Abstract

Background: In India, there is a high prevalence of ESBL producing organisms among intraabdominal isolates and in stool flora of ‘normal’ individuals. Hence, it may be presumed that unless antimicrobial therapy effective for ESBL flora is used perioperatively for abdominal surgery, the outcome will be adverse. We selected patients surgically treated for appendicitis as a model to explore the relevance of ESBL producing isolates in this retrospective observational study.

Aims and objectives: To assess the impact of ESBL producing isolates in patients surgically treated for acute appendicitis and to determine whether the perioperative antibiotic use needs to be changed in view of the high ESBL prevalence.

Method: Chart review of 221 consecutive patients who had undergone appendicectomy between January 2004 and December 2009.

Results: 55 of 221 patients had cultures of relevant specimens done based on the discretion of the treating surgeon. 40 yielded 1 or more organisms. 19 showed ESBL producing Enterobacteriaceae (ESBL +) and 21 showed non ESBL producing Enterobacteriaceae (ESBL -).

118 of 221 patients had presented without any complications and had a good outcome after surgery. The other 33 of 221 patients had complications like perforation or an abscess at presentation. Out of these, 16 patients received inappropriate therapy and 17 received appropriate therapy. The patients with appropriate therapy had good outcome. Among the 16 patients with inappropriate therapy 15 were ESBL + and 1 was ESBL -. Out of the 15 ESBL + isolates, 9 developed an initial postoperative complication like postoperative fever or wound infection. The cultures of the relevant specimen were done in all these 9 patients, all of which were positive. Therapy was changed in 7 of these 9 patients to pathogen directed therapy like amikacin, chloramphenicol and levofloxacin. Meropenem was used in only one case. All these 7 patients as well as the 2 patients whose treatment was not changed made a complete recovery.

Conclusion: For patients surgically treated for acute appendicitis, a change of perioperative antibiotics to those effective for ESBL + organisms is not needed at present only on the basis of ESBL prevalence rates. Routine cultures may not be necessary. Cultures are needed if there is a complication such as an abscess or perforation at presentation or an initial postoperative complication. A change to pathogen directed therapy, including even to older or non β-lactam antimicrobials may be needed in these cases. Our results support continuing the use of older antimicrobials rather than changing to carbapenems and β-lactamase-β-lactamase inhibitor combination in low risk surgically treated patients. This may prevent generation of further resistance without compromising outcomes.

Introduction

Resistance among the gram-negative bacteria is increasing all over the world. In India, the prevalence of ESBL producing organisms among gram-negative intraabdominal isolates is 60-70%. A significant proportion of stool flora of ‘normal’ individuals coming for health check also reveals ESBL flora. Hence, it may be presumed that unless antimicrobial therapy effective for ESBL flora is used perioperatively for abdominal surgery, the outcome will be adverse. This world entails the use of carbapenems or a β-lactamase-β-lactamase inhibitor combination for almost all patients which may generate further resistance.

Aims and Objectives

We selected appendicitis as a model to explore the relevance of ESBL producing isolates. Patients with appendicitis are in general younger, have less comorbidities and source control with surgery is easier. We assessed whether patients received appropriate or inappropriate perioperative antimicrobials and whether the receipt of inappropriate therapy impacted outcome in this observational retrospective study at a tertiary care private teaching hospital.

Patients and Methods

Charts of 221 consecutive patients who had undergone appendicectomy between January 2004 to December 2009 and had histologically proven appendicitis were selected for the study. The treating surgeons had obtained cultures when they thought was necessary and prescribed perioperative antimicrobials on the basis of their discretion. Additionally patients who had an initial post operative complication defined
Cefuroxime + metronidazole changed to Cefoperazone sulbactam 2
Superficial wound infection
Enterococcus 3
Staphylococcus 1
Enterobacter 2
Non ESBL Klebsiella 2
ESBL Klebsiella + Pseudomonas 2
ESBL Klebsiella 1
ESBL Klebsiella + Pseudomonas 2
Non ESBL E.coli 1
Enterobacter 2
Staphylococcus 1
Enterococcus 3
c
Cefuroxime + metronidazole changed to meropenem 1
Cefuroxime + metronidazole with added Amikacin 1
Cefuroxime + metronidazole changed to Linezolid 1
Cefuroxime + metronidazole changed to Chloramphenicol 1
Cefuroxime + metronidazole changed to Amoxicillin-clavulanic acid 1
Cefoperazone sulbactam 1

Table 2 : Perioperative antimicrobials

<table>
<thead>
<tr>
<th>Antimicrobials</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Cefazolin or Cefuroxime) + Metronidazole</td>
<td>165</td>
</tr>
<tr>
<td>Ceftriaxone + Metronidazole + Amikacin</td>
<td>34</td>
</tr>
<tr>
<td>Ciprofloxacin + Metronidazole</td>
<td>13</td>
</tr>
<tr>
<td>Amoxicillin-clavulanic acid</td>
<td>7</td>
</tr>
<tr>
<td>Cefoperazone sulbactam</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 3 : Initial post operative complications

<table>
<thead>
<tr>
<th>Reason</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial wound infection</td>
<td>3</td>
</tr>
<tr>
<td>Fever</td>
<td>2</td>
</tr>
<tr>
<td>Superficial wound infection + fever</td>
<td>3</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 4 : Change to pathogen directed therapy

<table>
<thead>
<tr>
<th>Change to antimicrobial therapy</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefuroxime + Metronidazole changed to Cefoperazone sulbactam</td>
<td>2</td>
</tr>
<tr>
<td>Cefuroxime + Metronidazole changed to Chloramphenicol</td>
<td>2</td>
</tr>
<tr>
<td>Cefuroxime + Metronidazole changed to Linezolid</td>
<td>1</td>
</tr>
<tr>
<td>Cefuroxime + Metronidazole with added Amikacin</td>
<td>1</td>
</tr>
<tr>
<td>Cefuroxime + Metronidazole changed to Meropenem</td>
<td>1</td>
</tr>
</tbody>
</table>

as wound infection or significant fever subsequently had cultures of relevant specimens done. All of these patients but one, subsequently received pathogen directed therapy based on the result of culture.

Results

Of the 221 patients analyzed, 55 (25%) patients had cultures of relevant specimens done based on the discretion of the treating surgeon. Out of these 55 patients, 40 (73%) yielded 1 or more organism as shown in Table 1.

Of these 40 isolates, 19 (48%) were ESBL producing Enterobacteriaceae and 21 (52%) were non-ESBL producing organisms.

Perioperative antimicrobials were prescribed as shown in Table 2.

118 of 221 patients had presented without any complications and had a good outcome after surgery. Of the 33 patients who had a complication such as abscess or perforation at the time of presentation, 24 made an uneventful recovery while 9 had an initial post operative complication as shown in Table 3.

These 9 patients had cultures of relevant specimens sent subsequently, all of which were positive. All these 9 patients with initial postoperative complications had initially received ESBL inappropriate therapy. This was later changed in 7 patients to pathogen directed therapy as shown in Table 4. In 2 patients with ESBL + isolates and an initial postoperative complication, the outcome was good although the initial inappropriate therapy was continued (Fig. 1).

Discussion

In patients undergoing appendicectomy for acute appendicitis, antimicrobial therapy provides surgical wound prophylaxis, treatment of pathogens potentially disseminated during the procedure and in addition ongoing therapy for the infection.

In the majority of patients in this study, no cultures were done. The patients could have therefore received discordant therapy going by the basis of high prevalence of ESBL producing isolates from intra abdominal infections. Yet the outcome with surgery was favorable in all but 9 who had an initial post operative complication. These 9 patients were among the 33 who had presented with a complication. The eventual outcome was however favorable in all 221 patients.

The result of the study raise doubts about the need for routine cultures; relevance of ESBL producing bowel flora in patients surgically treated for appendicitis and need for concordant therapy. Culture results are in any case not available to design initial empiric therapy. They are of help however to escalate antimicrobial therapy in cases with an adverse outcome or to select step down to oral therapy. Finally, cultures are the only way to track local epidemiological changes.

There may be a plausible reason for success even with seemingly inappropriate therapy. The various phylogenetic types of E coli in the host have an inverse virulence and resistance relationship. In cases with an initial post operative complication a favourable outcome was achieved by changing treatment to pathogen directed therapy or even without it. The changed therapy included older antimicrobials like amikacin, chloramphenicol and levofloxacin. Meropenem was used in only one case. This calls into question the recommendation to exclusively use carbapenems for ESBL + producing infections.

This study has important limitations. It included patients treated over a period of six years during which time the susceptibility of bowel flora could have changed. It was an observational study and not randomized, controlled or protocol driven. Antimicrobials were prescribed at the discretion of the treating surgeons initially and changed if there was an...
initial adverse outcome on the basis of the susceptibility of the organism. Some of the patients had received antimicrobials prior to hospitalization which could have impacted the outcome. However, the study reflects the real life situation in clinical practice.

Also these results pertain to patients with acute appendicitis only. Caution needs to be applied to extend these results to other patients who may have more complex intra abdominal disease, be less amenable to source control and may have more co-morbidities. It can be argued that the exclusive use of antimicrobials providing activity against ESBL producing flora in this study would have improved the outcome further, lessened the need for a subsequent source control procedure and reduced the length of stay. However, such a hypothesis has never been examined in a prospective fashion. Such a practice would involve the use of carbapenems or other agents effective for ESBL flora for all the patients, including the majority who had a favorable outcome without them.

**Conclusion**

On the basis of this study for patients surgically treated for appendicitis:

1. Empiric change of perioperative antibiotics is not needed at present for ESBL producing Enterobacteriaceae only on the basis of ESBL prevalence rates.
2. Routine cultures may not be necessary.
3. Cultures are needed if there is a complication such as an abscess or perforation at the time of presentation or if there is an initial post operative complication.
4. A change to pathogen directed therapy, even to older antimicrobials or non β-lactam antimicrobials may be needed in these cases.

Our results support continuing the use of older antimicrobials rather than changing to carbapenems and β-lactamase-β-lactamase inhibitor combination in low risk surgically treated patients. This may prevent generation of further resistance without compromising outcomes.

**References**