid source-control and rational, patient-tailored use of antibiotics[1,2]. Percutaneous cholecystostomy (PC) is an effective bridging or definitive treatment option for patients for whom early cholecystectomy is not preferred or who are at high surgical risk[1].

The duration and spectrum of antibiotic therapy are among the most debated issues during the post-PC period. The TG18 and World Society of Emergency Surgery (WSES) Guidelines generally recommend short-courses when adequate source-control has been achieved (most cases, 4-7 days), and suggest prolongation in the presence of Grampositive coccal bacteremia (especially *Enterococcus* or *Streptococcus*)[2-5]. This approach aligns with the STOP-IT paradigm, which supports short-course therapy after adequate source-control in intra-abdominal infections[6]. Nevertheless, recent reviews highlight the limited evidence supporting these recommendations and the need for personalization using realworld data[7,8].

Microbiologically, while *Enterobacterales*-particularly *Escherichia coli* (*E. coli*)-remain the most frequent pathogens in AC, a relative increase in *Enterococcus* spp. within PC populations has been reported and may thereby heighten the risk of discordance between empiric therapy and culture-based susceptibility results[9-11]. Reported empiric-culture concordance rates vary across PC cohorts. In a 10 year experience, Nitzan et al.[12] reported ≈67% concordance, whereas more recent cohorts suggest that discordance may have limited impact on outcomes when source-control is decisive.

Among biomarkers, procalcitonin (PCT) and C-reactive protein (CRP) may aid in discriminating the severity of AC. Some studies suggest that PCT outperforms CRP for diagnosis and severity, yet evidence regarding independent associations with mortality is inconsistent[13,14]. Therefore, PCT and CRP should be interpreted alongside severity grading and comorbidity burden.

This study aimed to evaluate, among AC patients undergoing PC at our center between 2019 and 2024, the microbiological profile, concordance between empiric antibiotic therapy and culture susceptibility, factors associated with mortality, and clinical outcomes.

## Materials and Methods

This study was a retrospective, single-center cohort analysis of adult patients who were admitted to the University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital, Department of General Surgery, between January

2019 and June 2024, had a diagnosis of AC, and were treated with PC. Diagnosis was based on clinical findings (right upper quadrant pain, fever, Murphy's sign), laboratory findings (leukocytosis, elevated liver function tests), and imaging findings (ultrasound or computed tomography showing wall thickening, pericholecystic fluid, and gallstones). Disease severity was graded I-III according to TG18. PC was preferred as a source-control method in patients at high surgical risk (American Society of Anesthesiologists ≥III) or with poor general condition.

From patient records, the following variables were collected: demographics (age, sex); clinical data (Tokyo Grade, comorbidities); laboratory (white blood cell count, CRP, PCT); treatment (initial empiric antibiotic regimen); microbiology (bile culture results and antibiotic susceptibility); and outcomes (length of stay, time to drain removal, mortality). Comorbidity burden was calculated using the Charlson comorbidity index (CCI), which included the presence of cerebrovascular disease, diabetes, chronic obstructive pulmonary disease (COPD), coronary artery disease, renal failure, dementia, and malignancy. Because hypertension is not included in the CCI, it was reported descriptively but excluded from CCI calculations.

During PC, bile samples were obtained using sterile techniques and cultured using standard laboratory methods. Empiric-culture concordance was defined as complete coverage of all cultured microorganisms by the initial empiric regimen, as determined by susceptibility testing. Patients with "no growth" were excluded from the concordance analysis. Empirical antibiotics were selected according to the TG18 and WSES 2020 recommendations (group 1: third-generation cephalosporin plus metronidazole; group 2: carbapenem; group 3: piperacillin/tazobactam). Antibiotic duration was generally ≤7 days; when resistant isolates, bacteremia, or a persistent systemic response were present, the duration was extended.

**Exclusion criteria were:** Age <18 years; acute cholangitis or pancreatitis not meeting TG18 criteria for AC; primary perforated cholecystitis with diffuse peritonitis requiring emergent cholecystectomy at presentation; lack of bile sampling at PC; bile culture sampled >48-72 h after initiation of antibiotics, or growth deemed a contaminant; missing culture/susceptibility results; missing essential variables (age, sex, Tokyo Grade, CCI, empiric regimen, CRP/PCT, length of stay, and drain times); loss to follow-up within 30 days; and early failure of source-control after PC necessitating urgent revision/surgery within 24 h.

### Ethics Approval

This study was approved by the University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital Non-Interventional Clinical Research Ethics Committee (approval no: 2024/10-13, date: 07.11.2024). The study was conducted in accordance with the principles of the Declaration of Helsinki.

### Statistical Analysis

Continuous variables were summarized as mean ± standard deviation or median [interquartile range (IQR)]; categorical variables were summarized as number (%). Appropriate parametric or non-parametric tests were used for group comparisons. Factors predicting mortality were assessed using multivariable logistic regression. Model 1 included age, sex, Tokyo Grade, logCRP, logPCT, and CCI; model 2 (subgroup) included age, Tokyo Grade, and empiric-culture concordance. Two-sided p-values were considered statistically significant. Analyses were performed using SPSS v26.0 (IBM Corp., USA).

## Results

Among 86 AC patients who underwent PC, the mean age was 72.1±14.0 years; 48.8% were female. The severity distribution was Tokyo Grade II (85%) and Grade III (15%). The mean CCI was 1.10±1.08. The most frequent comorbidities were hypertension (47.7%), diabetes mellitus (32.6%), and COPD (17.4%) (Table 1). The mean length of stay was 10.1±6.8 days, and the median time to drain removal was 38 days (IQR: 22-54); these did not differ significantly between concordant and discordant antibiotic groups (Table 1).

Initial empirical therapy consisted predominantly of a third-generation cephalosporin plus metronidazole (89.5%), with less frequent use of carbapenems (6.0%) and piperacillin/tazobactam (4.5%) (Table 1). This distribution shaped the coverage rates calculated against culture results (Table 2).

The most commonly isolated organisms in bile cultures were *E. coli* (35%), *Enterococcus* spp. (22%), and *Klebsiella* spp. (18%); lower frequencies included *Enterobacter* spp. (10%), *Streptococcus* spp. (5%), and others (mainly *Pseudomonas* and *Candida*), accounting for 8%. The overall culture positivity rate was 68.6% (Table 2).

Empiric-culture concordance was 57.1%. By organism, coverage was 90.4% for *E. coli*, 72.7% for *Klebsiella* spp., 50.0% for *Enterobacter* spp., 100.0% for *Streptococcus* spp., and 40.0% for the "other" group. Discordance was most pronounced for *Enterococcus* spp. (coverage: 31.0%), reflecting the predominance of cephalosporin-based empiric regimens (Table 2).

There were no significant differences between the concordant and discordant groups in length of stay, time to drain removal, or CCI (Table 1). Overall mortality was 10.5%. In multivariable analysis, age was independently associated with mortality [odds ratio (OR)=1.12, p=0.03], while a higher Tokyo Grade showed a nonsignificant trend (p=0.16). Empiric-culture concordance showed a protective trend for mortality (OR=0.23, p=0.12; Table 3).

## Discussion

In this singlecenter retrospective cohort study (2019-2024), we analyzed microbiology, empiric-culture concordance,

**Table 1. Demographic and clinical characteristics (n=86)**

| Variable | Value |
|---|---|
| Age (years), mean ± SD | 72.1±14.0 |
| Female sex, n (%) | 42 (48.8) |
| Tokyo grade II/III, n (%) | 73 (84.9)/13 (15.1) |
| CCI, mean ± SD | 1.10±1.08 |
| Comorbidities, n (%) | Hypertension 41 (47.7), diabetes mellitus 28 (32.6), COPD 15 (17.4), cerebrovascular disease 9 (10.4), malignancy 7 (8.1) |
| Empiric antibiotic regimen | 3rd-Generation cephalosporin+metronidazole 77 (89.5), carbapenem 5 (6.0), piperacillin/tazobactam 4 (4.5) |
| Length of stay (days), mean ± SD | 10.1±6.8 |
| Drain removal time (days), median (IQR) | 38 (22-54) |

SD: Standard deviation, CCI: Charlson comorbidity index, COPD: Chronic obstructive pulmonary disease, IQR: Interquartile range

**Table 2. Bile culture results and empiric therapy-culture concordance**

| Microorganism | n (%) | Covered by empiric regimen (%) |
|---|---|---|
| *Escherichia coli* | 21 (35.0) | 90.4 |
| *Enterococcus* spp. | 13 (22.0) | 31.0 |
| *Klebsiella* spp. | 11 (18.0) | 72.7 |
| *Enterobacter* spp. | 6 (10.0) | 50.0 |
| *Streptococcus* spp. | 3 (5.0) | 100.0 |
| Other (e.g., *Pseudomonas*, *Candida*) | 5 (8.0) | 40.0 |
| Total positive cultures | 59 (68.6) | - |
| Empiric-culture concordance | - | 57.1 |

**Table 3. Multivariable logistic regression analysis (mortality)**

| Variable | OR | 95% CI | p |
|---|---|---|---|
| Age (per 1 year) | 1.12 | 1.01-1.25 | 0.03* |
| Sex (female) | 0.81 | 0.19-3.48 | 0.78 |
| Tokyo grade (II–III) | 3.96 | 0.59-26.7 | 0.16 |
| log-CRP | 1.09 | 0.73-1.63 | 0.67 |
| log-PCT | 1.15 | 0.82-1.76 | 0.48 |
| CCI | 1.34 | 0.89-2.14 | 0.21 |
| Subgroup: culture concordance | 0.23 | 0.04-1.44 | 0.12 |

OR: Odds ratio, CI: Confidence interval, CRP: C-reactive protein, PCT: Procalcitonin, CCI: Charlson comorbidity index

and mortality among AC patients treated with PC. Culture positivity was 68.6%, empiric-culture concordance was 57.1%, and mortality was 10.5%. In multivariable analysis, age was the only independent predictor of mortality; higher Tokyo Grade showed a nonsignificant upward trend (OR=3.96, 95% confidence interval: 0.59-26.7, p=0.16). These findings are broadly consistent with larger series in the literature[2,4,7-9,12].

*E. coli* (35%), *Enterococcus* spp. (22%), and *Klebsiella* spp. (18%) were the leading organisms, consistent with the flora anticipated by TG18 and WSES[1,5]. The higher proportion of *Enterococcus* warrants attention. Although *E. coli* remains the main pathogen-reflecting the classical calculus-stasis-colonization pathway-aging, comorbidities, prior antibiotic exposure, and nosocomial contact may shift flora toward Gram-positive and resistant organisms[7,10]. Lahav et al.[4] reported *E. coli* in 33% and *Enterococcus* in 24%, while Nitzan et al.[12] reported 60% culture positivity and 67% concordance. Our 57% concordance rate likely reflects increased isolation of *Enterococcus* and widespread use of cephalosporin-based empiric therapy.

*Enterobacterales* constitute the classical etiologic group in AC. In our cohort, coverage was high for *E. coli* (90%) and *Klebsiella* spp. (73%), consistent with reports by Suh et al.[2] and Fico et al.[3]. The 2024 European Centre for Disease Prevention and Control Report notes extended-spectrum beta-lactamase (ESBL) rates of ≈31% in *E. coli* and ≈38% in *Klebsiella pneumoniae*[7]. Although such trends can drive carbapenem use, both TG18 and WSES advocate short, targeted therapy. Notably, high concordance within *Enterobacterales* did not translate into mortality differences after effective drainage, underscoring the primacy of source-control.

Historically regarded as secondary colonizers, enterococci may act as true pathogens in elderly PC patients, patients with comorbidities, and antibioticexposed PC patients[10,11]. In our cohort, *Enterococcus* spp. were isolated in 22% of cases, similar to Nitzan(14%)[12] and Lahav (24%)[3,4]. Given that most empiric regimens were cephalosporin-based, coverage was only 31%. Although we found no direct association between *Enterococcus* isolation and mortality, most discordant cases were linked to this organism, potentially prolonging clinical recovery. In highrisk scenarios (healthcareassociated AC, immunosuppression, high CCI), initial coverage with ampicillinbased agents or piperacillin/tazobactam can be considered; for vancomycin-resistant enterococci (VRE), linezolid or daptomycin are options[15-18].

*Streptococcus* spp. (5%) were within the expected range (3-10%)[18]. *Pseudomonas* spp. are typically encountered in nosocomial or postendoscopic retrograde cholangiopancreatography settings, where empiric coverage is often inadequate; piperacillin/tazobactam or a carbapenem may be preferred[1,5]. Candida species were rare (approximately 2%), but may require antifungal therapy in patients with malignancy or immunosuppression[19].

Empiric-culture discordance showed a protective trend compared with concordance (OR≈0.23) but did not significantly affect shortterm mortality, echoing Lahav et al.[4] who reported higher 90 day readmission among patients receiving discordant therapy (64% vs. 47%) without differences in mortality. These observations suggest that antibiotic concordance may impact longer-term morbidity rather than short-term mortality when source-control is prompt and effective[15]. Accordingly, source-control remains a prognostic factor that can outweigh the effects of empiric mismatch.

CRP and PCT were not independently associated with mortality in our cohort, aligning with prior work indicating utility for diagnosis and severity assessment but limited prognostic value for hard outcomes[13,14]. Biomarkers should therefore inform, rather than dictate, clinical decision-making alongside TG18 Grade and CCI.

### Study Limitations

This retrospective, singlecenter design limits statistical power for mortality analyses; molecular resistance genotyping (e.g., for ESBL, AmpC, and VRE) was not available. Strengths include a contemporary (post2019) cohort that reflects current antimicrobial stewardship principles and the applications of TG18/WSES. Prospective multicenter studies across diverse geographies are needed to refine local adaptations of guideline-based therapy.

## Conclusion

This single-center retrospective study demonstrates that among patients undergoing PC for AC empiric antibiotic-culture concordance was achieved in only 57% of cases. Despite this moderate concordance, mortality was primarily driven by age and disease severity (Tokyo Grade) rather than by microbiological mismatch. The findings emphasize that timely and effective source-control remains the cornerstone of management in this fragile, high-risk population. While discordant empiric therapy did not significantly affect short-term mortality, it may contribute to prolonged

hospitalization, recurrent infection, or readmission, highlighting the need for ongoing antimicrobial stewardship. From a microbiological perspective, *Enterobacterales* remain dominant and generally respond to cephalosporin-based regimens; however, the rising proportion of *Enterococcus* spp., largely uncovered by these agents, signals an evolving shift toward resistant or mixed biliary flora. Empiric regimens should therefore be individualized, considering patient age, comorbidities, prior healthcare exposure, and local resistance data. Routine broadening of coverage is unnecessary, but selective inclusion of Enterococcus-active agents may be justified in high-risk or healthcare-associated cases. In accordance with the TG18 and WSES recommendations, short-course targeted antibiotic therapy (≤7 days) following successful drainage should be prioritized. Future multicenter prospective studies integrating molecular resistance profiling and long-term outcomes (reinfection, reintervention, post-PC cholecystectomy) are warranted.

### Ethics

**Ethics Committee Approval:** This study was approved by the University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital Non-Interventional Clinical Research Ethics Committee (approval no: 2024/10-13, date: 07.11.2024).

**Informed Consent:** This study was a retrospective, single-center cohort study.

### Footnotes

### Authorship Contributions

Surgical and Medical Practises: O.B.N., F.D., S.Ö., E.K., S.Y., Concept: O.B.N., E.K., S.Y., Design: O.B.N., S.Ö., S.Y., Data Collection or Processing: O.B.N., F.D., S.Ö., Analysis or Interpretation: O.B.N., E.K., S.Y., Literature Search: O.B.N., F.D., S.Ö., Writing: O.B.N., F.D., E.K.

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