A randomized trial of one versus three doses of Augmentin as wound prophylaxis in at-risk abdominal surgery

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Summary: In a randomized prospective trial of prophylactic antibiotics in at-risk abdominal surgery, one dose of intravenous Augmentin (amoxycillin 250 mg and clavulanic acid 125 mg) on induction has been compared with three 8 hourly doses in 900 patients. Wound infection rates which included minor and delayed infections were very similar in those given one dose: 48/449 (10.7%) compared with those given three doses: 49/451 (10.9%) 95% confidence limits – 4.25% + 3.9%.

There were more septic and sepsis-related deaths in those patients given one dose (14 deaths) than in those given three doses (7 deaths) \( P > 0.1 \) 95% CL – 0.4% + 3.0%. However, there were more very elderly patients in the one dose group: 64% of the deaths were aged over 80 and all but one had an emergency operation. There was no difference in the other outcome measures studied which included non-fatal deep sepsis, length of postoperative hospital stay, duration of postoperative fever or the use of antibiotics for postoperative infection.

One dose of a suitable intravenous antibiotic gives prophylaxis against wound infection in at-risk abdominal surgery which is at least as effective as multiple doses. However, there may be a risk of overwhelming systemic sepsis in very elderly patients having emergency surgery.

Introduction

The idea of a single dose of a prophylactic antibiotic in at-risk abdominal surgery was first examined over a decade ago\(^1\)\(\text{-}\)\(^5\) and there are now numerous studies in the literature. However, many trials have tested a single dose of one agent against multiple doses of one or more other agents\(^6\) and few have achieved as many as 100 patients\(^7\)\(\text{-}\)\(^14\) in each arm of a randomized trial. Most studies have shown no significant difference between single and multiple dose regimes but there is a risk of a Type II error in concluding there is no difference when a real one exists, where small numbers are examined. We therefore set out to study a large number of patients in two hospitals within the same health district.

An agent, amoxycillin 250 mg/clavulanic acid 125 mg (Augmentin), was chosen which has been shown to be at least as effective as other single or multiple agents for prophylaxis in at-risk abdominal surgery.\(^15\)\(\text{-}\)\(^18\)

Patients and methods

Eligibility

All patients aged 16 or over admitted under two surgical firms at two adjacent district general hospitals for at-risk abdominal surgery with potential opening of a viscus were admitted to a prospective randomized trial. At-risk abdominal surgery included all appendicectomies, and all open gastric, oesophageal, colonic or biliary surgery. All patients coming to laparotomy for intestinal obstruction including that due to strangulated hernia were entered into the study as well as patients with intra-abdominal malignancy.

Exclusions (before randomization)

All patients known to be allergic to penicillin were excluded. If patients had received antibiotics within the previous 48 hours or if the surgeon considered that pre-operative antibiotics were essential they were also excluded. Patients who declined consent were not entered into the trial although all received prophylactic antibiotics.

Trial design

Eligible patients were randomly allocated to one or three doses of antibiotics by taking sequentially numbered stickers prepared from a table of random numbers. The first dose was given on induction of anaesthesia and those patients randomized to three doses received two additional injections 8 and 16 hours later.

Those patients found to have a purulent peritonitis were withdrawn from the study for
ethical reasons and were treated in the following way. Those patients randomized to one dose were
given eight doses of antibiotics while those ran-
domized to have three doses had no change of
antibiotic treatment.

The antibiotics

Augmentin is a 1:10 combination of amoxycillin
and clavulanic acid. Clavulanic acid is an inhibitor
of many bacterial beta lactamases and greatly
increases the active spectrum of amoxycillin includ-
ing Bacteroides sp. The trial drug was administered
by slow intravenous bolus injection as 1.2 g of
powder dissolved in 10 ml water.

Losses

All eligible patients who were not entered into the
trial were recorded and completeness was cross-
checked with the operating theatre records.

Withdrawals (after randomization)

Those patients who were ineligible on the protocol
were withdrawn together with those cases in which
the operation was cancelled after randomization.
Patients found to have faecal peritonitis were
withdrawn from the study so that treatment
options were free.

Deviations

The categories of patients who were not withdrawn
after randomization are as follows. Dose violations
were recorded if antibiotic doses were omitted or
delayed. Some patients received additional antibi-
totics either in continuity with the protocol doses
or after an interval. Those patients in whom the
operative findings did not necessitate opening a
viscus and those patients with missing data were
included in the study.

| Table I  | Reasons for withdrawal from the study |
| --- | --- | --- | --- |
| No operation | 5 | 7 |
| Pre-operative antibiotics | 4 | 6 |
| Operation not in criteria | 14 | 14 |
| Allergy to penicillin | 0 | 5 |
| Faecal peritonitis | 0 | 2 |
| Purulent peritonitis |
| (peritonitis protocol) | 5 | 7 |
| Total | 28 | 41 |

Concentration of drugs in plasma and tissue

In 23 patients plasma levels of amoxycillin and
clavulanic acid were measured at the time of skin
incision, at the time of skin closure and at 8 hours.
In eight patients drug levels in wound edge fat were
also measured at the time of wound closure.

Follow-up

All patients were seen at about one month post-
operatively and were specifically asked if there had
been any wound discharge after they left hospital.
If the outpatient record of wound status was equivocal, patients were contacted by telephone or
letter.

Risk factors

The following variables were considered: age, sex,
body mass index [BMI = weight in kg/(height in
metres)]², diagnostic category, degree of peri-
tonitis, grade of surgeon and dose violation (omit-
ted or delayed). Where sepsis found at operation
was considered to require continuation of antibiotics, continuous antibiotics were sometimes
given instead of the peritonitis protocol (3 versus 8
doses).

Outcome events

The outcome was assessed as follows: wound sepsis
was categorized as major, minor or late (criteria of
Pollock & Evans) and deep sepsis was recorded
separately. The causes of death within 30 days were
categorized as septic, sepsis-related (for example,
mesenteric infarction) or not septic (for example,
terminal malignancy, even if this occurred at
home). The number of postoperative days in which
fever was noted to be > 37.5°C was recorded.
Postoperative infection requiring antibiotics (inter-
val antibiotics) was considered an outcome event.
Length of postoperative hospital stay included the
day of discharge but not the day of operation.
Formal outcome evaluation of each patient was
completed and agreed between at least two authors
who were unaware of the number of antibiotic
doses given.

Consent

The trial protocol was approved by the district
ethical committee and all patients signed consent to
the investigation after verbal and written explana-
tion.
**Estimation of required sample size**

In order to estimate the number of patients required in each arm of the study to avoid a Type II error the following assumptions were made. The proportion of events was estimated to be 20% and a clinically important reduction would be from one-third to 13%. Using Feinstein’s formula with alpha 0.05 and beta 0.20, it was calculated that 437 patients would be needed in each arm of the trial.

**Statistical analysis**

Statistical analysis was performed using the Solo 101 statistical program (BMDP Statistical Software, Los Angeles, California, USA) on an Apricot Qi 650t microcomputer (Apricot Computers, Birmingham, UK). Data was entered on to a relational database management system (Paradox V3, Bolland International, Scotts Valley, California, USA) to ensure data integrity and transferred for statistical analysis. This allowed comparison of risk factors and outcomes. The two sample proportional test was used in most statistical comparisons testing at the 0.05% level.

**Results**

There were 995 eligible patients available for the study between May 1986 and June 1988. Over the same period 108 otherwise eligible patients were excluded: 60 patients had had antibiotics within 48 hours; 41 patients were said to be allergic to penicillin; and seven patients declined consent.

There were 18 losses of eligible patients due to administrative failure and there were 69 withdrawals of ineligible patients for reasons shown in Table I which included 12 patients with severe peritonitis who were re-allocated to the three versus eight dose protocol leaving 908 patients for analysis. Eight patients who died within 48 hours were not included in the wound infection analysis leaving 900 patients.

**Risk factors**

The two groups were well matched for risk factors (Table II) and for the numbers in each diagnostic category except that there were more patients over 80 years in the one dose group and there were more patients in this group with a normal appendix (Table II). There were more delayed or missed doses in those patients randomized to receive three doses (Table IV).

**Table II** Comparison of risk factors for wound infection between the two groups

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>One dose</th>
<th>Three doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 80 years</td>
<td>57</td>
<td>46</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>56 (21.8)</td>
<td>54.4 (21.6)</td>
</tr>
<tr>
<td>Males</td>
<td>186</td>
<td>195</td>
</tr>
<tr>
<td>BMI &lt; 26</td>
<td>221 (50%)</td>
<td>240 (53%)</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>100</td>
<td>110</td>
</tr>
<tr>
<td>(n = 446)</td>
<td></td>
<td>(n = 450)</td>
</tr>
<tr>
<td>Sepsis at operation (other than appendicectomy)</td>
<td>39 (11.6%)</td>
<td>37 (11.7%)</td>
</tr>
<tr>
<td>Appendix inflamed</td>
<td>71 (62%)</td>
<td>101 (76%)</td>
</tr>
<tr>
<td></td>
<td>(n = 114)</td>
<td>(n = 133)</td>
</tr>
<tr>
<td>Dose violation</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Continuous antibiotics</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Registrar operation</td>
<td>224</td>
<td>229</td>
</tr>
</tbody>
</table>

**Wound infection**

The overall wound infection rates were similar in both groups being 10.7% in patients receiving one dose and 10.9% in those receiving three doses (Table V). There was no difference in wound infection rates between the two hospitals when diagnostic categories were compared. There was a higher wound infection rate after appendicectomy in the three dose group and a lower rate after colorectal and biliary operations but none of these differences approached statistical significance. Major wound infection occurred in 3.9% of patients but 46% of wounds infections were delayed until after the patient left hospital. There was a non-significant trend to fewer major infections in the three dose group (15 vs 20) and more delayed infections (26 vs 19) but this was not reflected in postoperative pyrexia or length of stay.

**Other outcome**

There were more septic and sepsis-related deaths in those patients who only received one dose of antibiotics (14 vs 7 N.S.; see Table V).

The median age of these patients was 81 vs 79 years. Of the 14 deaths in the one dose group, nine patients were over the age of 80, eight of whom had an emergency operation and five patients developed a complication after major elective surgery. There were also more non-septic deaths in this group but this difference was not significant. There was no difference in any of the other outcome measures examined.

**Peritonitis protocol**

Twelve patients were treated with the peritonitis protocol, of which five were in the one dose group.
Table III  Diagnostic category and wound infection in the two groups

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>One dose Infected</th>
<th>One dose Total (%)</th>
<th>Three doses Infected</th>
<th>Three doses Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendix</td>
<td>11</td>
<td>114 (9.6)</td>
<td>21</td>
<td>133 (15.8)*</td>
</tr>
<tr>
<td>Colorectal</td>
<td>23</td>
<td>113 (20.4)</td>
<td>17</td>
<td>111 (15.3)$</td>
</tr>
<tr>
<td>Upper gastrointestinal tract</td>
<td>3</td>
<td>62</td>
<td>3</td>
<td>52</td>
</tr>
<tr>
<td>Biliary</td>
<td>6</td>
<td>96 (6.3)</td>
<td>3</td>
<td>99 (3.0)$</td>
</tr>
<tr>
<td>Small bowel</td>
<td>3</td>
<td>28</td>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td>Hernia (strangulated)</td>
<td>1</td>
<td>26</td>
<td>3</td>
<td>31</td>
</tr>
<tr>
<td>Laparotomy (no viscus open)</td>
<td>1</td>
<td>10</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>449 (10.7)</td>
<td>49</td>
<td>451 (10.9)$</td>
</tr>
</tbody>
</table>

*P > 0.01 95% CL (−14.3% + 2.0%); 1P > 0.2 95% CL (−4.6% + 15.2%); 2P > 0.2 95% CL (−2.7% + 9.1%); 3NS 95% CL (−4.25% + 3.9%).

Table IV  Deviations from the treatment protocol

<table>
<thead>
<tr>
<th>Deviation</th>
<th>One dose</th>
<th>Three doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced dose(s) antibiotics</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>No antibiotics</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Continuous antibiotics</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>Interval antibiotics</td>
<td>50</td>
<td>47</td>
</tr>
<tr>
<td>Missing data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Follow-up</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Height and follow-up</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

and received eight doses and seven were in the three dose group. The wound infection rates were 1/5 for those receiving eight doses and 4/7 for those receiving three doses of antibiotic. No death occurred nor was there an episode of deep infection.

Deviations

More patients in the group randomized to one dose continued to receive antibiotics in addition to the protocol (Table IV). Four patients were lost to follow-up, three having died at home before they could be reviewed.

Table V  Outcome of patients related to dose group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>One dose</th>
<th>Three doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound infection*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Minor</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Delayed</td>
<td>19</td>
<td>26</td>
</tr>
<tr>
<td>Total</td>
<td>48 (10.7%)</td>
<td>49 (10.9%)</td>
</tr>
<tr>
<td>Deep sepsis (non-fatal)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septic</td>
<td>7 (1)</td>
<td>2$</td>
</tr>
<tr>
<td>Sepsis-related</td>
<td>7 (1)</td>
<td>5 (1)$</td>
</tr>
<tr>
<td>Non-septic</td>
<td>17 (4)</td>
<td>10 (1)$</td>
</tr>
<tr>
<td>Total</td>
<td>31 (6)</td>
<td>17 (2)</td>
</tr>
<tr>
<td>Post-operative days of fever</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean* (days)</td>
<td>1.0</td>
<td>1.05</td>
</tr>
<tr>
<td>&gt; 10 days (patients)</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Length of postoperative stay</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean* (days)</td>
<td>9.4</td>
<td>10.2</td>
</tr>
<tr>
<td>15–29 days (patients)</td>
<td>44</td>
<td>49</td>
</tr>
<tr>
<td>30 + days (patients)</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td>Patients receiving interval antibiotics</td>
<td>30</td>
<td>47</td>
</tr>
</tbody>
</table>

*Figures in brackets denote death within 48 hours omitted for wound infection rates and means; 1P14 vs 7 septic or sepsis-related deaths – P > 0.1 95% CL (−0.4% + 3.0%); 1P > 0.2 95% CL (−0.7% + 3.45%).
Faecal peritonitis

Two patients from the three-dose group were withdrawn at the time of laparotomy for faecal peritonitis (Table I). One patient had a major wound infection but both survived.

Drug levels

The drug levels in serum and wound edge fat are detailed in Table VI.

Details of the microbiological isolates

Of those patients having a major wound infection whilst in hospital, 34 cultures were carried out and 20 showed a mixed growth of Gram-negative organisms. The most common organisms isolated were coliforms (23), Bacterioides (20), Proteus (5), Pseudomonas (3) and Enterococcus (3). Staphylococcus aureus was the sole organism isolated in only three out of 12 cultures and only one of these three was coagulase positive.

Of those patients having a delayed wound infection after leaving hospital, 38/44 (86%) did not have a wound culture carried out. Three of the six cultures showed a mixed growth of Gram-negative organisms, two grew Staphylococcus aureus and one was sterile.

There were only four positive cultures in patients with deep sepsis in the absence of a wound infection. All grew Coliform organisms and three showed Bacterioides sp. in addition.

Discussion

Although no formal meta-analysis of one versus three doses of antibiotics has been carried out except in biliary tract surgery,22, the present study adds weight to the conclusion from DiPiro’s review of the literature6 that there is no advantage to giving more than one dose in terms of wound prophylaxis or deep infection.

There were more septic and sepsis-related deaths in the one dose group but this may have been due to the greater number of very elderly patients in this group. A total of 64% of these deaths were of patients over 80 and all but one had an emergency operation. However, the possibility that sepsis-related death may be more common in those patients only receiving one dose is not excluded. This has not been noted in previous trials8,9,12–14 but mortality has not always been reported.7,10,11 There was no death in those patients with purulent or faecal peritonitis but all these patients received at least three doses.

Of those patients with purulent peritonitis, there were fewer wound infections in those patients receiving eight compared with three doses but the numbers were too small to draw any conclusion from this group.

The overall wound infection rate was lower than in our most recent study23 and it is possible that more attention has been paid to surgical discipline in the present study. The difference is partly explained by the addition of all biliary cases to the present study instead of a selective policy but the levels of infection are still high compared with some reports.8,10,11,24

The levels of clavulanic acid in the wound fat at the time of wound closure were much lower than that found by Pollock et al.25 although the methods and the assay were apparently the same. This study showed an advantage to giving a prophylactic injection of Augmentin into the site of the incision versus intravenously, although this was not shown in a previous experimental model.26

It seems unlikely that a reduction in wound infection rates will be achieved by variations in the dosage regimes of the current generation of antibiotics and, although improved technique probably is an important factor, it is difficult to explore this by a randomized trial. However, the reduction of wound infection rates over time underlines the risks of using historical controls.

Multiple dose regimes of prophylactic antibiotics are still widely used in clinical practice and the present study confirms that there is no justification for this practice with the sole possible exception of the very elderly having emergency abdominal surgery.

Table VI Serum levels of antibiotics in serum and fat perioperatively

<table>
<thead>
<tr>
<th></th>
<th>Incision serum (n = 23)</th>
<th>Closure serum/ fat (n = 23/8)</th>
<th>8 hours serum (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxycillin, mean (± SD) (μg/ml)</td>
<td>41.2 (29)</td>
<td>5.2 (4)/1.5 (2)</td>
<td>4.2 (7)</td>
</tr>
<tr>
<td>Clavulanic acid, mean (± SD) (μg/ml)</td>
<td>5.2 (4)</td>
<td>2.5 (2)/*</td>
<td>0.4 (0.6)*</td>
</tr>
</tbody>
</table>

*All but two samples below lower limit of assay 0.23 μg/ml; *seven samples below lower limit of assay 0.08 μg/ml.
Acknowledgements

We thank Mr D. Keown, Mr N.J. Griffiths and Mr C. Derry for permission to study patients under their care.

We thank Mr M. Gleeson, Mr C. Holcombe and Mr C. Couch for their help with the trial.

We also thank Dr R. Horton of Beecham Pharmaceuticals for the amoxycillin and clavulanic acid assays.

References

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Notes

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It is no easy task to compress information about a major subject into a handbook which is small enough to fit into the pocket of a white coat. Professors Niswander and Evans have managed to achieve this task excellently. They and their publishers have also been able to include sufficient diagrams and illustrations to stop this little book from being boring, and there is the wealth of references that one expects from a North American production.

The manual is divided into four sections. These deal with pregnancy (in 20 chapters), the fetus (in six chapters), labor (sic) and delivery (in six chapters), and the newborn (in five chapters). There is a fairly comprehensive index, although there was no reference to cord prolapse – which is dealt with in the text on page 451.

This book is aimed primarily at students and house officers. To ensure that the subject matter was appropriate for this readership, the unusual decision was taken to invite senior house officers and young attending physicians to write some of the chapters – although only seven of the 30 contributors are professors. This strategy has resulted in a most useful manual. Its usefulness is enhanced by its being spiral bound. It is highly recommended.

A.M. Weindling
Department of Child Health, University of Liverpool, Mersey Regional Neonatal Intensive Care Unit, Liverpool Maternity Hospital, Oxford Street, Liverpool L7 7BN.


This little book gives excellent up to date advice on all common medical and surgical emergencies likely to be encountered. It gives practical hints on how to deal with those small problems which inevitably arise when a senior opinion is unavailable. The format of succinct descriptions together with useful line diagrams makes the book readable and informative.

Appropriate management and disposal of conditions, often a cause of great concern to the junior doctor working in accident and emergency (A&E), is clear and precise. The inclusion of algorithms for the management of chest pain, multiple injuries and the Mental Health Act, to name three, give a clear indication of how to deal with some difficult aspects of emergency medicine. The sections concerned with the management of patients suffering from multiple injuries and poisoning are particularly informative. The section on medico-legal aspects highlights, in a readable fashion, an increasingly important aspect of medicine.

This book is recommended as essential reading for all doctors involved in the management of acutely ill and injured patients, not only those working specifically in the accident and emergency department. Ideally it should be read before dealing with emergencies but its small size allows it to fit comfortably into a white coat for a rapid source of reference.

M. Hunt
Accident and Emergency Department, Basildon Hospital, Basildon, Essex SS16 5NL.

Erratum


The Editorial Office apologises for an error in the doses of the constituents of Augmentin used. The correct dose of amoxycillin and clavulanic acid in Augmentin intravenous (Co-amoxiclav) is 1 g and 200 mg respectively/ampoule.