The primary purpose of this peer-reviewed journal is to provide a formal publication option for research completed by MSUCOM students, residents and faculty. SMRJ's mission is to advance medicine and medical education through the timely publication of peer-reviewed clinically-oriented research, clinically-relevant basic science research, healthcare quality research, and medical education research from MSUCOM and the osteopathic medicine community, with the ultimate goal of improving patient care and the education of patients and care providers. SMRJ is the official scholarly publication of the Statewide Campus System (SCS) of MSUCOM. It provides a forum for communicating research findings, clinical practice observations, philosophic concepts, and other biomedical and medical education advances to MSUCOM medical students, residents, fellows and faculty, and any other interested readers.

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Welcome to our Fourth SMRJ Journal Issue!

We would like to welcome you again to the final issue of Volume Two of The Spartan Medical Research Journal (SMRJ)! We have the distinct pleasure of serving as your Editorial Office team for this issue.

As noted inside the cover of this issue, the purpose of our online peer-reviewed journal is to provide a convenient, formal publication option for research, quality improvement papers with some case reports and other types of papers. We have received submissions from both Michigan State University COM students, residents, fellows and faculty and scholars outside of the MSU community. We continue to receive submissions from both SCS-affiliated and non-affiliated researchers from other states.

Those of us at the Statewide Campus System continue to depend on a large number of colleagues to generate these journal issues, especially from our growing number of expert reviewers. Our editorial office team offer many thanks to the experts who reviewed these nine Volume 2(2) submissions. We are still recruiting expert reviewers from all medical specialty areas to be members of our SMRJ Editorial Board. If you have an interest in participating as a reviewer, please contact Chief Editor Corser.

If you have comments or suggestions, also please contact us at any time. Remember that we also accept Letters to the Editor and other types of submissions. We hope that you enjoy reading this issue!

Sincerely,

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ORIGINAL CONTRIBUTION

Factors Influencing Length of Stay in Cholecystectomy Patients in a Community Hospital

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ABSTRACT


CONTEXT: Gallstone disease is a major health problem addressed by general surgeons, with approximate incidence of 10-15% in the Western world. With increasing focus in the healthcare literature on cost containment, controlling excess lengths of hospital stay (LOS) in this population is paramount. The aim of this study was to determine the factors that influence LOS in cholecystectomy patients to examine whether results would indicate a possible improvement in perioperative patient care and decrease costs at our community hospital in a suburban setting. METHODS: This is a retrospective review during a two-year period from 1/1/2013-12/31/2014 of patients admitted from the emergency department and undergoing cholecystectomy during the same admission. The study team analyst conducted univariate analysis for significant predictors of length of stay. RESULTS: The authors identified a total analytic sample of 312 subjects who met inclusion criteria. Sample patients admitted to the surgical service had a statistically significant shorter LOS than those patients who were not (3.4 days +/- 1.7 vs 5.6 days +/- 3.0; p value <0.0005). There was also a moderate positive correlation between decreased time to surgery and LOS (Pearson R-value 0.420, p value < 0.0005). Patients admitted to non-surgical services were more likely to have comorbidities like COPD, DM, arrhythmia, CAD, anticoagulation, CHF and previous abdominal surgeries. However, when placing each comorbidity into an analysis of covariance, patients admitted to surgical services still had a significantly shorter LOS (p value < 0.0005). CONCLUSIONS: Admission to a non-surgical service and increased length of time to surgical intervention were associated with prolonged LOS and potentially increased cost in cholecystectomy patients in this study sample. Though patients admitted to non-surgical services are “sicker,” they still had prolonged LOS when controlling for comorbidities. Based on these findings, the establishment of an acute care surgery service may help to address this disparity in care. Keywords: cholecystectomy, length of stay, gallbladder disease
INTRODUCTION

Gallstone disease (i.e., cholelithiasis) is a major health problem frequently addressed by general surgeons. This condition affects approximately 10-15% of adults in the Western world population during their lives.\textsuperscript{1,2} Approximately 6.3 million men and 14.2 million women in the US are afflicted with the condition.\textsuperscript{1,2} The primary risk factors include being female, older, an ethnic/family history, obesity, metabolic syndrome, rapid weight loss, certain diseases (e.g., cirrhosis, Crohn’s disease), and gallbladder stasis.\textsuperscript{2} Those individuals with cholelithiasis may either be asymptomatic or experience symptoms from intermittent cystic duct obstruction (i.e., epigastric or right upper quadrant abdominal pain) after eating fatty foods, with nausea and vomiting. Evaluation in an emergency department typically includes a laboratory workup (i.e., electrolytes, renal function tests, alkaline phosphatase, liver enzyme evaluation, complete blood count) with assessment for obstructive jaundice and an abdominal ultrasound or CT scan.

Gallstone disease can present in a wide variety of clinical scenarios. Patients may experience symptomatic cholelithiasis (also known as gallbladder colic) with intermittent obstruction of the cystic duct resulting in the classic symptoms already described. Complete obstruction results in bacterial infection of the gallbladder (i.e., acute cholecystitis). Obstruction of the common bile duct (i.e., choledocholithiasis) results in obstructive jaundice, and may lead to reflux of the pancreatic duct (leading to gallstone pancreatitis). Choledocholithiasis may also result in infection of the biliary system (i.e., ascending cholangitis), which has been associated with severe sepsis and high mortality.\textsuperscript{2} Gallstones are also a risk factor for gallbladder cancer, although this is very rare (found in 0.3% of patients with gallstones).\textsuperscript{1}

In patients with asymptomatic cholelithiasis, 1-4% will have their conditions progress annually to complications.\textsuperscript{1} Due to the morbidity and mortality associated with the more severe complications of gallstone disease, cholecystectomy is generally recommended for lower-risk patients with symptomatic cholelithiasis. Today, most cholecystectomies are performed using a minimally invasive laparoscopic procedure, with rates of intraoperative conversion to open surgery varying widely from 1 to 15%.\textsuperscript{3} An alternative to surgery generally reserved for higher-risk patients includes percutaneous drainage of the gallbladder.\textsuperscript{1} Additionally, some patients with choledocholithiasis
frequently require endoscopic retrograde cholangio-pancreatography (ERCP) with retrieval of stones and possible stenting of the biliary system before cholecystectomy. There are currently no medications proven to treat cholelithiasis. Providers can prescribe ursodeoxycholic acid to prevent stone formation in high-risk populations without affecting symptoms.1

One older article estimated that more than 700,000 cholecystectomies were annually performed in the US.4 The incidence of gallbladder disease has increased by over 20% during the last 30 years in the US and is now estimated to annually cost approximately 6.2 billion dollars.5 With the increased focus on cost containment, improved control of prolonged hospital length of stay (LOS) in cholecystectomy patients is paramount.5

One major factor used to control costs in surgical patients is decreasing the time period to surgical intervention when needed. Previous studies have demonstrated that decreased time to surgical intervention results in lower hospital costs and is not associated with worse outcomes.6-12 It has also been well documented that earlier operative intervention tends to be superior to delayed intervention, especially in the acute cholecystitis population.6,10-12 However, agreed upon criteria for “early” surgical intervention continue to be debated.12 The literature reveals the most cited criteria as surgery with 72 hours of presentation.12 Experts have also demonstrated that early operative intervention is associated with shorter LOS, reduction in mortality, complications (e.g., bile duct leaks and injuries, wound infections, conversion to open rates and blood loss).6,12

In 2014, a research group analyzed the factors associated with increased LOS for acute cholecystitis patients (e.g., worsening disease severity and comorbidities).13,14 The cholecystectomy patients in this study with longer LOS accrued increased total surgical costs by up to 64% on the fifth hospital day ($11,087 for day of admission, and $18,196 by the fifth day), although postoperative LOS did not change.7 Thus, advocating for “earlier” surgery and preventing prolonged LOS appears to be key for achieving most efficient patient care.

To date, studies addressing LOS in biliary disease have primarily focused on a specific etiology (i.e., most often acute cholecystitis), and not the entire range of biliary
disease. As a result, there is still limited information regarding the factors impacting LOS in all cholecystectomy patients. In this study, we were therefore interested in examining the factors that influenced LOS for all cholecystectomy patients at a community hospital with the goal of improving perioperative patient care and decreasing hospital costs. Given that the vast majority of cholecystectomies performed at our institution were laparoscopic (i.e., approximately 6% rate of conversion from laparoscopic to open during the analytic period), the authors made no distinction made between open and laparoscopic cholecystectomy cases.

METHODS

Saint Joseph Mercy Oakland Hospital is a 443-bed facility located in Pontiac, MI. The community has a population of 59,889 people, with an average age of 33.5 years, and an estimated per capita income of $16,087. Racial make-up includes 50.9% black, 25.7% white, 15.8% Hispanic, 4.9% 2 or more races, and 2.9% Asian.

Before data collection, the hospital institutional review board had approved the study. This retrospective review examined data from a two-year time period from January 2013 through December 2014 that included patients admitted from the emergency department and undergoing cholecystectomy during their same hospital stay. We identified adult sample patients using a program called Discern Analytics®, searching for the term “cholecystectomy.” Exclusion criteria included patients less than 18 years of age, undergoing a scheduled cholecystectomy or one due to prior work-up, patients not admitted through the emergency department, cholecystectomy performed as a secondary procedure, and pregnant women.

We performed an additional review of 33 subjects with prolonged LOS, defined in this study as a LOS $\geq 10$ days. Thirty-two of these patients were admitted to a nonsurgical service and one subject was admitted to a surgical service. Based on consensus of independent review by the authors, subjects admitted with non-gallbladder disease or had prolonged LOS for reasons unrelated to gallbladder disease or postoperative complications were excluded. Data were collected concerning patient demographics such as patient age, gender, self-reported race, and comorbidities. Further collected data
included type of admitting service, time to surgery, pre and postoperative diagnosis, LOS, postoperative morbidity and mortality, and 30-day readmission rates.

All statistical analyses were conducted using SPSS version 22 software. Univariate analysis examined potential predictive factors suggested in the literature to have an effect on LOS. These factors included type of admitting service, presence of comorbidities, preoperative diagnosis, and length of time to surgical intervention. A series of t-tests were then completed to compare LOS differences in these variables. Since the authors also selected time to surgery as a potential continuous variable predictor of increased LOS, a series of Pearson’s r correlation tests were also conducted. The authors collected additional data regarding discharge location (e.g., home, skilled nursing facility, etc.) to evaluate possible relationships between these rates and LOS.

After we determined that sample patients' admitting service was a significant predictor of LOS, we conducted further analyses. We used a series of Chi-square tests to compare the LOS of patients admitted to surgical or non-surgical services controlling for presence of comorbidities. We entered these comorbidity analytic terms in an analysis of covariance (ANCOVA) as equally weighted covariates with the dependent LOS variable and additional independent variable type of admitting service. Finally, we completed additional t-tests to examine the significance of differences in time to surgery between surgical vs. non-surgical admitting service patients.

RESULTS

There were 854 cholecystectomies performed at Saint Joseph Mercy Oakland Hospital during the two-year analytic period. Of these, 542 (63.5%) subjects were excluded based on our selected exclusion criteria. The majority of excluded patients were outpatient and/or elective cholecystectomies. Data from 312 (36.5%) sample patients who met inclusion criteria were analyzed.

The demographic characteristics of sample patients can be seen in Table 1. Upon chart review, the average age of the subjects was 54.5 years of age (±20.3, range 18-92 years). Two hundred and eleven (68%) subjects were female, and one hundred and one (32%) were male. The racial profile of the sample was skewed toward Caucasians since although ~51% of the given community population self-reported being African-American,
the profile of this sample was: 72.6% white (n = 230), 13.8% African American (n = 43), 6.7% Hispanic (n = 21), 1.0% Asian (n = 3), and 5.4% unknown or other (n = 17). Patients were about evenly split between admission to a surgery service (48.3%, n = 153) or nonsurgical service (51.7%, n = 164).

This was a relatively healthy sample of patients. The incidence of individual comorbidities documented were as follows:

- Chronic obstructive pulmonary disease (COPD) (n = 16, 5.1%),
- Other lung disease (n = 9, 2.9%),
- Some form of diabetes (DM) (n = 56, 17.9%),
- Cirrhosis (n = 0, 0.0%),
- Other liver disease (n = 3, 1.0%),
- Heart valve disease (n = 0, 0.0%),
- Cardiac arrhythmias (n = 21, 6.7%),
- Coronary artery disease (CAD) (n = 38, 12.2%),
- Taking an anticoagulate (n = 11, 3.5%),
- Congestive heart failure (CHF) (n = 19, 6.1%), and
- Previous abdominal surgery (n = 150, 47.3%).

As previously mentioned, intraoperative conversion to an open cholecystectomy was n = 14 (4.5%) in this sample. Postoperative complications were also rare in study patients. The incidence of each study complication was as follows: postoperative bile leak (n = 6, 1.9%), surgical site infection (n = one, 0.3%), pneumonia (n = three, 1.0%), myocardial infarction (n = one, 0.3%), intra-abdominal infection (n = three, 1.0%), death (n = four, 1.3%). There were zero instances of biliary duct injury observed in this cohort. We concluded that the size of this sample subgroup with complications was too small to conduct further analyses.

Post-hospital patient disposition frequencies were as follows: home n = 306 (98.1%), subacute rehabilitation n = three (1.0%) and acute rehabilitation n = two (0.6%). Since most sample patients were discharged home, there was no further statistical evaluation. Similarly, the 30-day readmission rate for sample patients was relatively low, at n = 50 (16.0%). Of these readmissions, 25 (50.0%) were for reasons related to
gallbladder disease (i.e., defined as any reason directly related to postoperative complaints or complications).

We conducted a univariate analysis to assess factors that affected LOS. Factors found to be significantly associated with increased LOS included admission to a non-surgical service (5.56 days vs. 3.43 days, p < 0.0005) and increased time to surgery (Pearson r 0.434, p < 0.0005). Non-significant factors included comorbidities and preoperative diagnosis. Due to these findings, the authors performed further analyses concerning evaluating admitting service. (Table 2)

As seen in Table 2, patients admitted to non-surgical services were also significantly “sicker,” meaning they were more likely to have one of each of the following comorbidities: COPD, DM, CAD, on an anticoagulation medication, CHF and previous abdominal surgeries (p < 0.0005). However, none of these individual comorbidities were statistically significant when placed into an ANCOVA model. The only p value that remained significant was the type of admitting service, with patients admitted to the non-surgical services having longer LOS (p < 0.005) when controlling for comorbidities. Patients admitted to a non-surgical service also had increased time to surgical intervention (Mean 2.27 days, ± 2.52) compared to surgical service admission patients (Mean 0.93 days ± 0.94 days; p < 0.0005).

DISCUSSION

In our study, admission to a non-surgical service and increased length of time before surgical intervention were significantly associated with longer LOS in cholecystectomy patients. Based on prior studies, the estimated total savings for the patients admitted to the surgical service in this study setting may have totaled $4,156 in surgery and $6,390 in extra hospital LOS costs.6-12 This could have conceivably resulted in an average total per patient cost savings of $10,546.

The overall findings of this study are similar to other surgical conditions in the literature. For example, two studies have demonstrated that patients admitted to a medical hospitalist service with small bowel obstruction had increased length of stay and increased charges as compared to patients admitted to the surgical service.15,16 However, the data for gallbladder disease as a whole remains lacking. One study has shown that
patients admitted to a surgical service receiving a cholecystectomy for acute mild gallstone pancreatitis had shorter time to surgery, shorter LOS and lower hospital costs compared to patients admitted to the medical service.\textsuperscript{17}

In this community-based setting, patients admitted to non-surgical services were more likely to have documented comorbidities with longer LOS and increased time to surgery when controlling for those comorbidities. Since this was a retrospective review, we could not make a clear distinction between admission time and time of diagnosis, or stratify by the type of varied symptoms that patients may have had at time of presentation. For example, providers may have admitted some patients to the hospital with sepsis of unknown origin with the diagnosis of cholecystitis later made. Such patients may have been admitted to a non-surgical service with increased time to surgical evaluation, increased time to surgery and prolonged LOS. Although we did conduct ANCOVA analyses to attempt to control for certain comorbidities, it would have been ideal if we could have actually matched patients in the surgical and non-surgical admitting services to control for these comorbidities. Further studies of this type are warranted.

One possible means of decreasing LOS and hospital costs in this population is implementation of an acute care surgery (ACS) service.\textsuperscript{18-20} This care delivery model involves creation of a specific surgical hospital service for the evaluation and treatment of emergent non-trauma patients admitted under a variety of surgical emergencies. These types of admitting services have been created in the US and Canada to supplement trauma surgeons’ operative workload and provide more timely care to emergency surgical populations.\textsuperscript{18,20}

Several suggested benefits of ACS services include improved scheduling and operating suite predictability for surgeons, improved patient access to surgical intervention and improved post-discharge follow-up.\textsuperscript{18} More efficient workup and management of complex surgical conditions has also been shown, with a cost savings potential for health care systems.\textsuperscript{19,20} When implemented for cholecystectomy patients, authors have initially shown reductions in time to surgical evaluation and to operative room, fewer complications and shorter LOS.\textsuperscript{21} In one study, there was a significant relative cost savings of $3,225.00 measured for cholecystectomy patients under an ACS service (i.e., $13,128.00 under the traditional model and $9,903.00 in ACS).\textsuperscript{21} In another
study, an ACS service at a larger institution initiated dedicated operating room time that even further improved time to surgery.\textsuperscript{22}

There are several limitations to this study. The study was set at a single institution using a smaller retrospective convenience sample. The generalizability of our results to other organizations may be limited, and we may have had an inadequate level of statistical power to detect meaningful relationships possibly detectable in a larger sample. Additionally, the results of this study may have been subject to unmeasured confounding influences.

**CONCLUSIONS**

In conclusion, these results indicate that providers may expect longer LOS for many cholecystectomy patients admitted to a non-surgical service with increased length of time to surgical intervention. These results and the findings of earlier studies suggest that certain factors can be targeted to decrease LOS in this gallbladder disease population. One may argue with this conclusion since our sample patients admitted to non-surgical services were “sicker,” although we still found them to have longer LOS and greater time to surgical intervention when controlling for comorbidities. Ideally, ACS can have helped providers achieve a more rapid evaluation of potential “gallbladder patients” in the emergency department by surgical team providers. Further studies are required to evaluate the actual cost savings derived from these types of hospital admission services to optimize the outcomes in this growing population of patients.

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The authors declare no conflict of interest.

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Karen Hagglund, MS, participated in statistical planning and conducted analyses.
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15. Bilderback PA, Massman JD, Smith RK, La Selva D, Helton WS. Small bowel obstruction is a surgical disease: Patients with adhesive small bowel obstruction requiring operation have more cost-effective care when admitted to a surgical service. *J Amer Coll Surg* 2015;221(1):7–13.


### Table 1: Sample Demographics
(N = 317 Cholecystectomy Patients)

<table>
<thead>
<tr>
<th>Demographics for Study Subjects</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average age</strong></td>
<td>54.2 (+/-20.3, range 18-92)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>214 (68%)</td>
</tr>
<tr>
<td>Male</td>
<td>103 (32%)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>230 (72.6%)</td>
</tr>
<tr>
<td>African American</td>
<td>45 (14.2%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>21 (6.6%)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (0.9%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>18 (5.7%)</td>
</tr>
<tr>
<td><strong>Admitting Service</strong></td>
<td></td>
</tr>
<tr>
<td>Admitted to surgical service</td>
<td>153 (48.3%)</td>
</tr>
<tr>
<td>Admitted to nonsurgical service</td>
<td>164 (51.7%)</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>12 (5.0%)</td>
</tr>
<tr>
<td>Other lung disease</td>
<td>9 (2.8%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>57 (18.0%)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other liver disease</td>
<td>3 (0.9%)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>22 (6.9%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>39 (12.3%)</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>11 (3.5%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>20 (6.3%)</td>
</tr>
<tr>
<td>Previous abdominal surgery</td>
<td>150 (47.3%)</td>
</tr>
</tbody>
</table>
## Table 2:
### Analyses of Patients Admitted to Surgical Admitting Service Versus Non-Surgical Service*

<table>
<thead>
<tr>
<th>Analysis of Admitting Service</th>
<th>Surgical</th>
<th>Non-Surgical</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>1.3% (n=2)</td>
<td>8.6% (n=14)</td>
<td>0.004</td>
</tr>
<tr>
<td>Other lung disease</td>
<td>1.3% (n=2)</td>
<td>4.3% (n=7)</td>
<td>0.175</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13.1% (n=20)</td>
<td>22.7% (n=37)</td>
<td>0.029</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>0% (n=0)</td>
<td>0% (n=0)</td>
<td>n/a</td>
</tr>
<tr>
<td>Other liver disease</td>
<td>1.3% (n=2)</td>
<td>0.6% (n=1)</td>
<td>0.612</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>3.9% (n=6)</td>
<td>9.8% (n=16)</td>
<td>0.047</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>0% (n=0)</td>
<td>0% (n=0)</td>
<td>n/a</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>5.2% (n=8)</td>
<td>19.0% (n=31)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>0.7% (n=1)</td>
<td>6.1% (n=10)</td>
<td>0.011</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>2.0% (n=3)</td>
<td>10.4% (n=17)</td>
<td>0.002</td>
</tr>
<tr>
<td>Previous abdominal surgery</td>
<td>39.2% (n=60)</td>
<td>54.9% (n=89)</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Time to surgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.94 days (+/- 0.94)</td>
<td>2.39 days (+/- 2.61)</td>
<td>&lt;0.0005</td>
<td></td>
</tr>
<tr>
<td><strong>LOS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.5 +/- 1.8 days</td>
<td>5.6 +/- 3.0</td>
<td>&lt;0.0005</td>
<td></td>
</tr>
<tr>
<td><strong>Readmission</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.5% (n=13)</td>
<td>23.5% (n=38)</td>
<td>&lt;0.0005</td>
<td></td>
</tr>
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*please contact the corresponding author regarding any questions relating to the data in this table.
Endoscopic Combined Snare-Forceps Technique for Removing Flat Sessile Polyps

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ABSTRACT

JONES MW, HENNING W. Endoscopic Combined Snare-Forceps Technique for Removing Flat Sessile Polyps. Spartan Med. Res. J. Vol. 2, No. 2, pp. 14-21, 2017. CONTEXT: Current endoscopes have limitations during use in polypectomies. Specifically, polyps that are flat, broad-based and sessile are more difficult to resect. Routine polypectomy procedures allow one endoscopic device to be used at a time limiting the endoscopist. More advanced scopes are not readily available at smaller community hospitals, limiting the endoscopist to using the resources available to them. METHODS: The modification of the standard polypectomy method described here employs both an endoscopic forceps and an endoscopic snare to be used simultaneously during colonoscopy with a single lumen colonoscope. The forceps is introduced into the endoscope so the head is just projecting from the distal end of the scope. The snare is then placed just proximal to the head of the forceps outside of the endoscope. The endoscope is reinserted into the colon until the polyp is reached. Using the snare the polyp is elevated and then the snare secured around the base. RESULTS: This resulted in easier, faster, and more complete removal of flat sessile and poorly located pedunculated polyps on the first try. This technique has been employed successfully in over 20 patients at our institution. CONCLUSIONS: This new method adds another technique for endoscopists when presented with difficult polypectomies. Keywords: endoscopy, polyps, snare, forceps

INTRODUCTION

Colorectal polyps are abnormal growths found as a protuberance in the colonic lumen resulting from overgrowth of the epithelial lining of the mucosa.1 These can arise anywhere within the gastrointestinal tract, and have the potential of malignant transformation resulting in colorectal cancer.

Polyps are classically categorized into non-neoplastic (i.e., hyperplastic, inflammatory, mucosal, and hamartomatous (normal tissue growing in a disorganized mass) polyps and neoplastic (i.e., adenomas).1 Adenomas are considered precursors to colorectal cancer. It is believed that more than 80% of colon cancers arise from
adenomas. The prevalence of adenomas is 25% at age 50, nearly 50% at age 70, and continues to increase with age.

Common risk factors for developing adenomas include increasing age, increased body mass index, African American ethnicity, male sex, lack of physical activity, and a history of smoking. Seldom, these can develop secondary to hereditary syndromes like familial adenomatous polyposis syndrome and hereditary non-polyposis colorectal cancer. Polyps can be further classified on endoscopy based on their appearance. They can be pedunculated, meaning they arise from a stalk. A sessile polyp is attached by a broad base, typically without a stalk.

The presentation of polyps also varies. Some polyps can be found incidentally during a screening colonoscopy, while other polyps present with clinical signs and symptoms such as bleeding, obstruction, intussusception, or tenesmus (i.e., the sense of having to have a bowel movement). Currently, the most effective screening procedure is the colonoscopy.

A colonoscope is an instrument that providers use to directly visualize the entire colon starting at the anus and ending at the cecum. This procedure can be performed both by General Surgeon and Gastroenterologist depending on the availability of the specialist in that region. At the time of colonoscopy, one has the ability to resect and biopsy any lesions identified during the examination. There are two types of biopsy instruments commonly used. A forceps-grasping device is an instrument used to either biopsy or completely remove small polyps. A snare device is an instrument with a wire loop, which can be tightened around the base of a polyp. Once it is closed around the polyp, one can transect the polyp with this device. The majority of polyps can be removed using these two devices; however, some polyps can pose a significant challenge.

Certain types of colonic polyps can present a challenge during endoscopy. These include polyps with broad bases, flat sessile polyps, and polypoid lesions located within colonic folds. In the case of large sessile polyps, it usually is not feasible to remove the entire polyp with endoscopic forceps, and it is often challenging to encircle the base with an endoscopic snare. This results in removal of a polyp in fragments, which does not ensure complete excision and is relatively time-consuming.
Incomplete resection of the polyp is undesirable, unless surgical resection is planned. If an incomplete polypectomy is performed, the residual tissue may undergo malignant transformation.\(^1\) It may also lead to incorrect diagnosis as many early colon cancers are located deep within the polyp that was not removed.\(^3,4\) Polyps that cannot undergo complete resection will be referred for a surgical consultation. Most of these patients ultimately will undergo a colon resection.\(^5\)

Numerous innovative techniques have been devised to facilitate easier polypectomy in these difficult scenarios.\(^6\) Submucosal injection with saline has proven effective in raising flat lesions to allow better access to the base of the polyp for snare removal.\(^7\) A suction maneuver combined with saline injection has also been described. After submucosal saline is instilled, the endoscope is positioned over the polyp and suction is applied. The scope is then slightly withdrawn temporarily tenting the polyp, which affords better access to its base. Other techniques employing double-channel scopes, endo-loops with snares, and hot avulsion procedures have also been described.\(^7,8,9,10\)

The authors have found that the introduction of endoscopic forceps through a single-lumen colonoscope along with an endoscopic snare secured to the distal portion of the forceps externally led to easier and more complete removal of flat, broad-based, sessile polyps. The forceps is used to tent the polyp away from the colon wall. While the snare is opened, the secured forceps grasping the polyp “directs” the snare down to the targeted area. The open snare is then placed around the base of the lesion for polypectomy.

**METHODS**

During this procedure, a standard single-lumen colonoscope is used. Once the lesion is located during colonoscopy, the scope is then removed. The forceps is introduced into the endoscope so the head is just projecting from the distal end of the scope. The snare is then placed just proximal to the head of the forceps outside of the endoscope. (Figure 1) The jaws of the forceps must be allowed to open and close freely. The endoscope is then reinserted and carefully advanced through the colon until the desired polyp is reached.
Care must be taken to ensure the tip of the endoscope with the slightly protruding forceps is kept centered in the lumen of the colon to prevent mucosal injury or perforation. This maneuver will pull the endoscopic snare along with the scope to the target. The process of performing the colonoscopy with withdrawal and reinsertion adds familiarity of the anatomy of that particular patient’s colon. This in turn makes it easier to keep the scope centered in the lumen.

Once the target is reached, the forceps is advanced and used to grasp the polyp. The lesion is then tented away from the bowel wall. The endo-snare is then opened, slid down the forceps and placed around the base of the polyp. (Figure 2) Care must be taken to avoid including too much depth of the colon wall with the specimen to avoid perforation. The authors have found this technique to be useful in removing large pedunculated polyps located behind folds or in areas difficult to access. The insertion technique is the same. The polyps are grasped with the forceps and pulled into the endoscopist’s field. This provides better visualization of the lesion’s base to ensure complete removal. The author just recently had a patient with a one-centimeter polyp hidden behind a colonic fold in the sigmoid colon. Using this technique, the author was successful in elevating the polyp out from behind the fold and securing the snare around the base. This resulted in complete resection of the polyp without great difficulty.

RESULTS

The described technique has proven to be very effective in our practice for difficult polypectomies. We have been able to implement this technique successfully in over 20 polypectomies at our institution. Not only have the authors found it to allow for more complete resection of polyps, it has led to an easier and faster resection as well. To date, we have not experienced any complications with this technique; however, this method does have some limitations.

This method is less effective when attempted for more proximally located polyps or polyps in tortuous colons. A tortuous colon can be defined as a colon with many sharp turns and bends making it difficult to navigate through. Advancement to the targeted area may be more difficult and good judgment must be used when performing this maneuver. Care must also be taken to ensure that the externally located snare wire advances easily
with the scope and does not form a bow string configuration at bends as this could injure the colon or prevent progression of the endoscope. If this does occur, the snare can be secured externally farther up the scope with a silk suture, which may lessen the bowstring effect.

It was also suggested to secure the snare directly to the tip of the endoscope, therefore eliminating the risks associated with advancing the scope with the slightly exposed forceps. This proved unsuccessful, as the snare could not be advanced over the forceps.

CONCLUSIONS

While colonoscopies are valuable for colorectal screening, current colonoscopes have disadvantages. Most standard scopes are equipped with a single working lumen. There are more advanced scopes with two working lumens but these aren’t usually readily available in a community hospital setting. A major disadvantage is the inability to use more than one endoscopic instrument at a time.

This simple technique requires no additional training or special modifications to a single lumen endoscope. It has shown improved efficacy in complete removal of both flat, broad based sessile polyps and poorly accessible pedunculated polyps. Use of this technique could potentially prevent colectomy for incomplete polypectomy, and avoid the unnecessary morbidity and mortality of undergoing a formal colonic resection.

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REFERENCES


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Figure 1:
Demonstration of the Endoscopic Snare
Secured to the End of the Endoscopic Forceps.
Figure 2:
The Snare Being Placed at the Base of the Polyp as the Lesion is Tented Using the Forceps.
Case Series

Alpha 1 Antitrypsin Deficiency: Two Cases of Heterozygous S and Clayton Null Alleles

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ABSTRACT


CONTEXT: Alpha-1 antitrypsin deficiency (AATD) is a disorder that can lead to early onset lung and liver disease and is considered to be underdiagnosed. The purpose of this paper is to demonstrate the importance of early detection using genotyping of AATD by presenting two very rare cases of this disorder and to remind clinicians to maintain a high level of suspicion for this disorder. METHODS: Two unrelated patients presented to different pulmonology offices in Grand Blanc, MI and were screened for AATD for different reasons. Testing for both patients included alpha-1 antitrypsin enzyme levels, phenotyping, and genotyping. RESULTS: Both individuals were heterozygotes for S allele and Q0Clayton allele. The Q0Clayton allele is a very rare Null allele that is defined this way because these individuals do not produce any alpha-1 antitrypsin. CONCLUSIONS: These cases highlight the need for early testing of patients with risk factors for AATD. Also demonstrated is the need to include genotype testing to accurately identify the risk of developing emphysema and cirrhosis. Lower morbidity and mortality may result if AATD is detected early. Keywords: alpha-one antitrypsin, clayton, null allele, emphysema

INTRODUCTION

Alpha-1 Antitrypsin Deficiency (AATD) is an inherited disorder that has been associated with early onset emphysema and liver cirrhosis.¹ However, some individuals with AATD may not have any clinical manifestations of disease or signs and symptoms may present later in life. This disorder is considered to be largely underdiagnosed ¹ and a targeted screening approach is recommended for its detection in adults.² Chronic obstructive pulmonary disease (COPD) with panacinar emphysema is the most frequent cause of morbidity and mortality in AATD.¹
While smoking tobacco is a major risk factor for developing COPD in the general population, individuals who smoke and also have AATD have been shown to follow a more rapid disease progression.³ COPD typically develops much earlier in these patients, often in the third decade of life, earlier than both nonsmoking individuals with AATD and smokers without.¹

Liver disease is the second most frequent clinical manifestation of AATD.¹ It may present as cholestasis in infancy or chronic liver disease in childhood. Deficient adults over the age of 50 are at risk for cirrhosis and hepatocellular carcinoma.² Additional extrapulmonary manifestations of AATD include necrotizing panniculitis, systemic antineutrophil cytosplasmic antibodies (ANCA) positive vasculitis, psoriasis, urticaria, pancreatitis, and angioedema.¹

The clinical manifestations of this disorder come from mutations in the SERPINA1 gene on chromosome 14 that alter the production of the protein alpha-1 antitrypsin (AAT).⁴ It is one of many serine protease inhibitors and helps to protect lung tissue from neutrophil elastase. Neutrophil elastase is a serine protease, an enzyme that causes breakdown of protein including that of alveolar tissue during inflammatory responses. AAT is primarily synthesized in hepatocytes but also in white blood cells and the cells that line the airway and intestine. This protein is secreted into the serum and functions in tissues with significant neutrophil burden. During an acute phase response, serum levels rapidly increase several-fold.⁴

To date over 100 genetic variants of AAT have been identified. The normal genetic variant or allele is designated M and the two most common deficient variants are the S and Z variants. The Z mutation leads to abnormal folding of AAT as it is produced, thereby altering the way it interacts with other enzymes and molecules. This leads to polymers that form inclusion bodies within hepatocytes unable to be secreted into the serum. Therefore, secretion of the protein into the serum is prevented and it instead accumulates within the liver. This results in not only liver disease but also a significant deficiency in serum AAT,⁴ hence the name of the disease. Lung damage results from the imbalance of neutrophil elastase and AAT. Pulmonary irritants including tobacco smoke and environmental pollutants further raise levels of neutrophil elastase and lead to worsening of the AAT-protease balance.²
The risk for emphysema increases as AAT levels decrease below 60 mg/dL (reference range 90-200 mg/dL). Severe cases are often homozygotes with the Z mutation and associated with severe reduction of serum AAT levels ≤ 80%.5 The S variant is associated with levels ≤ 60% although it is not associated with significant disease. Furthermore, the S variant leads to a smaller accumulation of polymers in hepatocytes than the Z variant with no clinical consequences.4

There is a rare group of AAT alleles that are not detected either during transcription or translation that are referred to as Null alleles. These type of alleles are not associated with liver disease because there is generally no accumulation of polymers within the hepatocytes. A homozygous null allele will lead to development of emphysema even earlier than a ZZ homozygote. It has been estimated that the frequency of all null alleles is about 1/100th that of the Z allele in the North American white population.4

**Case Descriptions**

Patient One was a Caucasian female in her later 20s who was referred to the pulmonology service for evaluation for AATD due to her strong family history. Her past medical history was significant for uterine cancer status post hysterectomy, uncontrolled type 2 diabetes, liver dysfunction, and obesity. She had never smoked and denied alcohol or illicit drug use. Her father had developed severe emphysema and died at age 49 and her paternal aunt had deficiency but was not currently being treated.

At the time of referral, she had no respiratory complaints and her physical exam was unremarkable. Laboratory data included a slight elevation in ALT and elevated Gamma-Glutamyl Transferase. Her HgbA1C was 11.1%. A pulmonary function test (PFT) showed normal lung function. Immunoassay revealed AAT level of 35.4 mg/dL in the setting of an elevated C-reactive protein (CRP) level of 33 indicating an active inflammatory response. Isoelectric focusing showed a phenotype of SS and genetic sequencing demonstrated that this patient has the S/Q0Clayton genotype.

The patient was counseled concerning the importance of avoiding pulmonary irritants and testing of other family members was encouraged. Since the patient had no
Concerning pulmonary test results, exam findings, or symptoms, the authors did not initiate treatment for AATD despite her low levels of AAT.

Patient Two was a Caucasian male in his early 50s who was referred to the pulmonology service to evaluate persistent dyspnea of two months duration that became worse with exertion. A cardiac workup was unremarkable. Past medical history included allergic rhinitis, diabetes mellitus, and hypertension. He quit smoking 10 years ago after smoking three packs per day for 15 years. Family history was positive for coronary artery disease. His physical exam was unremarkable. A PFT revealed restrictive changes and no bronchodilatory reversibility although inadequate respiratory effort was noted. His AAT level was 35.1 mg/dL and his CRP was 2.11 mg/dL. Phenotype revealed S band and genotyping revealed S/Q0Clayton. This patient was offered enzyme replacement therapy.

DISCUSSION

The authors completed a literature review and found that the Q0Clayton mutation is very rare. It has only been reported in a U.S. Caucasian family, a Korean family, and a Japanese family. A total of 11 cases of S/Null genotype were found. Of S/Null genotypes two were heterozygotes of Q0Clayton and Siiyamma which is a specific S variant with more severe disease than other S variants. No other cases were described with S and the Clayton null allele.

The DNA sequence for the Q0Clayton allele is a mutation of the normal M1 AAT allele. There is a cytosine insertion that leads to a frameshift mutation causing a premature stop codon at amino acid 374. This cytosine insertion occurs at a location in the DNA sequence that is described as a mutational hot spot due to the many mutations that occur at this location. The resultant protein is smaller and is retained in the rough endoplasmic reticulum where it undergoes degradation prior to translation into AAT. Because the mRNA is degraded there is no protein production and therefore no retained protein to cause hepatocellular damage.

These cases demonstrate the importance of genetic sequencing of the SERPINA1 gene when testing for AATD. Phenotyping using electrophoresis may lead to an assumption that these patients were homozygous S which has much lower
frequency of clinical manifestations. Phenotyping does not detect null alleles. Genotyping allows identification of the null alleles and specific mutations using polymerase chain reaction amplification and sequencing.\(^9\)

These cases also emphasize the synergistic role of tobacco smoke and AATD in causing pulmonary disease. Patient One had significantly deficient levels yet has no pulmonary complaints. These levels of AAT provide decreased protection from inflammatory degradation. We wondered if she would already have evidence of pulmonary disease if she were a smoker or exposed to other irritants. Unfortunately, the natural history of AATD suggests that she may still develop emphysema. Patient Two was a former smoker with current pulmonary symptoms. Patients with AATD who smoke have been found to lose FEV1 at a rate of 70-130 mL per year compared to nonsmokers who lose lung function at 40-70 mL per year indicating a more rapid decline in lung function in smokers.\(^3\)

Patient One had an elevated CRP at the time of testing AAT levels, perhaps indicating an acute inflammatory response. It is important to be aware that AAT levels rise during an acute phase response or exposure to high estrogen states\(^10\) because this will alter testing for AATD. While Patient One has low levels despite elevated CRP, some patients with AATD may have normal levels of AAT if tested during an acute phase response and may need to be tested after inflammation resolution. This patient may have even lower levels of AAT if CRP is indicative of acute phase response and AAT levels tested after its resolution.

**CONCLUSIONS**

In order to intervene and slow the progression of this disease, clinicians need to maintain a high index of suspicion to detect AATD at an early age. Patients with COPD, non-responsive asthma, cryptogenic liver disease, and a family history of AATD in first-degree relatives (e.g., parent sibling or child) should all be screened for AATD. Knowledge of the disorder in deficient patients may provide added incentive to avoid pulmonary irritants.

If patients can quit smoking, change occupations if they are exposed to occupational irritants, and aggressively avoid second-hand tobacco smoke, dusts, and
fumes they may experience a slower progression of the disease, lower morbidity and lower mortality. Clinicians should offer these patients preventative measures including vaccinations for influenza, pneumococcus, and hepatitis and undergo hepatic screening. Furthermore, AATD patients will be offered AAT augmentation therapy to slow disease progression. Cigarette smoking is highly addictive and few patients quit successfully. However, patients identified with AATD who do not yet smoke may be less likely to start smoking. In one study, individuals identified with AATD at birth demonstrated lower rates of smoking at adolescence compared to control subjects.\(^2\)

As therapy for AATD advances, early detection will be more important. Full genotype analysis will help prevent false negative results as it did for our patients. We hope that the devastating consequences of this disease may be prevented or at least delayed in these two patients since they were identified early and provided proper counseling.

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Case Report

A Rare Case of Olmesartan-Induced Enteropathy

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ABSTRACT

HANNA R, RAHMAN A, VIVEK K. A Rare Case of Olmesartan-Induced Enteropathy. Spartan Med. Res. J. Vol. 2, No. 2, pp. 29-37, 2017. CONTEXT: Olmesartan (brand name Benicar) is an antihypertensive drug clinicians commonly use to treat high blood pressure. Olmesartan induced enteropathy (OSE) is a rare entity that authors first identified in 2012. The etiological basis of OSE remains unclear, although authors have suggested that this condition could be due to alterations in cell-mediated immune responses induced by the drug. The objective of the case report is to describe a patient who presented with diarrhea and was eventually diagnosed with OSE. METHODS: A female patient in her later 60s presented to an emergency room after two recent hospitalizations with profound diarrhea, generalized weakness and weight loss. She underwent a diagnostic workup including endoscopy and colonoscopy. RESULTS: The patient’s endoscopy with duodenal biopsy revealed villous atrophy with attenuated and blunted villi with intraepithelial CD3 positive T lymphocytes, suggestive of gluten-induced enteropathy. When the patient’s symptoms did not improve after the authors placed her on a gluten free diet for a few days, they further investigated her for secretory diarrhea, including Gastrin, Somatostatin and Vasoactive Intestinal Peptide lab values that they found to be within normal limits. CONCLUSIONS: Due to the patient’s lack of improvement with initial treatment, the authors suspected OSE and stopped her olmesartan and the patients’ symptoms gradually improved in three weeks. Keywords: olmesartan, enteropathy, diarrhea, endoscopy

INTRODUCTION

Olmesartan is an Angiotensin II receptor blocker (ARB) approved in 2002 for treatment of hypertension. In 2012, authors first described a sprue-like enteropathy associated with olmesartan in the literature, with more cases since reported.1,2,3 This led the FDA to categorize olmesartan-induced enteropathy (OSE) as a drug-induced adverse reaction in 2013.4 However, knowledge concerning this condition is still not widespread in the clinical setting. Early diagnosis and discontinuation of olmesartan can help in preventing severe and life-threatening conditions.2,4 It is an immune-mediated entity found to be associated with a past history of autoimmunity, presence of anti-nuclear
antibodies, positivity of DQ2 and DQ8 haplotypes and presence of polyclonal intraepithelial lymphocytes.

The mechanism of OSE is still unknown. It has been postulated that villous atrophy has been caused by AT2 receptors activated by Angiotensin II. Treatment primarily includes discontinuation of the medication as well as monitoring the patient for three to four weeks for improvement in symptoms. In this paper, we present a case of OSE in which a patient presented with severe diarrhea, generalized weakness and weight loss.

**Case Report**

A female in her later 60s with a history of hypertension on amlodipine and olmesartan presented to an emergency room with complaints of profound diarrhea and generalized weakness that had started a month ago along with a twenty-pound weight loss. Her recent medical history was notable for two recent hospital admissions with similar complaints and an extensive workup for diarrhea, including an endoscopy and a colonoscopy, which were negative. The patient had not recently travelled out of her mid-Michigan town.

Stool studies for infectious etiology were negative. During this visit to the emergency room, providers found her to be hypotensive with a blood pressure of 70/50 Mm Hg and heart rate of 120, and extremely lethargic. The patient’s physical examination was remarkable for dry mucous membrane, although there were no other focal findings. Her initial lab tests revealed a renal insufficiency with a Creatinine of 3.5 mg/dl, which improved with aggressive hydration.

Her stool studies for celiac disease serology were also negative. She had a borderline positive ANA test at a titer of 1:160 with a homogeneous pattern. Homogenous pattern is a diffuse type of fluorescent pattern seen on indirect fluorescent antibody test. After two days in the hospital, she had a repeat endoscopy with duodenal biopsy, which revealed villous atrophy with attenuated and blunted villi with intraepithelial CD3 positive T lymphocytes (Images 1 and 2), suggestive of gluten enteropathy.

She was placed on gluten free diet for four weeks without a significant improvement in her symptoms. She was further investigated for secretory diarrhea, including Gastrin, Somatostatin and Vasoactive Intestinal Peptide laboratory markers that
were each within normal limits. Due to her lack of improvement, the authors started to suspect OSE. Once olmesartan was stopped, the patients’ symptoms gradually improved within three weeks.

**DISCUSSION**

Olmesartan induced enteropathy is likely an immune-mediated condition that has been associated with a history of autoimmunity, presence of anti-nuclear antibodies, and presence of polyclonal intraepithelial lymphocytes. The histology associated with OSE is characterized by villous atrophy and increase in intra-epithelial lymphocytes such as CD3 and CD8 in the small bowel. Authors have also found this histology in other disorders such as Crohn’s disease, enteric infections, collagenous sprue, tropical sprue, common variable immunodeficiency, hematological malignancies and autoimmune enteropathy.

Various medications such as neomycin, sulindac, colchicine and immune-suppressants such as azathioprine, mycophenolate mofetil, methotrexate, vincristine and ipilimumab can cause similar histological changes in small bowel. The mechanism of these changes in OSE is still unknown but it has been postulated that villous atrophy in this condition is caused by AT2 receptors activated by Angiotensin II. Angiotensin II binds to two receptor forms, AT1 and AT2. AT1 receptor activates growth-promoting factors whereas AT2 receptors cause apoptosis of enterocytes by causing upregulation of pro-apoptotic proteins such as Bax and GATA-6 and by inhibiting anti pro-apoptotic proteins such as Bcl-2.

Recently, it has also been shown that drugs that inhibit AT1 receptors can cause translocation of AT 2 receptors from cytosol to the external membrane in the presence of high concentrations of Angiotensin II. Olmesartan has been shown to have a high affinity for AT1 receptors, but when AT1 receptors are saturated with olmesartan, then Angiotensin II starts binding to AT2 receptors resulting in apoptosis of enterocytes and villous atrophy. According to another hypothesis, increased bacterial counts were reported which was possibly secondary to alteration in luminal microbiome, but antibacterial medications were not found to be helpful. In addition, one literature review found positivity of DQ2 and DQ8 haplotypes and absence of celiac disease serologies in patients with OSE.
There are various clinical features of OSE. In one systematic literature review, 54 patients were studied and according to their results, nausea and vomiting were present in 45% of cases, fatigue in 56% of cases, diarrhea in 95% of cases, weight loss in 89% of cases, abdominal pain in 37% and bloating in 29% of cases.\textsuperscript{11} The mean age of onset of symptoms was 69 years with age range of 47 years to 87 years,\textsuperscript{11} and the mean duration of olmesartan therapy before patients developed symptoms in several studies was found to be between six months and seven years.\textsuperscript{2,11,15-18} The most common laboratory findings found to be associated with OSE are normochromic normocytic anemia and hypoalbunemia.\textsuperscript{11}

Endoscopic examination with high definition scopes usually shows marked villous atrophy and flattening of duodenal villi.\textsuperscript{11} Other endoscopic findings found in OSE are nodularity in duodenal bulb\textsuperscript{16} and duodenal ulcers,\textsuperscript{17} although normal duodenal patterns can also be found.\textsuperscript{18} Histopathologically flattening of villous pattern is the most common finding observed in various studies.\textsuperscript{1,2}

Also, the most common misdiagnosis in patients with these findings is celiac disease, with patients not improving after following a gluten free diet.\textsuperscript{1,19,20} The absence of two main histopathological findings that can sometimes be helpful to distinguish OSE from celiac disease are the absence of duodenal intraepithelial lymphocytes and a thickened sub epithelial collagen band.\textsuperscript{21}

In one systemic literature review, only 65% and 33% of patients with villous atrophy diagnosed histopathologically had increased duodenal intraepithelial lymphocytes and sub epithelial collagen band respectively, though large studies are still needed to describe this association.\textsuperscript{11} Also, improvement in symptoms, clinical remission and return of duodenal mucosa to its normal architecture after discontinuation of olmesartan have been found in various case studies of olmesartan induced enteropathy.\textsuperscript{2,5}

The proposed reasons for unusual enteropathy associated with olmesartan as compared to other ARB antihypertensive medications include different pharmacokinetic properties.\textsuperscript{10} Two other ARBs that were rarely found be associated with enteropathy are valsartan\textsuperscript{22} and irbesartan.\textsuperscript{23}

Recently, skin lesions associated with OSE have also been described.\textsuperscript{24} These lesions appear simultaneously with digestive symptoms of OSE and also regress.
completely after discontinuation of olmesartan.\textsuperscript{24} Certainly, more case reports, case series and studies are required to confirm the association of these skin lesions with olmesartan.\textsuperscript{24} In order to differentiate these lesions from dermatitis herpetiformis associated with celiac disease, biopsy of lesions should be done.\textsuperscript{24} According to one case report, the biopsy in OSE showed pemphigoid or acquired bullous epidermolysis-like histological findings.\textsuperscript{24}

\textbf{CONCLUSIONS}

Olmesartan induced enteropathy is an immune-mediated entity and the histology associated with this condition is characterized by villous atrophy and increase in intra-epithelial lymphocytes such as CD3 and CD8 in the small bowel. In this case study, endoscopy with duodenal biopsy also revealed villous atrophy with attenuated and blunted villi with intraepithelial T lymphocytes positive for CD3 cells. Other endoscopic findings found in OSE are nodularity in duodenal bulb and duodenal ulcers. In some cases, normal duodenal patterns have also been found with symptoms including diarrhea, generalized weakness and weight loss.\textsuperscript{18}

Also, the most common misdiagnosis in patients with these findings is celiac disease, though OSE patients have not shown improvement after following a gluten free diet. Recently, skin lesions have also been found to be associated with OSE.\textsuperscript{24} The treatment includes stoppage of olmesartan. OSE should be suspected in patients with these types of symptoms that remain unexplained by other common causes of enteropathy such as celiac disease and other autoimmune enteropathies.

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TABLES AND FIGURES

Image 1:
Duodenum Biopsy (40x) showing Partial Villous Atrophy (Attenuated/Blunted Villi) and Increased Intraepithelial Lymphocytes.
Image 2: Duodenum Biopsy (100x) showing Partial Villous Atrophy (Attenuated/Blunted Villi) and Increased Intraepithelial Lymphocytes.
Case Report

Posterior Inferior Cerebellar Infarct in a Younger Adult Male with Vertigo and Ataxia

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ABSTRACT

VANWAGNER AJ, DOERR B, HERNANDEZ S. Posterior Inferior Cerebellar Infarct in a Younger Adult Male with Vertigo and Ataxia. Spartan Med. Res. J. Vol. 2, No. 2, pp. 38-49, 2017. CONTEXT: Vertigo is a common complaint in patients who present to the emergency department. It can be a manifestation originating from several different disease processes. Although most patients with vertigo, especially younger patients, will have a benign disorder, up to 3% of such patients will have a cerebellar infarct. Although ruling out these types of fatal diagnoses is essential for emergency medicine physicians, this task can be especially complicated. Classic signs of a cerebellar infarct include symptoms suggestive of central vertigo with focal neurologic deficits on physical exam. Up to 10% of patients with cerebellar infarctions, however, present to the emergency department with vertigo and no focal neurologic deficits. METHODS: The following case report discusses a male in his late twenties with the chief complaint of vertigo. RESULTS: On initial exam, he had no focal neurologic deficits but did have other concerning symptoms including severe ataxia. Imaging subsequently revealed the patient to have sustained a cerebellar infarct. CONCLUSIONS: When differentiating benign forms of vertigo from cerebellar infarcts or other central causes, the clinician should take into account risk factors such as central symptoms including neurologic deficits and severe ataxia. Implementing this strategy may decrease morbidity and mortality associated with cerebellar infarctions. Keywords: cerebellar infarct, vertigo, ataxia, neurological deficit

INTRODUCTION

Vertigo is a common complaint in patients presenting to the emergency department, as well as other outpatient settings. Vertigo has been defined as a pathologic illusion of movement.1 A first step in evaluating a patient with vertigo is distinguishing between central and peripheral etiologies.2 Clinicians can evaluate symptom onset, intensity, duration, direction of nystagmus (i.e., involuntary eye movement), associated neurologic findings and auditory findings as well as positional effect.2 Peripheral vertigo is generally characterized by sudden onset and severe
intensity which last seconds to minutes. In this type of vertigo, nystagmus is classically horizontal with symptoms exacerbated by head position. Peripheral vertigo generally lacks neurologic findings, although there may be tinnitus (i.e., perception of ringing in ears) or decreased hearing. Peripheral etiologies include benign paroxysmal positional vertigo, labyrinthitis, Meniere’s disease, vestibular neuritis, and acoustic neuroma. 

Central vertigo can present gradually and mild in intensity and continue for weeks to months. It may also present as sudden and severe in nature, lasting seconds to minutes. Other characteristics of central vertigo include nystagmus in any direction, symptoms not exacerbated by body position, and the presence of neurologic findings. Central causes are generally more serious and include vascular disorders such as cerebellar masses, hemorrhage and infarction. It is therefore crucial to differentiate between central and peripheral vertigo as certain causes of central vertigo can be fatal when left untreated.

The posterior inferior cerebellar artery (PICA) is a branch of the vertebral artery and one of three supplying arteries to the cerebellum. The other two branches are the anterior inferior cerebellar artery (AICA) as well as the superior cerebellar artery (SCA). A large infarction of the PICA classically causes symptoms of lateral medullary syndrome (i.e., Wallenberg syndrome). These symptoms include vertigo, ipsilateral facial numbness, loss of corneal reflex, Horner’s syndrome (i.e., ipsilateral miosis, ptosis and anhidrosis), pharyngeal and laryngeal paralysis, and contralateral loss of pain and temperature sensation in the extremities.

Not all patients, however, present with these symptoms. Up to 10% of patients with cerebellar infarctions will present with vertigo and no other focal neurologic deficits. This is significant as the clinical consequences of cerebellar infarctions can be serious and demand prompt medical attention. These complications include obstructive hydrocephalus, brainstem compression and subsequent death. Macdonell et al. analyzed cerebellar infarctions in patients to determine the frequency of life-threatening events and found that the fatality rate of cerebellar infarction was greater than other forms of brain infarction. These risks can be decreased by early recognition, strict monitoring and neurosurgical intervention if complications develop.
The diagnostic imaging tests of choice are currently Magnetic Resonance Imaging (MRI) and Magnetic Resonance Angiography (MRA) images of the brain. Computed Tomography (CT) scan combined with Computed Tomography Angiography (CTA) of the head are generally the initial imaging modalities used, although an infarction cannot be excluded as the sensitivity of CT has been shown to be only 26% in acute ischemic stroke. This makes a thorough patient history collection and physical examination critical during their diagnosis for vertigo.

Although providers should conduct a further workup on emergency department patients with possible central vertigo symptoms, patients may report frequently overlapping symptomatic findings. The most common cause of cerebellar infarction in all age groups is cardio embolic events and atherosclerosis. Therefore, risk factors are also used to select patients predisposed to central etiologies as a cause of their vertigo. These include hypertension, diabetes mellitus, smoking and a history of vascular disease.

A study by Furman et al. in 2015 recommended immediate neuroimaging be obtained in older patients presenting with acute sustained vertigo and vascular risk factors, new severe headaches, or whose examinations are not typical for peripheral vestibulopathy. In patients younger than 40, the major etiology of cerebellar infarct is vascular events (67%), most commonly intracranial vertebral artery dissection, followed by cardioembolic events (20%), (e.g., a paradoxical emboli from a patent foramen ovale (PFO)). Additional risk factors include hypercoagulable disease states (e.g., Factor V Leiden, malignancy, Protein C and S deficiency) as well as recent head or neck trauma.

Case Report

An African American male in his late 20s presented to the McLaren Macomb Emergency Department with his mother complaining of vertigo and nausea and vomiting for at least four hours. These symptoms had begun at approximately 4:00 am before his arrival. At that time, he awoke and felt the sensation that the room was spinning around him. He immediately noticed a headache located mainly in the left frontal-temporal region. He attempted to get out of bed and had difficulty ambulating
secondary to severe vertigo. At this point, he had multiple episodes of vomiting. He first presented to the emergency department at approximately 8:00 am. The authors evaluated and treated him with anti-nausea medication, as well as intravenous fluid hydration and Ativan. He was determined to be stable for discharge with documented resolution of symptoms and sent home with a prescription for Antivert for symptoms as needed.

Once home, he reported significant worsening of his symptoms. The patient was having an increasingly difficult time ambulating, with worsening intractable nausea and vomiting as well as increasing headache. His mother then brought him back to the emergency department for further evaluation at about 11:00 pm. He denied any neck pain, head or neck trauma, numbness or weakness in his extremities, visual changes, chest pain or dyspnea. He denied ever having symptoms like this in the recent past.

Past medical history revealed the patient had hypertension but was not currently on any medical treatment. He denied any surgeries in the past. He did admit to active tobacco use (i.e., a pack per day for seven years) but denied illicit drug use or alcohol use. His maternal grandmother had sustained at least one transient ischemic attack, and his mother suffered from occasional migraines.

On presentation, the patient’s vital signs were as follows: blood pressure 138/80, temperature 97.7, pulse 86, respirations 16, and oxygen saturation 98%. Physical exam revealed the patient to appear uncomfortable, grimacing in pain due to his headache and laying in the left lateral decubitus position as he stated this helped his symptoms. Neurologic examination was unremarkable except for noted ataxia. He had no limb ataxia, and no evidence of cranial nerve, motor or sensation deficits. The patient did attempt to walk but needed support in order to ambulate in the emergency department. The authors found no meningeal signs. There was no appreciable nystagmus, and the Dix-Hallpike maneuver (a physical exam test used to identify benign paroxysmal positional vertigo) was negative.

Laboratory studies showed a somewhat elevated white blood cell count of 13.7mcL. All other laboratory values were within normal limits. The authors ordered a CT and CTA of the brain that showed an area of hypo-attenuation with loss of the gray-
white matter junction in the left cerebellum. This was consistent with an ischemic infarction along the distribution of the posterior inferior cerebellar artery. (Figure 1)

The patient was administered 325 mg aspirin and a MRI and MRA of the brain was then ordered. The patient was no longer a candidate for tissue plasminogen activator (TPA), (i.e., a thrombolytic agent in ischemic strokes) since he was beyond the therapeutic treatment window. The authors admitted him to the hospital Intensive Care Unit with frequent neurology checks as well as consults to interventional neurology, neurology and neurosurgery.

They also obtained further imagining including CTA of the neck, results of which were unremarkable. The MRI and MRA of the brain showed a large subacute left cerebellar infarct with mass effect and narrowing of the fourth ventricle without any evidence of hydrocephalus. A repeat CT brain was also ordered the next day, demonstrating increased dilation of third and lateral ventricles. (Figure 2)

On the first day after hospital admission, the patient became more somnolent (i.e., sleepy, drowsy) and was diagnosed with obstructive hydrocephalus by neurosurgery. He went to the operating room for a right frontal external ventricular drain and his symptoms slowly improved throughout the rest of his stay. The hematology service also evaluated the patient for a possible hypercoagulable state. This workup was negative except for elevated antithrombin-III level as well as heterozygous MTHFR gene, which was not likely the cause of the infarct per hematology. The authors next obtained a transthoracic echocardiogram with bubble study. This test involves injection of agitated saline into a vein followed by a heart echocardiogram, allowing the physician to visualize direction of blood through the heart chambers. The results of this study were suggestive of a patent foramen ovale possibly putting the patient at risk for a paradoxical emboli.

After hospital Day 14, the patient was discharged with recommendations for tobacco cessation and was started on an antihypertensive medication. He was instructed to attend follow up clinic appointments at suggested intervals. At the time of discharge, the patient was no longer ataxic, and was without any neurologic deficits and deemed stable by all consultants.
DISCUSSION

This case demonstrates the difficulty in distinguishing between cerebellar infarctions and other benign forms of vertigo in the emergency department and in outpatient medical settings. Clinicians use central vertigo symptoms as well as risk stratification to determine those in need of further workup, although cerebellar infarcts have the ability to present with isolated vertigo in patients without significant risk factors. For this reason, studies have shown the misdiagnosis of cerebellar infarcts in emergency departments to be about 35%.³

On initial physical exam, this particular patient had no focal neurologic abnormalities. Furthermore, classifying this patient correctly into central vertigo had been difficult since he possessed many characteristics of peripheral vertigo. (Table 1). His symptoms were sudden in onset and severe in intensity and had persisted for hours. His vertigo was somewhat positional as laying on his left side seemed to improve his symptoms. He revealed no focal neurologic deficits on exam, and there was no obvious nystagmus appreciated. With the exception of his hypertension and tobacco use, this patient was an otherwise healthy male in his late twenties.

Although this patient did possess these two risk factors, his young age may have deterred clinicians from considering a more serious diagnosis such as cerebellar infarction. He had not sustained any recent neck or head trauma nor had a known history of hypercoagulable disease. Although providers had found him to have a patent foramen ovale during his hospital stay, this information was not available in the initial workup and management in the emergency department. Risk stratification in this instance can help little in helping providers decide whether neuroimaging would be beneficial. This patient could have been discharged home without further imaging based on his lack of central symptoms as well as relative young age and lower risk factors.

A 2015 review by Nelson et al highlights the importance of other physical findings that should be considered during clinical decision making for the vertiginous patient with severe ataxia and direction changing nystagmus.⁸ Although many patients with vertigo will present with some form of ataxia, general vertigo of central origin impairs their gait to a greater degree than peripheral causes.⁵ Patients with peripheral vertigo tend to be
hesitant to move as this increases their symptoms, but are usually able to ambulate without assistance. Conversely, 71% of patients with cerebellar infarctions and isolated vertigo will also present with inability to ambulate without support.9

This particular patient had acute, severe ataxia that did not resolve during his emergency department stay. The acute onset of his ataxia should have also raised concern, as ataxia of sudden onset suggests cerebellar hemorrhage or infarction, while ataxia that is slowly progressive suggests chronic cerebellar disorders.4 This highlights the need for imaging in patients first presenting with severe ataxia and a chief complaint of vertigo, even in the absence of significant risk factors and other central symptoms. Although this patient did not present with any focal neurologic deficits and his vertigo seemed to have many characteristics of peripheral vertigo, he was unable to ambulate without assistance in the emergency department warranting further neurologic imaging including MRI and MRA.

CONCLUSIONS

This report highlights a case of a male in his late twenties who presented to the emergency department with vertigo and severe ataxia. Despite the lack of focal neurologic deficits upon presentation and relative low risk of the patient, his providers subsequently obtained a CTA of the brain that showed a left cerebellar infarct in the distribution of the PICA. It can be very difficult to differentiate benign forms of vertigo from life threatening forms that require immediate medical attention.

Providers should attempt to classify patients based on their peripheral versus central symptoms. This can be complicated since patients may have overlapping symptoms. Providers should consider additional risk factors, with patients possessing several key risk factors warranting neuroimaging. This case demonstrates that despite diligence with the above strategies, some patients with cerebellar infarctions may be misdiagnosed. Physicians should focus on other patient symptoms, such as acute, severe ataxia, when distinguishing peripheral vertigo from cerebellar infarcts or other central causes. One can argue that providers should always order further diagnostic
imaging including MRI and MRA of the brain for patients with vertigo and acute, severe ataxia.

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The authors declare no conflict of interest.

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TABLES AND FIGURES

Figure 1:
CT Demonstrating an Acute Left Cerebellar Infarct in the Distribution of the Posterior Inferior Cerebellar Artery. Pictures are from Caudal (top left) to Cranial (Bottom Right) Direction.
Figure 2:
CT Demonstrating Progressed Dilation of Third and Lateral Ventricles.
Table 1: Characteristics of Peripheral and Central Ataxia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Peripheral</th>
<th>Central</th>
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<tr>
<td>Onset</td>
<td>Sudden</td>
<td>Gradual or sudden</td>
</tr>
<tr>
<td>Intensity</td>
<td>Severe</td>
<td>Mild</td>
</tr>
<tr>
<td>Duration of Symptoms</td>
<td>Usually seconds to minutes; Intermittent in nature</td>
<td>Usually weeks, months; Continuous in nature</td>
</tr>
<tr>
<td>Direction of nystagmus</td>
<td>One direction, usually horizontal</td>
<td>Vertical, down beating</td>
</tr>
<tr>
<td>Effect of head position</td>
<td>Worsened by position, often single critical position</td>
<td>Little change, associated with more than one position</td>
</tr>
<tr>
<td>Neurologic findings</td>
<td>None</td>
<td>Usually present</td>
</tr>
<tr>
<td>Auditory findings</td>
<td>May be present, including tinnitus</td>
<td>None</td>
</tr>
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A Rarer Case of Spontaneous Coronary Artery Dissection causing Acute Coronary Syndrome in a Puerperal Woman

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ABSTRACT

ASFAR M. A Rarer Case of Spontaneous Coronary Artery Dissection causing Acute Coronary Syndrome in a Puerperal Woman. Spartan Med. Res. J. Vol. 2, No. 2, pp. 50-58, 2017. CONTEXT: Chest pain is one of the most common complaints of patients presenting to the emergency room department. There are many causes of chest pain and providers must always consider acute coronary syndrome (ACS). Spontaneous coronary artery dissection is a very rare cause of ACS but providers must consider this possibility in younger patients without risk factors or a history of coronary artery disease. This rare phenomenon is commonly associated with pregnant women or those in the postpartum period. METHODS: This is a case report study describing a classic scenario of a postpartum female in her early 30s who presented with spontaneous coronary artery dissection. Providers obtained the usual tests of an electrocardiogram (EKG) and blood work. She then had a heart catheterization performed. The patient was conservatively managed through use of medications without any use of invasive measures. The patient also had other images of the chest taken to rule out other causes of chest pain such as pneumothorax and pulmonary embolism. RESULTS: There were EKG changes noted, as well elevated troponin levels suggestive of heart damage. The heart catheterization results showed coronary artery dissection involving the artery that correlated with the EKG changes. CONCLUSIONS: Spontaneous coronary artery dissection is a rare phenomenon that can present as ACS. Pregnant and postpartum women are at higher risk to develop this condition. It is essential to consider this condition along with other causes of chest pain. Keywords: myocardial infarction, catheterization, acute coronary syndrome, coronary artery dissection

INTRODUCTION

Spontaneous coronary artery dissection is defined as a non-traumatic and non-iatrogenic condition resulting in dissection of the coronary arterial wall. ¹ The mechanism of this rare disease is not well known, but there are a few suggestions that have been proposed previously. A tear in the intimal layer may lead to creation of true and false arterial lumens. The artery is made of three layers known as the intima, media and
adventitia. The inner layer is the intimal layer that may develop a tear leading to the dissection. Another thought is bleeding of the vasa vasorum (i.e., the blood vessels that supply the media and adventitia layers) while the intima remains intact resulting in intramural hematoma.²

The estimated occurrence of acute coronary syndrome (ACS) from spontaneous coronary artery dissection in the general population is 0.1 to 0.4 percent.³ This percentage is much larger when considering the condition as a cause of ACS in women especially those whom are young with ages below 50 at or around the peripartum period. In a recent study, spontaneous coronary artery dissection was found to be responsible for 22.5% of women younger than 60 years old with ACS findings. The patient in this case report demonstrates a classic presentation of a patient who would have a spontaneous coronary artery dissection.

**Case Report**

The patient in this case report is a female in her early 30s who presented to the emergency department at McLaren Macomb medical center for evaluation of chest pain. The pain started suddenly an hour and a half prior to her arrival to the hospital while she was sitting on the couch. She admitted to two episodes of vomiting as well as bilateral upper extremity paresthesias but denied any other symptoms. Her paresthesias symptoms were numbness and tingling that occurred on and off since her onset of chest pain. She has a recent history of childbirth by vaginal delivery approximately two weeks prior to presentation. Her pregnancy and delivery were uneventful and she had been doing well prior to the symptoms that started on this day.

The patient had a past medical history that consisted of anemia and hypothyroidism. She had a previous surgery history of dilation and curettage but denied other surgeries. Her only home medication was a thyroid medication. She denied any history of tobacco, alcohol, illicit drug use or any history of risk factors for cardiac disease. Physical examination of the patient did not show any significant findings. Her vitals were within normal limits and she was in no acute distress.

Diagnostic testing in the emergency department showed abnormal findings of elevated troponin level of 12.5 ng/ml, which at the facility considered normal levels to be
less than 0.039 ng/ml. Troponins are enzymes that are measured in the blood stream and when are present, it suggests that there is heart damage. CT pulmonary angiogram was obtained and the results were unremarkable for pulmonary embolism, a condition where there is blood clots in the lungs. Initial EKG obtained on presentation showed ST depression in the inferior leads with possible prior anterior-septal infarction. (Figure 1) The inferior leads are II, III and AVF on an EKG as delineated by the blue arrows on the figure. Although this does not mean there is a heart attack occurring at this time, it does mean that there is ischemia to the heart muscle.

The patient was taken to the catheterization lab by the cardiology team. The result of the procedure was consistent with spontaneous dissection of the right coronary artery. (Figure 2) There was no intervention performed. The cardiothoracic surgeon who decided that there is no need for surgical intervention also evaluated the patient. She was medically managed and discharged home with aspirin, atorvastatin, metoprolol, and Plavix. Her hospital course was uncomplicated and she was discharged home in stable condition.

DISCUSSION

Spontaneous coronary artery dissection is a phenomenon becoming more recognized in the recent literature as a cause of ACS. The typical patient to develop this condition is more commonly to have a history such as the one presented in this case report. In one study that contained a large series patient sample over three decades with spontaneous coronary artery dissection, the mean age was 43 years and 82 percent were women. Postpartum status was present in 18 percent of the women.

It has been well known that during pregnancy many hormonal changes occur including several cardiocirculatory effects. There is loss of normal elastic fibers and increase in fragmentation of reticular fibers that reduce wall strength which may lead to the dissection. There is also an increase in the risks of developing arterial dissection in women with chronic hormonal pregnancy and multiple births. Although there is no single disease that is known to cause spontaneous coronary artery dissection, there are additional associated factors such as systemic inflammatory and vascular disorders.
Fibromuscular dysplasia is well known to be associated with spontaneous coronary artery dissection.\textsuperscript{8} Other possible factors associated with this rare phenomenon include migraines and tortuosity of the coronary arteries. Tortuosity is the bending and twisting of vessels that commonly occurs in the human body. In one retrospective study with 40 Australian patients with spontaneous coronary artery dissection, migraines were reported in 43 percent of the patients.\textsuperscript{8} Another retrospective study showed tortuosity to be more often present in those with dissections.\textsuperscript{9} However, this cannot be determined as a true cause due to its presence in other vasculopathies such as fibromuscular dysplasia. Due to these common associated diseases, patients with spontaneous coronary artery dissection should be screened for fibromuscular dysplasia and involvement of other vessels such as the iliac, renal and cerebral arteries.

The patient in this case report had dissection of the right coronary artery, which correlated with the EKG changes seen. However, this is not the artery most commonly involved in spontaneous coronary artery dissection. The left anterior descending is the most frequently affected vessel in this disease.\textsuperscript{10} The right coronary artery is also very common but more so in men.\textsuperscript{11} Spontaneous coronary artery dissection may also present in men in any form of ACS. A case series study reported five patients in south Asia 1994 to 2015 in which four patients were young men.\textsuperscript{12} They were managed conservatively with medications only and no surgical intervention was performed. Each of these patients had a favorable long-term prognosis.

There are no current guidelines for the management of spontaneous coronary artery dissection due to limited data and clinical experience. Similar to acute myocardial infarction, various treatments include conservative management, percutaneous coronary artery intervention (PCI), and coronary artery bypass grafting and fibrinolysis may be used. Most cases with spontaneous coronary artery dissection are preferred to be managed conservatively.\textsuperscript{13} This includes use of beta blockers, aspirin, Plavix and statins as were used in the patient’s case. In patients with ongoing ischemia or those that are hemodynamically unstable, the use of PCI or surgery may be required. There is high complication rate with PCI despite similar five-year outcomes when compared with conservative management. The PCI failure rate have shown to be as high as 53% in
some studies. Fibrin thrombolytic therapy is not recommended either due to it resulting in progression of dissection.

The overall prognosis in patients with spontaneous coronary artery dissection varies and there is a high rate of recurrent events. Multiple retrospective studies have been used to demonstrate the rate of recurrence with wide range of results. Another study of 75 patients report a reoccurrence rate 24 percent over a 15-year period. However, another study showed an estimated ten year rate of death and dissection recurrence was as high as 47 percent. It is clear that patients with spontaneous coronary artery dissection must have long term follow up and should be educated on their condition. Although these patients can present with just chest pain alone. They may also have a heart attack presentation with multiple symptoms such as nausea, vomiting, difficulty in breathing, dizziness or even present in arrest.

CONCLUSIONS

Spontaneous coronary artery dissection is somewhat rarer phenomenon that should be considered as a possible cause of ACS. Pregnant women or those in the postpartum period are at higher risk to develop this condition. Therefore, the patient presented in this case report can be considered a classic case. Although there is literature concerning the cause and management of this disease, there are still many more questions that need to be answered regarding this phenomenon. Guidelines concerning standard management have yet to be determined. To date, medical management has been viewed as a standard of care approach unless a patient is hemodynamically unstable or their symptoms persist. Long-term follow up remains key to optimal patient care and patients should be educated concerning their prognosis and potential recurrence risks.

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TABLES AND FIGURES

**Figure 1:**
EKG showing ST depression in the inferior leads (II, III, AVF) with possible prior anterior-septal infarction.
Figure 2:
Dissection of the right coronary artery is shown in all views of angiogram.
Case Report

Pelvic Abscess with Presentation as Inability to Ambulate

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ABSTRACT

DAMER SA. Pelvic Abscess with Presentation as Inability to Ambulate. Spartan Med. Res. J. Vol. 2, No. 2, pp. 59-72, 2017. CONTEXT: Intra-abdominal abscesses are localized collections of pus confined in the peritoneal cavity by an inflammatory barrier. They are generally classified as intraperitoneal, retroperitoneal, or visceral and develop after perforation of a hollow viscus or by extension of infection or inflammation resulting from other conditions such as appendicitis or diverticulitis. Intra-abdominal abscesses are highly variable in presentation and clinicians must have a broad differential to avoid an inaccurate diagnosis. In this paper, presenting clinical symptoms as well as diagnosis and treatment methods are discussed in the context of this atypical presentation of a pelvic abscess. METHODS: This retrospective case report presents a male patient in his early 60s who presented to the emergency department with atypical symptoms of a pelvic abscess. The author obtained all diagnostic information from patient interview and electronic health record. RESULTS: The patient’s history of end stage renal disease and diverticulitis with colostomy placement led to this atypical presentation of an intra-abdominal abscess. The patient’s abscess abutted the iliopsoas muscle that had given rise to his referred bilateral hip pain. CONCLUSIONS: This report presents a case of a male in his early 60s who presented to the hospital with complaint of bilateral hip pain and inability to ambulate. Providers admitted him to an internal medicine service and he was diagnosed with a recurrent pelvic abscess extending to his left iliopsoas muscle. Completed studies had failed to demonstrate any intrinsic pathology to the hips themselves. This case demonstrated an atypical presentation of a pelvic abscess, but brought up the theory that the etiology of the symptoms could be due to referred pain to the hips from the abscess. Further studies are required to investigate the percentage of pelvic abscess patients who primarily present with a component of hip pain. Keywords: pelvic abscess, intra-abdominal abscess, psoas abscess, iliopsoas syndrome

INTRODUCTION

Intra-abdominal abscesses are localized collections of pus confined in a patient’s peritoneal cavity by an inflammatory barrier. This barrier may be comprised of omentum (i.e., fat attached to the bowels), bowel adhesions, or the organ from which the abscess originated.¹
Many intra-abdominal abscesses develop by extension of infection or inflammation resulting from conditions such as appendicitis, diverticulitis, Crohn’s Disease, pancreatitis, pelvic inflammatory disease, or any condition causing generalized peritonitis (i.e., inflammation of the membrane lining the abdominal wall). Prior abdominal surgery is another significant risk factor.

Traumatic abdominal injuries such as lacerations and hematomas of the liver, pancreas, spleen, and intestines can also lead to abscess formation. The abscesses usually contain a mixture of bacteria from the gastrointestinal tract. Most frequent isolates include Escherichia coli (E. coli), Klebsiella, and Bacteroides fragilis. Neisseria gonorrhoeae and chlamydial species are the most common organisms involved in pelvic abscesses.

Intra-abdominal abscesses are highly variable in clinical presentation, although the majority of patients appear with abdominal symptoms or symptoms of sepsis. There may include persistent abdominal pain/tenderness, distention, mass, or ileus. Nausea, anorexia, and weight loss are also common. Other signs signifying possible infection include fever, fast heart rate or leukocytosis (i.e., high white blood cell count).

Physicians should have a higher suspicion for this condition in patients with predisposing primary intra-abdominal disease or those with history of abdominal surgery. If the abscess is deeply seeded, however, many of these classic features may be absent. The only initial clues may be fever, persistent gastrointestinal dysfunction, or non-localizing debilitating illness. Symptoms may be masked by analgesics (i.e., pain relievers) or empiric antibiotic administration.

One important clinical manifestation that can play a role in the presentation of an intra-abdominal abscess is referred pain. Referred pain is pain perceived at a location other than the site of the painful stimulus/origin. This type of pain is the result of a network of interconnecting sensory nerves that supplies many different tissues. When there is an injury at one place in the network, this pain can be interpreted in the brain to radiate nerves and cause pain elsewhere in the related areas of the network.

In patients with subphrenic (i.e., below the diaphragm) abscesses, irritation of contiguous structures may produce shoulder pain, hiccups, non-productive cough,
chest pain, shortness of breath or pneumonia. With pelvic abscesses, frequent urination, diarrhea, or tenesmus (i.e., continual feeling that one has to defecate) may occur.¹

Diagnosis of intra-abdominal abscesses includes a combination of laboratory studies and diagnostic imaging. Complete blood count, basic metabolic panel and blood cultures can help the most in diagnosis.¹ Blood cultures indicating polymicrobial (i.e., several bacterial strains) bacteremia strongly implicate the presence of an intra-abdominal abscess.¹ Plain abdominal radiograph are rarely diagnostic but may frequently indicate the need for further investigation if certain abnormalities are present. These may include localized ileus, extraluminal gas, air-fluid levels or displacement of organs.

Ultrasonography is a readily available, portable, inexpensive test and the findings can be quite specific when correlated with the patient’s clinical signs. In experienced hands, ultrasonography has an accuracy rate greater than 90% for diagnosing intra-abdominal abscesses.¹ CT of the abdomen and pelvis with oral and intravenous contrast is the preferred diagnostic modality with greater than 95% accuracy.¹

Appropriate treatment by clinicians can be frequently delayed due to the obscure nature of many conditions resulting in abscess formation, making diagnosis and localization difficult. Treatment modalities include antibiotic therapy, percutaneous drainage and surgical intervention. Pharmacologic therapy involves administration of empiric antibiotics. While colonic flora consists of near 400 species, an average of only four to six species are generally recovered from intra-abdominal infections.⁴ Combination antibiotic therapy or broad-spectrum single-agent therapy is most often recommended. Therapy can then be adjusted after report of culture results.

For patients with mild to moderate community-acquired infections and few risk factors for resistance or treatment failure, coverage for streptococci, Enterobacteriaceae, and anaerobes is sufficient. Single agent regimens include Ertapenem, Zosyn, or Timentin. Combination regimens include cefazolin, cefuroxime, ceftriaxone, cefotaxime, ciprofloxacin, or levofloxacin with Flagyl. For high-risk community infections, an agent with gram-negative activity broad enough to cover pseudomonas and Enterobacteriaceae resistant to non-pseudomonal cephalosporins should be chosen. Single agent regimens may include imipenem-cilastatin, meropenem, or Zosyn. Combination regimens include cefepime, ceftazidime, ciprofloxacin or levofloxacin with Flagyl. In health-care associated
infections with known colonization of methicillin-resistant Staphylococcus aureus (MRSA), vancomycin should be added. In patients who are known to be colonized by highly-resistant organisms, to include vancomycin-resistant enterococci (VRE), agents such as linezolid and daptomycin should be used.⁴

Physicians should often consider an infectious disease consult. Percutaneous CT guided catheter drainage is the standard treatment of most intra-abdominal abscesses.² Surgical drainage becomes mandatory when residual fluid cannot be evacuated with catheter irrigation, manipulation, or additional drain placement.

Intra-abdominal abscesses have a mortality rate of 10 to 40%.⁵ Outcome depends on the patient’s primary illness and general medical condition rather than on the specific nature and location of the abscess. Risk factors include multiple surgical procedures, age older than 50 years, delay in initial intervention greater than 24 hours, immunocompromised conditions, poor nutritional status, multiple organ failure, and complex, recurrent, or persistent abscesses.⁴ Multiple organ failure is a primary cause of death.⁴

Case Report

A Caucasian male in his early 60s presented to the McLaren Macomb Emergency Department (ED) with a complaint of bilateral hip pain and inability to ambulate. The pain had been present for the past four-to-five days and was progressive in nature. The patient admitted to being fairly active and normally able to ambulate without the assistance of a cane or walker up until symptoms began. He described his pain as 10 out of 10 constant pain in the anterior bilateral hip joints with mild radiation into his lumbar back and groin, with no radiation into his legs. His pain increased with ambulation but improved with rest. He attempted to take three doses of aspirin at home without any relief in his symptoms and began using a walker to help him ambulate.

The patient had an extensive medical history. This history included sigmoid diverticulitis with sigmoid colectomy in 2012, deep vein thrombosis, duodenal ulcer, benign prostatic hypertrophy and hypertension. He also suffered from chronic obstructive pulmonary disease, chronic thrombocytopenia, peripheral vascular disease, atherosclerotic coronary artery disease and paroxysmal atrial fibrillation. He had been
diagnosed with end stage renal disease and was on hemodialysis. He subsequently had multiple hemodialysis catheter infections with bacteremia (MRSA), obstructive uropathy with chronic hydronephrosis, and several peritoneal and pelvic abdominal abscesses. He denied having noticed any recent changes in his ostomy output.

The patient’s past surgical history included inferior vena cava filter placement, cholecystectomy, sigmoid colectomy with end colostomy, numerous cystoscopies, bilateral ureteral stents, peroneal abscess incision and drainage, esophagogastroduodenoscopy, colonoscopy, several IR drainages of pelvic abscesses, exploratory laparotomy with enterolysis, temporary catheter placement, and numerous arteriovenous fistula creations.

The patient took amiodarone, Prilosec, Imdur, and aspirin. He had no allergies to any medications. He denied use of nicotine, alcohol or any illicit drugs. He lived with and took care of his elderly mother. His father had died from a cerebral vascular accident and his mother had a history of coronary artery disease.

Physical exam revealed a well-nourished, well-hydrated male who was in no acute distress. He had been brought from home via ambulance as ambulation was too painful. His vital signs demonstrated hypotension with a blood pressure of 71/51. Patient admits that this was his typical baseline. His pain was worse on the right than the left. He had increased tenderness to log roll, axial compression, and passive flexion of the right hip when compared to the left.

He had intact two-point discrimination and light touch in the L2-S1 nerve distributions bilaterally. He had intact +2 out of 4 dorsalis pedis and posterior tibial pulses found with Doppler ultrasound. He elicited 5 out of 5 muscle strength in his bilateral lower extremities. There was no tenderness to palpation over the greater trochanteric region of either hip. He had a negative straight leg raise bilaterally. The patient had severe brawny edema and dryness to his lower extremities.

Laboratory studies demonstrated a normocytic anemia, chronic thrombocytopenia, hyponatremia, and chronic kidney disease. His sedimentation rate and c-reactive protein levels were elevated. When the patient was sent over for x-ray imaging, left hip, right hip, and pelvis x-rays demonstrated no abnormalities. Lumbosacral x-ray demonstrated mild scoliosis with diffuse moderate degenerative change. (Image 1) The patient was offered
pain medication but refused any other treatment. He was admitted to the hospital due to his intractable bilateral hip pain and inability to ambulate. Orthopedics, Nephrology, and Physical Therapy/Occupational Therapy consults were placed.

Orthopedics was the first service to evaluate the patient on hospital Day 2 and ordered a CT of the abdomen and pelvis with contrast. This study found that superior to the bladder, there was a 4.9 x 3.8 cm fluid collection with peripheral enhancement concerning for abscess. (Image 2) Internal Medicine then evaluated the patient and reviewed the results of the CT scan. Blood cultures were obtained and the General Surgery service was consulted. A repeat CT with oral contrast was ordered by General Surgery on hospital Day 3. This test showed that the adjacent loops of the intestines along the anterior and superior margin of the fluid collection were partially opacified without obvious extravasation of oral contrast in the region, suggesting fistula (i.e., communication with the bowel). (Image 3)

The blood cultures grew out E. coli x 2 after 24 hours. The patient was placed on Zosyn and vancomycin. On hospital Day 5, Interventional Radiology performed CT guidance drainage of the pelvic abscess with catheter placement. Culture results would later grow E. coli. The Urology service was also consulted as the patient had history of hydronephrosis due to obstructive uropathy with bilateral stent placement. This service was asked to evaluate the need for stent replacement and integrity of the bladder with its close approximation to the abscess.

On hospital Day 6, the patient went to the operating room with Urology for a bilateral retrograde urogram. The study demonstrated findings consistent with communication of the urinary bladder with the abscess cavity previously drained. The stents were exchanged, a urinary catheter was placed and a urine sample was obtained for which culture results came back positive for E.coli. The patient remained on Zosyn.

As the patient continued to experience significant bilateral hip pain, an MRI of the patient’s thoracic/lumbar spine and bilateral hips was ordered on Day 7. A thoracic spine MRI demonstrated a small central disc protrusion at the Thoracic 4-T5 level. No spinal canal stenosis or foraminal encroachment. The MRI of the lumbar spine and bilateral hips was unable to be completed since the patient could not tolerate the pain long enough to have the study performed.
The pelvic drain was removed between hospital Days 9 and 11, although progress notes are unclear as to the specific day. On hospital Day 15, the patient was discharged to a subacute rehabilitation unit on a two-week course of oral Augmentin. He had worked with Physical Therapy throughout his hospital stay. The patient slowly regained some ability to ambulate but it is unknown whether or not this was from resolving his pelvic abscess or due to rehabilitation with Physical Therapy. He was to follow up with the urologist in two-to-three weeks for urinary catheter removal.

DISCUSSION

This case describes a patient who suffered from the inability to ambulate who was eventually diagnosed with an intra-abdominal abscess. This patient had presented to the emergency department with bilateral hip pain which would be an unusual presenting symptom for his diagnosed pathology. As earlier described, most common complaints associated with an intra-abdominal abscess include abdominal pain/tenderness, distention, nausea, anorexia, fever, fast heart rate or high white blood cell count. The patient met none of these criteria. Throughout the patient’s hospital stay, he never had a complaint related to his gastrointestinal system. On Day 3 of his hospitalization, he spiked a white blood cell count but remained afebrile throughout his course. The question arises as to whether the patient’s complaint has any relation to the intra-abdominal abscess found on CT imaging.

After an in-depth review of the patient’s medical record, it was revealed that he had an extensive medical history. The patient has suffered from diverticulitis with perforation and abscess formation. He had several drainages of the abscess completed by an interventional radiologist prior to, and after his sigmoid colectomy with end ileostomy that was performed in September 2012.

Throughout his multiple hospitalizations, he had recurrence of an intraperitoneal abscess that was located superior to the bladder and adjacent to the left iliopsoas muscle. Several studies showed altered attenuation of the iliopsoas muscle and evidence that the abscess was contiguous with the muscle. CT imaging conducted in December, 2012 indicated that the abscess involved the left iliopsoas bursa. It is this
involvement/extension for which the patient’s presenting complaint could possibly have relation to his found pathology, however no direct data concerning this existed.

The psoas muscle arises from the transverse processes and lateral aspects of the vertebral bodies between the 12th thoracic and 5th lumbar vertebrae. It courses downward passing deep to the inguinal ligament and anterior to the hip joint capsule to form a tendon that inserts into the lesser trochanter of the femur. The iliacus muscle joins the psoas to insert via the same tendon. These two muscles are the main hip flexors. The tendon is separated from the hip capsule by the iliopsoas bursa. This bursa is the largest bursa in the body, and exists to help reduce rubbing between the iliopsoas muscle and the femur. This bursa communicates with the hip joint space in up to 15% of persons which may facilitate spread of infection between these sites.6

The iliopsoas muscle can be involved in several pathologic conditions to include iliopsoas tendinitis/bursitis, iliopsoas syndrome and psoas abscesses. Although uncommon injuries, iliopsoas tendinitis/bursitis occurs when the tendon and bursa becomes inflamed. They are overuse injuries that result from overloading the hips with repetitive movements.7 People who participate in activities such as golf, hockey, cheerleading, gymnastics, and resistance training are most susceptible to injury. Iliopsoas syndrome frequently begins as a bilateral muscle spasm which eventually becomes prominent on one side.

Psoas abscesses are a collection of pus in the iliopsoas muscle compartment which may arise from contiguous spread from adjacent structures or by hematogenous route from a distant site.6 They are divided into primary and secondary abscesses. Primary abscess occurs as a result of hematogenous or lymphatic seeding. Risk factors include diabetes, IV drug abuse, HIV, renal failure or other forms of immunosuppression. Secondary abscesses occur as a result of a direct spread of infection to the psoas muscle from adjacent structures. The structures include vertebrae, hip arthroplasty, GI tract, aorta, and genitourinary tract.

Symptoms of iliopsoas tendinitis/bursitis and psoas syndromes include pain, tenderness, swelling, heat or redness and loss of normal mobility. Signs of psoas abscess include back or flank pain, fever, inguinal mass, limp, anorexia, and weight loss. Pain can
be present in up to 91% of cases with localization to the back, flank, or lower abdomen and possible radiation to the hip and/or posterior thigh.\textsuperscript{6}

Originally described in 1881, the classic clinical presentation of a psoas abscess included back pain, limp and fever.\textsuperscript{8} Newer case studies have demonstrated that these symptoms may only be present in 30% of cases.\textsuperscript{8} Many patients present with nonspecific complaints such as malaise, low grade fever, abdominal/flank discomfort, a flexed and externally rotated hip and pain on movement of the hip. Pain is due to irritation of muscle belly and referred pain from nerve roots L2-L4. Due to the vague and nonspecific presenting symptoms of a psoas abscess, they are commonly misdiagnosed, although data concerning the misdiagnosis rate is sparse.\textsuperscript{8} One case studied reported a psoas abscess that was previously misdiagnosed as a deep vein thrombosis.\textsuperscript{9}

After review of the presenting symptoms of iliopsoas bursitis/tendonitis, syndrome and psoas abscess, the clinical conclusion can be made that this patient may have been suffering from referred pain to the hip from his pelvic abscess that abutted the left iliopsoas muscle. This is a speculation since there are no direct reports available concerning a direct correlation between this man’s pelvic abscesses and hip pain.

However, several discrepancies arose during his workup. The patient had suffered from right hip pain yet the patient’s abscess directly invaded the left iliopsoas muscle. He also had more pain when asked to perform hip flexion and preferred to lay flat on his back without axial loading. Research has found a correlation with patients suffering from psoas abscesses and that they prefer to lay with their hips flexed.\textsuperscript{6} In addition, the patient had presented several times in the past for recurrent pelvic abscess and failed to complain of hip pain during those admissions. Finally, the patient may have had pathology of his lumbar spine or hips that could have been identified if the patient had been able to tolerate the MRI imaging procedure.

In support of the theory of the patient’s suffering from referred pain, the patient did experience pain upon movement of the hip and had improvement in his symptoms after IR drainage and antibiotic administration. Hip pain, especially in Crohn’s patients should prompt consideration of a psoas abscess as the incidence has been estimated to be between 0.4 and 4.3%.\textsuperscript{6} Psoas abscess has also been described in the setting of appendicitis, colorectal cancer, ulcerative colitis and following abdominal surgery so
evidence exists with other GI pathology. While a question was made during the patient’s hospital stay as to whether his symptomatology was somehow related to his pathology versus incidental, the author does not believe the theory of referred pain is far-fetched.

CONCLUSIONS

This report presents a case of a Caucasian male in his early 60s who presented to the emergency department with complaint of bilateral hip pain and inability to ambulate. He was admitted to the hospital and found to have a recurrent pelvic abscess which extended to his left iliopsoas muscle. The patient failed to demonstrate the typical symptoms of a pelvic abscess and therefore his pathology was not revealed initially in the emergency department. It was not until the patient had been hospitalized for a day and his medical record had been thoroughly reviewed, when his diagnosis was made. Even then, his presenting complaints could not be fully explained. Additional imaging studies failed to demonstrate any intrinsic pathology to the hips themselves.

This case demonstrated an atypical presentation of a pelvic abscess, but questions remained as to whether the patient’s symptoms were due to referred pain to the hips. Conditions such as iliopsoas tendinitis/bursitis and psoas syndromes present with pain, tenderness, swelling, heat or redness and loss of normal mobility while signs of a psoas abscess include back or flank pain, fever, inguinal mass, limp, anorexia, and weight loss. These clinical findings are more consistent with what the patient in the case study had presented to providers. Further investigations are required to determine the percentage of patients with pelvic abscesses who initially present with a component of hip pain.

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REFERENCES

Image 1:
Pelvis X-ray
Image 2:
Fluid Collection - 4.9 x 3.8 cm.
Image 3:
Pelvic Abscess without Signs of Communication with Bowel.
Brief Report

Utilizing PDSA Cycle to Implement a Chest Pain Accelerated Diagnostic Protocol

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ABSTRACT

BRECKNER G, WALKER J, HANLEY K, BUTKI N. Utilizing PDSA Cycle to Implement a Chest Pain Accelerated Diagnostic Protocol. Spartan Med. Res. J. Vol. 2, No. 2, pp. 73-84. 2017. CONTEXT: The authors in the Emergency Department (ED) at McLaren Oakland utilized the Plan-Do-Study-Act (PDSA) model to implement, evaluate and incrementally modify a Chest Pain Accelerated Diagnostic Protocol (CP-ADP) using the History, EKG, Age, Risk Factors, Troponin (HEART) Score at their institution. The objective of this study was to evaluate the ability of patients who presented to the ED with chest pain and fell into the low risk category based on their HEART Score to receive adequate outpatient follow-up for their chest pain. METHODS: Modifying protocols implemented at other institutions, in 2016 the authors developed CP-ADP utilizing the HEART Score to risk-stratify patients presenting to the ED with chest pain as low, moderate or high risk for major adverse cardiac events (MACE). Patients identified as low risk were offered the options of hospital observation or being discharged home with outpatient follow-up within seven days. Patients who were risk-stratified into the medium or high risk for MACE were admitted into the in-patient setting for cardiac evaluation. Once implemented, the protocol was evaluated to measure patient follow-up within thirty days. RESULTS: During a five-month period, 50 patients presenting to the ED with chest pain were risk-stratified as low risk for adverse cardiac events and opted for discharge from the ED to follow-up in the outpatient setting. A total of 18 patients were lost to follow up, and two patients subsequently returned to the ED for further evaluation of their chest pain and were admitted to the inpatient setting. These two patients were not included in the analysis. Thirty patients were successfully contacted by telephone 30 days post-discharge. Of those 30 patients contacted, none experienced any MACE events. However, only 14 (47%) low risk patients followed up with a primary care provider or cardiologist and only four (13%) received provocative cardiac testing (i.e., stress testing). CONCLUSIONS: Only 47% of patients discharged from the ED received outpatient follow-up and only 13% received cardiac testing. As a result of the study, the multi-disciplinary Chest Pain Committee has progressed to the Act ‘A’ step of the PDSA cycle to modify the authors’ protocol to ensure more clinically appropriate outpatient follow-up for patients discharged under the CP-ADP. Keywords: quality improvement, patient safety, QI/PS, HEART score

INTRODUCTION

Myocardial infarction is one of the leading causes of death in the world.1 However, the majority of patients presenting to emergency departments (ED) with a chief complaint
of chest pain are not found to have emergent cardiac causes for their chest pain.\textsuperscript{2,3} In fact, only about 10\% of all patients presenting to emergency departments with chest pain are diagnosed with acute coronary syndrome (ACS), a condition earlier known as myocardial infarction or heart attack.\textsuperscript{1} As a result, the need for cardiac chest pain risk assessment tools and learning how to best use these tools, has become of increasing importance.

In addition, the high medical-legal risk that physicians feel associated with patients presenting to ED with chest pain highlights the need for a validated risk stratification tool to identify patients who can be safely discharged from the ED.\textsuperscript{4} The historical practice at McLaren Oakland hospital has been to admit patients presenting with chest pain to the hospital inpatient or observation units for further cardiac evaluation. This, however, is an expensive practice. It is estimated that admitting patients to the hospital only to result in testing with negative findings costs $5-10 billion annually in the United States.\textsuperscript{5}

In addition to costs, there are also patient safety concerns associated with unnecessary hospital admissions. Patients admitted to hospitals for cardiac evaluation often receive an escalation in studies and testing which has led to overutilization of invasive procedures such as cardiac catheterization.\textsuperscript{2}

In 2013, the HEART score was developed for use as a cardiac risk assessment tool.\textsuperscript{1} The HEART score produces a numeric score based on five patient factors: History, EKG findings, Age, Risk factors and Troponin results. The HEART score has been shown to accurately risk stratify patients for the potential to experience major adverse cardiac events (MACE).\textsuperscript{1} Particularly useful, the HEART score identifies patients at low risk who can be safely discharged from the ED, reducing unnecessary hospital admissions.\textsuperscript{2,6} The HEART score also identifies those patients at higher risk who require further workup and possible admission.\textsuperscript{7}

In the HEART Score validation study, less than 1\% of low risk patients experienced MACE within 30 days of their ED visits.\textsuperscript{1} Using this metric and a shared decision making between the patient and the physician regarding discharge options, low risk chest pain patients can be safely discharged from the ED with close primary care or cardiology outpatient follow up.
In 2016, the McLaren Oakland Chest Pain Committee was charged with designing an evidence-based protocol to discharge low risk chest pain patients that best fit the interest of the patients and institution. The interests of the patients include safe identification of serious cardiac diseases balanced with cost reduction, both direct in terms of payment and co-pays and indirect such as loss of work and productivity during the time in the hospital. The interests of the institution include providing thorough and safe patient care balanced with the costs of low reimbursed observation stays consuming resources.

The protocol was entitled Chest Pain Accelerated Diagnostic Protocol (CP-ADP). The Chest Pain Committee was also charged with the task of continuously evaluating and improving the protocol until it successfully met the best interests of patients and the institution. The Chest Pain Committee sought to develop a model that focused on Quality Improvement (QI), viewing health care as process and system improvement opportunities. The Chest Pain Committee chose the PDSA model to evaluate and modify the CP-ADP.8,9 (Appendix 1)

**Objectives**

The goal of this Quality Improvement/Patient Safety (QI/PS) project was to utilize the PDSA model to design, evaluate and improve the McLaren Oakland CP-ADP to meet the needs of patients presenting to the ED with chest pain. The authors primarily wanted to ensure that chest pain patients who were opting for discharge with outpatient follow-up received appropriate outpatient follow-up and cardiac testing. Secondarily, the authors wanted to monitor the incidence of MACE in the patients discharged home under the CP-ADP protocol.

**METHODS**

The McLaren Oakland Chest Pain Committee selected the HEART Score as the institutional cardiac risk stratification tool for patients presenting to the ED with a chief complaint of chest pain and who received a cardiac work up (i.e., basic lab work, troponins). The PDSA model was utilized to implement and modify the CP-ADP. (Appendix 2)
During the Plan stage of the cycle, the multidisciplinary Chest Pain Committee consisting of representation from emergency medicine physicians, cardiologists, nursing administration, hospital administration, laboratory, medical imaging and cardiovascular services researched multiple risk assessment tools. Since it is simple to use and it was designed specifically for use in the ED, the authors were most confident with the HEART Score as the tool for our institutional CP-ADP. A literature review of best practices utilizing the HEART Score identified CP-ADP protocols successfully implemented at other institutions.\(^5\) The Chest Pain Committee modified existing protocols to meet our institutional needs such as using three-hour troponin intervals and designing discharge forms consistent with institutional specifications.

The CP-ADP stratified patients as 'low risk' if the patient had a HEART score of less than 3 and had 2 negative troponin tests 3 hours apart. Once stratified as low risk, a shared decision-making process was implemented and the patient would be offered inpatient admission or discharge home with close outpatient follow-up. The shared decision-making conversation was not scripted. Rather, the launch of the CP-ADP included educating the emergency medicine providers concerning the results of previous HEART Score studies. This knowledge empowered the emergency medicine providers with the flexibility to tailor the shared decision-making conversation to the needs of individual patients.

The CP-ADP was launched in April 2016. The launch included a series of one-hour educational training sessions delivered each month for a three month period for emergency medicine physician staff, including attending and resident physicians. The training included instruction on calculating the HEART Score, methods for communicating with patients regarding their HEART score, shared decision-making processes offering the patients inpatient observation versus discharge with outpatient follow-up and instruction on utilizing the Chest Pain Discharge Form. Non-Human Subject IRB exemption was granted from the McLaren Oakland IRB for this project prior to any data collection.

As stated previously, HEART is an acronym for the components of the score: History, Electrocardiogram, Age, Risk factors, and Troponin. Troponin is a protein released into the blood when the heart muscle is damaged, such as occurs in a heart
attack. Each of these components is graded as 0, 1, or 2 points. The HEART score is the sum total of these components.² (Appendix 1)

The CP-ADP was used by ED physicians to stratify patients who presented to the ED with chest pain as “low risk” if their total HEART Score was 0-3 and had two negative (reference range 0-0.056 mg/dl) troponin levels three hours apart. For low-risk patients, the shared decision-making discussion was implemented.

As part of the shared decision-making process, the patients were offered the following options:

a) Inpatient hospital observation,

b) Discharge with outpatient follow up with the patient’s established primary care physician or established cardiologist within seven days, or

c) Discharge with outpatient follow up using one of two hospital-employed primary care physicians who agreed to see patients within seven days of discharge.

Regardless of discharge follow-up option chosen, patients were provided specific CP-ADP discharge instructions to return at any time if their chest pain worsened or if they changed their mind and wished to come back to receive inpatient evaluation.

All patients who chose the option for discharge under the CP-ADP between August 1, 2016 and Dec 31, 2016 (n = 50) were contacted by telephone 30 days after their ED discharge. They were asked the following three questions during post-discharge phone evaluations:

1. Had the patient experienced any MACE within the 30 days post-discharge period? (MACE events include death, myocardial infarction, or need for coronary revascularization).

2. Had the patient completed a follow up clinic appointment within seven days with a primary care physician or cardiologist?

3. Had the patient received any type of provocative cardiac testing (i.e., cardiac stress test)?

RESULTS

During the data collection period, a total of 50 patients were discharged after being risk-stratified as “low risk” in the CP-ADP. Of these 50, 18 (36.0%) patients had non-
working phone numbers or were unable to be reached by telephone after three attempts. Two (4.0\%) patients opted to return to the ED for further evaluation of their chest pain and were subsequently placed in cardiac observation. One patient was in the hospital obtaining a cardiac workup at the time of contact and the other was discharged from the hospital after a negative cardiac workup three days prior to the follow up call. Neither of these patients were included in the project analyses. Therefore, a total of 30 (60\% of discharged sample) patients were successfully contacted and used to evaluate the CP-ADP.

Of the 30 total patients who were contacted, none (0\%) experienced any MACE events. 14 (47\%) of the 30 patients received outpatient follow up within seven days following discharge from the emergency room and four (13\%) had received provocative cardiac testing. (Figure 1)

**DISCUSSION**

Based on these project results, the HEART score is easy to learn and use and has allowed us to accurately risk-stratify patients with a chief complaint of chest pain who present to the emergency department.

Previous project results have also given us additional insight into the HEART score and chest pain in the ED. Numerous studies and articles have demonstrated the financial burden that is encountered by the workup and admission of low risk patients.\(^5\) In addition, physicians also inevitably feel a responsibility to ensure a safe discharge for patients who present to their ED with a chief complaint of chest pain.\(^4\) It is important that there are studies which can give them that reassurance to practice appropriately.

The purpose of this study was to utilize the PDSA model to evaluate and modify the CP-ADP to meet the local needs of our patients and institution. This study specifically quantified the Study, ‘S’ portion, of the PDSA cycle as part of the evaluation and modification of the CP-ADP. The McLaren Oakland CP-ADP modified its design based on published and validated ADP’s from other institutions.\(^5\) Based on these initial project results, low risk chest pain patients were appropriately discharged home for continued follow-up. In our study population, it was found that these low risk patients could be safely discharged with no MACE.
While the authors were encouraged by the fact that none of the patients discharged experienced MACE, these findings demonstrated a need for modification of the ADP to ensure better outpatient follow-up.

The multidisciplinary Chest Pain Committee has met multiple times discussing the data and the results of the Chest Pain ADP evaluation. After healthy discussion among the ED providers, cardiologists, primary care providers and hospital administration, a modified ‘physician directed follow-up’ is currently in the Plan stage. The physician-directed follow up consists of, with the patient’s permission, forwarding the patient’s contact information directly to the office of a hospital-employed primary care physician. The office of the primary care physician will directly contact the patient to schedule a follow-up appointment. Once the revised plan is finalized, the cycle will continue with implementation of the revised plan (DO) and evaluation of the revised plan (Study). The authors anticipate multiple future PDSA cycles of our CP-ADP to maximize the benefit of the protocol for our patients presenting to the ED with chest pain.

Secondarily, as a result of the PDSA cycle evaluation conducted in this study, patients can feel reassured that those who are stratified into low risk categories based on their HEART Score can safely follow up outpatient with their primary care physician with an acceptably low risk for MACE.

The authors report no external funding source for this study.

The authors declare no conflict of interest.

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REFERENCES


Figure 1:
Patient Outcomes Following Discharge from the ED

- Total Patients: 50
- Contact made: 25
- No MACE: 20
- Follow up: 15
- Provocative testing: 5

Patients (N=50)
Appendix 1: HEART Score for Chest Pain Table

### HEART score for chest pain patients

<table>
<thead>
<tr>
<th></th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History (Anamnesis)</strong></td>
<td></td>
</tr>
<tr>
<td>Highly suspicious</td>
<td>2</td>
</tr>
<tr>
<td>Moderately suspicious</td>
<td>1</td>
</tr>
<tr>
<td>Slightly suspicious</td>
<td>0</td>
</tr>
<tr>
<td><strong>ECG</strong></td>
<td></td>
</tr>
<tr>
<td>Significant ST-deviation</td>
<td>2</td>
</tr>
<tr>
<td>Non-specific repolarisation disturbance / LBBB / PM</td>
<td>1</td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>2</td>
</tr>
<tr>
<td>45 – 65 years</td>
<td>1</td>
</tr>
<tr>
<td>≤ 45 years</td>
<td>0</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>≥ 3 risk factors or history of atherosclerotic disease</td>
<td>2</td>
</tr>
<tr>
<td>1 or 2 risk factors</td>
<td>1</td>
</tr>
<tr>
<td>No risk factors known</td>
<td>0</td>
</tr>
<tr>
<td><strong>Troponin</strong></td>
<td></td>
</tr>
<tr>
<td>≥ 3x normal limit</td>
<td>2</td>
</tr>
<tr>
<td>1-3x normal limit</td>
<td>1</td>
</tr>
<tr>
<td>≤ normal limit</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Risk factors for atherosclerotic disease:**

- Hypercholesterolemia
- Hypertension
- Diabetes Mellitus
- Cigarette smoking
- Positive family history
- Obesity (BMI>30)

http://www.heartscore.nl/score/
Appendix 2:
Plan-Do-Study-Act (PDSA) Model

**PLAN**
Define the objective, questions and predictions. Plan to answer the questions (who? what? where? when?)
Plan data collection to answer the questions

**DO**
Carry out the plan
Collect the data
Begin analysis of the data

**STUDY**
Complete the analysis of the data
Compare data to predictions
Summarise what was learned

**ACT**
Plan the next cycle
Decide whether the change can be implemented
Appendix 3:
CP-ADP Discharge Form

1. Your Chest Pain Diagnosis:
Our testing so far has not shown any evidence of a heart attack. This is based on a blood test, an electrocardiogram (ECG), your exam, and your risk factors. Risk factors used to determine your risk area: history, ECG, age, risk factors for heart disease, Troponin blood test.

However, even if everything today is normal, your chest pain may be an early warning sign of a possible FUTURE heart attack or heart complication.

2. Your Personal Risk Evaluation:
Your risk of having a heart attack or heart complication within the next 30 days can be determined by comparing you to people with similar factors who also came to the emergency department with chest pain.

Of every 100 people with risk factors like yours who came to the emergency department with chest pain, one had a heart attack or heart complication within 30 days of their ED visit; 99 did not.

3. Further Evaluation:
Further evaluation and testing will help check if your heart is working correctly.

a. I would like to be discharged from the ED and will follow up with my primary care physician in one week for further evaluation.

b. I would like to be discharged from the ED and follow up with a McLaren Oakland primary care physician. I can call Dr. M. Schury at 248-334-4982 or Dr. R. Keim at 248-334-0847 who have committed to following up within one week.

c. I would like to be placed in Observation for further testing. I understand that this will increase my length of stay in the ED and in the hospital.

I understand my personal risk evaluation and have had all questions answered. If my symptoms worsen, I will return to the ED immediately.

Patient/Caregiver Signature ___________________________ Date _______ Time ______

Physician Signature ___________________________ Date _______ Time ______
Comparison of Acute Kidney Injury during Treatment with Vancomycin and either Piperacillin-Tazobactam or Meropenem

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ABSTRACT

CANNON JM, DOUCE RW, GRUBBS ER, WILLS CB, KHAN A, SCHMIDT EM, WANG MS. Comparison of Acute Kidney Injury during Treatment with Vancomycin and either Piperacillin-Tazobactam or Meropenem. Spartan Med. Res. J. Vol. 2, No. 2, pp. 85-98, 2017. CONTEXT: Empiric antibiotics are often required in hospitalized patients with serious infections who may be septic and at risk for drug resistant organisms. The purpose of this study was to evaluate the observed incidence of acute kidney injury (AKI) in a sample of adult patients receiving either piperacillin-tazobactam and vancomycin or meropenem-vancomycin for at least 72 hours. METHODS: Single-center, retrospective matched cohort at a 200-bed Regional Community Medical Center. Adult patients were included in the sample if they were without preexisting renal dysfunction and admitted over an 18-month time period to receive either the combination of piperacillin-tazobactam and vancomycin or meropenem-vancomycin. Sample patients were evaluated for AKI. This condition was defined by the authors as an increase in serum creatinine of 0.5mg/ml or an increase of 50% above baseline during the duration of antibiotic treatment. RESULTS: A total of 266 patients receiving either combination of antibiotics were evaluated for AKI. The incidence of AKI was significantly higher in the piperacillin-tazobactam and vancomycin group (n = 74/292, 25%) compared with the meropenem-vancomycin group (n=8/74, 9.5%, p=0.008). CONCLUSIONS: The results of this study suggest that the combination of piperacillin-tazobactam and vancomycin is associated with an increased incidence of AKI. Higher vancomycin trough concentrations were associated with increased risk for development of AKI. Keywords: vancomycin, piperacillin-tazobactam, meropenem, nephrotoxicity

INTRODUCTION

Empiric antibiotics are often required in hospitalized patients with serious infections who may be septic and at risk for drug resistant organisms.1,2 As sepsis-associated mortality is reduced with earlier antibiotics initiation, initial broad spectrum combination
antibiotic therapy is often essential.⁰¹,³ These regimens typically include antibiotics that require coverage for both methicillin resistant *Staphylococcus aureus* (MRSA) and gram negative bacteria including *Pseudomonas aeruginosa*.¹⁴ Combination therapy in these instances may often include vancomycin, which covers MRSA, and an extended-spectrum beta lactam agent such as piperacillin-tazobactam (brand name Zosyn).

Both of these drugs have been in use for many years. It has been recognized that vancomycin, which covers MRSA, can cause nephrotoxicity.² Piperacillin-tazobactam is a beta lactam antibiotic and member of the penicillin family of antibiotics. It is a broad-spectrum antibiotic with a scope of activity that covers gram-positive organisms, gram-negative organisms and anaerobes, but does not cover MRSA.⁵ Gram-positive organisms include *staphylococcus* and *streptococcus* species of bacteria, while *Escherichia coli*, Klebsiella species, and *Pseudomonas aeruginosa* predominate among gram-negative isolates.⁶

Both medications can also cause severe sepsis, although studies have demonstrated bacteremia (bacteria in the bloodstream) in gram negative patients at a higher frequency than gram positive bacteremia among septic patients.⁶ In terms of kidney failure, piperacillin-tazobactam monotherapy has been shown to elevate creatinine, a marker of kidney function, in only 0.4% of patients.⁵ It has only recently been demonstrated that the combination of piperacillin-tazobactam with vancomycin can further increase the risk of nephrotoxicity.⁷⁻¹⁸

Renal function is often measured by serum creatinine, and an acute increase often represents kidney failure.¹⁹ It has been previously shown that an increase in serum creatinine (SCr) of ≥ 0.5mg/dl is associated with increased odds of death by 6.5 times, an average increased length of stay (LOS) of 3-5 days, and increased hospital costs of $7500.²⁰

Due to the reported nephrotoxicity associated with the vancomycin and piperacillin-tazobactam combination, alternative regimens may be necessary. A possible alternative initial therapy for sepsis that would cover MRSA and *pseudomonas aeruginosa* might include vancomycin and meropenem (brand name Merrem).⁷ Meropenem is a carbapenem and part of the beta lactam family of antibiotics. It has a spectrum of coverage similar to piperacillin-tazobactam and has a rate of creatinine increase of less
than 1%. To our knowledge, only two other published studies have examined the rate of acute kidney injury (AKI) occurring when a carbapenem is combined with vancomycin across multiple disease states.\textsuperscript{7,14}

The purpose of this retrospective study was to investigate whether the risk of AKI was greater in a convenience sample of hospitalized patients receiving the combination of piperacillin-tazobactam with vancomycin verses meropenem with vancomycin.

**METHODS**

**Study Setting**

This study was conducted at Lakeland Regional Medical Center, a 200-bed hospital with both teaching and non-teaching inpatient services in St. Joseph, Michigan. It is a Level 3 Trauma Center with an adult intensive care unit, a medical, oncological, post-surgical, orthopedic, neurological, and pediatric unit. Before data collection, the study was approved by the Lakeland Regional Medical Center Institutional Review Board.

**Study Design and Population**

This was a single-center, retrospective, matched cohort study comprised of patients admitted to Lakeland Regional Medical Center between March 2012 and October 2014. The authors obtained pharmacy logs to review patients who had received Piperacillin/tazobactam-vancomycin (PT-vancomycin) or meropenem and vancomycin. The typical dose of piperacillin-tazobactam was either 3.375 grams, 4.5 grams, or 4.5 grams every six hours, depending on the patient’s treated condition, as higher doses are recommended for hospital-acquired pneumonia. The typical meropenem dose was one gram every eight hours.

The authors based any dosage adjustments on individual factors such as age and renal function. Vancomycin dosing was per discretion of the provider or prescribed as ‘pharmacy to dose’. When ordered as pharmacy to dose the clinical pharmacists monitored vancomycin levels, renal function, and adjusted the doses accordingly.

Patients were included in the analytic sample if they were over 18 years old, without pre-existing renal dysfunction, and received a minimum of 72 hours of a combination of either PT-vancomycin or meropenem with vancomycin for any indication.
For both cohort groups, providers started concurrent therapy with required 48 hours of vancomycin initiation. At least one Vancomycin trough level and three serum creatinine levels were required during their hospital stay.

The authors excluded patients from the study if they possessed any signs of pre-existing renal dysfunction. This was defined as a baseline serum creatinine concentration of >1.5mg/dL (a marker of kidney function), a history of renal replacement therapy, or recent AKI within the past six months. Patients were excluded if they had not received at least 72 hours of concomitant antibiotics or if they received both piperacillin/tazobactam and meropenem at any point during their hospitalization. If a patient had multiple admissions during the study period, only the first hospitalization was used for the purposes of this study.

**Study Outcome**

The primary result was the difference in the incidence of nephrotoxicity in patients either on PT-vancomycin or meropenem-vancomycin. This was defined as an increase in serum creatinine of 0.5mg/mL or an increase of 50% above the baseline. Other variables that were examined included: any concomitant use of nephrotoxic medications, advanced age, diabetes, and elevated Charlson Comorbidity Index (CCI) score. A CCI score was formulated to classify comorbid sample patients according to their risk of death from those diseases at the time of inclusion into the study.22

**Data Collection**

The authors captured study data using the Lakeland Health electronic medical record system. The authors included patient data concerning:

- age
- gender
- height
- weight
- intensive care unit admission vs. all other units
- serum creatinine (on three separate dates if possible)
- number of days to increased serum creatinine if applicable
- antibiotic start and stop dates
- vancomycin serum concentration levels and dates drawn
• concomitant nephrotoxins (e.g., aminoglycosides, amphotericin, acyclovir, NSAIDs, loop diuretics)
• complete blood count on antibiotic initiation
• targeted medical condition diagnoses used to calculate CCI
• infectious disease diagnosis.

Statistical methods included the use of the chi-square test of association, Fisher's Exact Probability Test, and ANOVA. Computations were performed via the VassarStats computational software (MW, RD).

RESULTS
A total of 454 patients who received piperacillin-tazobactam and vancomycin during the study period were first identified. Within this sample, 162 patients were excluded, either due to baseline renal insufficiency, prolonged use of multiple classes of antibiotics, and/or missing data concerning dates. Excluded patients were similar in age to the study population in the piperacillin-tazobactam and vancomycin group (65.6 vs. 65.3, p = 0.840), but slightly older in the meropenem and vancomycin group (67.5 vs. 60.3, p = 0.014). A total of 292 patients were treated with a combination of piperacillin-tazobactam and vancomycin and 74 patients were treated with meropenem-vancomycin.

Patients in the piperacillin-tazobactam and vancomycin group were slightly older (65.3 vs. 60.3 years, p = 0.013) on average than the meropenem-vancomycin group. (Table 1) Patients in the meropenem-vancomycin group were more likely to have been in the intensive care unit (31.1% vs. 15.8%, p = 0.003) and to have received contrast dye than the piperacillin-tazobactam and vancomycin group (50% vs. 31.2%, p = 0.003). There were no statistically significant differences found between sample subgroups in terms of gender, history of hypertension, elevated vancomycin trough, NSAID use, diuretic use, or ACE inhibitor use. The incidence of AKI was higher in the piperacillin-tazobactam group than the meropenem-vancomycin group (25% vs. 9.5%, p = 0.008).

Table 2 compares patients with renal toxicity versus no renal toxicity in the two cohorts. In the piperacillin-tazobactam and vancomycin group, there were no differences in average age (65.7 vs. 64.6 years, p = 0.62), gender (60.8% male vs. 55.6% female, p = 0.27), or ICU stay (20.3% vs. 14.2%, p = 0.27). Patients whose vancomycin troughs,
which are steady state concentration levels, were >20 mcg/mL were more likely to have renal insufficiency (41.9% vs. 15.6%, p = 0.01). Patients whose vancomycin troughs were > 15 mcg/mL were also more likely to have renal insufficiency (62.2% versus 38.1%, p = 0.001).

Comparing patients with renal toxicity versus no renal toxicity in the meropenem-vancomycin group, there were no differences in average age (60.8 vs. 58.3, p = 0.73), gender (62.5% male vs. 45.5%, p = 0.46), or ICU stay (50% vs. 28.8%, p = 0.23). The average baseline creatinine was higher in the renal toxicity group (1.16 vs. 0.82, p = 0.009). There was a trend toward elevated vancomycin trough, trough > 15 mcg/mL in the renal toxicity group (75% vs. 36.4%, p = 0.055), although this was not statistically significant. Overall, the risk of renal failure with vancomycin in combination with meropenem vs. piperacillin-tazobactam was 0.3571 (95% CI 0.1637 to 0.7787, p=0.008), as indicated in Table 3.

DISCUSSION

Our study compared the incidence of AKI between an extended beta lactam, piperacillin-tazobactam plus vancomycin with a carbapenem (meropenem) plus vancomycin. Our analysis found that the use of the piperacillin-tazobactam and vancomycin combination was associated with a statistically significant increased incidence of AKI compared to the meropenem-vancomycin combination. This finding occurred despite the observation that the patients in the meropenem and vancomycin group were significantly more likely to have been in the intensive care unit, had a higher average creatinine and had received contrast dye.

Among patients who developed renal insufficiency on piperacillin-tazobactam and vancomycin, the biggest predictor of renal insufficiency was an elevated vancomycin trough. More specifically, patients with troughs over 15 and 20 mcg/mL were more likely to have developed renal insufficiency. However, the authors did not find an association with other nephrotoxic agents and renal insufficiency. Among those patients who had developed nephrotoxicity in the meropenem-vancomycin group, there was a trend toward elevated trough levels, although our sample size was too small to test this pattern for possible statistical significance.
Since vancomycin is a common component of empiric dual antibiotic regimens where MRSA, gram negative and anaerobic coverage is sought, examining incidence rates of AKI with various vancomycin combination therapies is important. In this study, AKI incidence was significantly greater in the vancomycin and piperacillin-tazobactam group compared to the vancomycin-meropenem group (table 1).

To our knowledge, this is the third published study examining the differential rates of AKI with these two commonly used antibiotic combinations across multiple disease states. A single center retrospective study comparing the nephrotoxicity of vancomycin plus meropenem in 75 patients with vancomycin plus piperacillin-tazobactam in 108 patients was unable to demonstrate statistical significance.7 However, the results of another prospective study demonstrated statistical significance in comparing AKI in a group that had received vancomycin plus either meropenem or cefepime with a group that received PT-vancomycin.14

The specific mechanism of action linking increased incidence of AKI with the combination of PT-vancomycin remains unknown. The two identified mechanisms of AKI, namely acute interstitial nephritis with piperacillin-tazobactam and direct cellular necrosis with vancomycin may interact either additively or synergistically. Additional studies are needed to further elucidate and validate this hypothesis.

Despite the risk of nephrotoxicity associated with piperacillin-tazobactam and vancomycin, switching to alternative regimens that cover MRSA and Pseudomonas carries significant AKI risks as well. Previous studies have demonstrated cefepime and vancomycin as carrying less of a risk for nephrotoxicity.12,14 However, cephalosporins have been demonstrated to carry a higher risk of contributing to Clostridium difficile infections.24 Although our study results demonstrated a decreased risk of renal insufficiency in the meropenem-vancomycin group, meropenem should still be used with caution due to a potential rise in organisms carrying Klebsiella producing carbapenemases (KPC).26 The rationale for this being that KPC organisms cause resistance in almost all beta-lactam antibiotics.26 A future study examining piperacillin-tazobactam and other anti-MRSA antibiotics (such as linezolid or daptomycin) should be considered. Finally, an additional consideration would be to encourage discontinuation of
vancomycin when possible, as IDSA antimicrobial stewardship guidelines encourage narrowing of therapy, if clinically appropriate.27

This study illustrates the challenges associated with antimicrobial usage in complex clinical scenarios. Antibiotic stewardship has become increasingly important in the age of multi-drug resistant infections. Strategies such as de-escalation of antibiotic therapy and reducing unnecessary antibiotic usage are also important in reducing unintended side effects.27 Alternative strategies of piperacillin-tazobactam have also been discussed and could potentially have an effect on patients’ renal function.26

This study has several limitations that are worth noting. Data were collected retrospectively from a convenience sample without the benefit of blinding from the electronic health record. Our retrospective design also made it difficult for us to ensure the comparability of the two study groups. In fact, we realized that there were likely confounding differences in disease severity and complexity between patients who received either the vancomycin-PT combination or the vancomycin-meropenem combination that also could have influenced renal function. Still, we attempted to control for potential confounders by including concomitant use of nephrotoxic drugs and illness severity (as reflected by the Charlson Comorbidity Index).

We believe that our findings, combined with those of previous studies,10 should prompt further investigation in this area primarily since the antibiotic combinations investigated here are so very commonly used in numerous hospitalized patients across the United States. Although the incidence of AKI was relatively low when vancomycin was solely used, patient receiving the combination of vancomycin and piperacillin-tazobactam had a significantly increased risk of developing AKI.

CONCLUSIONS

In conclusion, this study demonstrated an increased risk of developing AKI with the combination of vancomycin and piperacillin-tazobactam compared to the combination of vancomycin and meropenem. Research groups have not yet definitively identified the specific mechanism underlying the increased incidence of AKI with the piperacillin-tazobactam and vancomycin combination regimen. Larger robust studies are required
before national groups can formulate conclusive clinical guidelines with respect to use of vancomycin in combination with piperacillin-tazobactam.

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The authors declare no conflict of interest.

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REFERENCES


# Tables and Figures

## Table 1:
**Comparison of Piperacillin/tazobactam with Vancomycin Versus Meropenem with Vancomycin**

<table>
<thead>
<tr>
<th></th>
<th>Piperacillin-tazobactam (N=292)</th>
<th>Meropenem (N=74)</th>
<th>p-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>65.3±15.5</td>
<td>60.3±16.1</td>
<td>0.013</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>168 (60.0%)</td>
<td>35 (47.3%)</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>ICU during hospital stay</strong></td>
<td>46 (15.8%)</td>
<td>23 (31.1%)</td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td><strong>Baseline creatinine (mg/dL)</strong></td>
<td>0.92±0.28</td>
<td>0.88±0.32</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Vancomycin trough &gt; 15 mcg/mL</strong></td>
<td>130 (44.5%)</td>
<td>30 (40.5%)</td>
<td>0.60</td>
</tr>
<tr>
<td><strong>Vancomycin trough &gt;20 mcg/mL</strong></td>
<td>64 (21.9%)</td>
<td>21 (28.4%)</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>WBC (mm³)</strong></td>
<td>14.0±6.8</td>
<td>13.0±9.3</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Diabetic</strong></td>
<td>123 (42.1%)</td>
<td>36 (48.6%)</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>NSAID</strong></td>
<td>30 (10.3%)</td>
<td>5 (6.8%)</td>
<td>0.39</td>
</tr>
<tr>
<td><strong>ACE Inhibitor</strong></td>
<td>101 (34.6%)</td>
<td>26 (35.1%)</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Loop diuretic</strong></td>
<td>138 (47.3%)</td>
<td>40 (54.1%)</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>IV contrast</strong></td>
<td>91 (31.2%)</td>
<td>37 (50%)</td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td><strong>Charlson score</strong></td>
<td>2.8±2.4</td>
<td>2.2±1.9</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Creatinine &gt; 1.5 x baseline or 0.5 increase</strong></td>
<td>74 (25%)</td>
<td>8 (9.5%)</td>
<td><strong>0.008</strong></td>
</tr>
</tbody>
</table>

*p-value calculated by two-tailed Fischer exact probability unless otherwise specified

^p-value calculated by Chi-square test
Table 2:
Patients with Renal Insufficiency Versus No Renal Insufficiency

<table>
<thead>
<tr>
<th></th>
<th>Renal insufficiency</th>
<th>No renal-insufficiency</th>
<th>p-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Piperacillin-tazobactam</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>65.7</td>
<td>64.6</td>
<td>0.62 ^</td>
</tr>
<tr>
<td>Gender</td>
<td>45/74 (60.8% male)</td>
<td>122/218 (55.6%)</td>
<td>0.50</td>
</tr>
<tr>
<td>ICU</td>
<td>15/74 (20.3%)</td>
<td>31/218 (14.2%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Baseline creatinine (mg/dL)</td>
<td>0.92</td>
<td>0.90</td>
<td>0.71 ^</td>
</tr>
<tr>
<td>Vancomycin trough &gt; 15 mcg/mL</td>
<td>46/74 (62.2%)</td>
<td>83/218 (38.1%)</td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>Vancomycin trough &gt;20 mcg/mL</td>
<td>31/74 (41.9%)</td>
<td>34/218 (15.6%)</td>
<td><strong>&lt;0.001</strong></td>
</tr>
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<tr>
<td><strong>Meropenem</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>60.8</td>
<td>58.3</td>
<td>0.73 ^</td>
</tr>
<tr>
<td>Gender</td>
<td>5/8 (62.5%)</td>
<td>30/66 male (45.5%)</td>
<td>0.46</td>
</tr>
<tr>
<td>ICU</td>
<td>4/8 (50%)</td>
<td>19/66 (28.8%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Baseline creatinine (mg/dL)</td>
<td>1.16</td>
<td>0.82</td>
<td><strong>0.009 ^</strong></td>
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<tr>
<td>Vancomycin trough &gt; 15 mcg/mL</td>
<td>6/8 (75%)</td>
<td>24/66 (36.4%)</td>
<td>0.055</td>
</tr>
<tr>
<td>Vancomycin trough &gt;20 mcg/mL</td>
<td>4/8 (50%)</td>
<td>17/66 (25.8%)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

* p-value calculated by two-tailed Fischer exact probability unless otherwise specified
^ p-value calculated by Chi-square test
Table 3: Risk of Renal Failure with Vancomycin in Combination with Meropenem Versus Piperacillin-Tazobactam

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Odds ratio</td>
<td>0.3571</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.1637 to 0.7787</td>
</tr>
<tr>
<td>z statistic</td>
<td>2.589</td>
</tr>
<tr>
<td>Significance level</td>
<td>$P=0.008$ $^\wedge$</td>
</tr>
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</table>

$^\wedge$ p-value calculated by two-tailed Fischer exact probability