'85 Symposium on Chemotherapy in Seoul

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Selected papers

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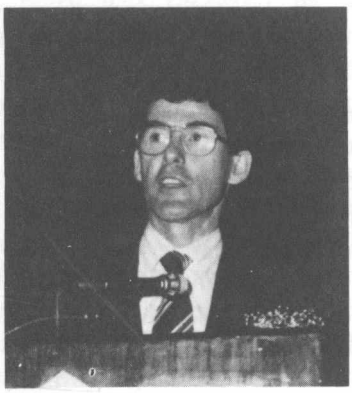

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Antibiotic prophylaxis in gastro-intestinal surgery

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INFECTION FOLLOWING GASTRIC SURGERY

The incidence of infection after various types of gastro-duodenal surgery was reported by Stone who noted that infection occurred after operations for duodenal ulcer in only 2% of the cases. However, there was a much higher rate of infection after surgery for gastric ulcer and gastric cancer. In our studies, we found that with patients requiring operations, high counts of gastric bacteria occurred when the pH of gastric secretion was in the order of 5, 6 and 7. We analysed the correlation between wound infection and bacteria counts in the stomach of a group of surgical patients who were not receiving antibiotics and found that in patients with counts greater than 5×10^6 organisms per ml, wound infection was almost inevitable. In the majority of patients with less than this density, however, wound infection rates were much lower.

Analysis of counts of bacteria according to pathology shows that patients with duodenal ulcer usually have sterile gastric content; those with gastric ulcer have counts with a median in the order of 1×10^5 organisms per ml; and in those with gastric cancer, the median counts exceeded 1×10^7 per ml organisms. Similarly high counts of bacteria were found in patients receiving H_2 antagonist drugs immediately prior to operation and in patients who had a previous gastrectomy.

We recently analysed the bacterial flora in patients with gastric carcinoma. *Bacteroides fragilis* was isolated from gastric juice in one-third of the patients. When we analysed the organisms responsible for post-operative sepsis, we discovered that *B. fragilis* was present in one-third of the isolates.

We conducted a clinical trial of the use of cefuroxime in patients having gastric resection for cancer. We found that in the non-treated group there was a 42% infection rate. When cefuroxime was used in the

wound topically, there was a reduction in infection to 26%, but when cefuroxime was given intravenously there was a significant reduction in the incidence of infection to 12%. Many of these residual infections were due to anaerobic bacteria.

I believe that patients with cancer, gastric ulcer, previous gastrectomy and patients receiving H_2 antagonist drugs need single dose, preoperative antibiotic cover with a cephalosporin. At our hospital, we have a policy of aggressive management for patients with bleeding peptic ulcer disease and we recognise that these are high risk patients with a clot in the lumen of the stomach. In a study of the use of a single dose of cefuroxime in patients with bleeding peptic ulcer disease, we recorded a wound infection rate of only 6%. In a recent study of antibiotic prophylaxis in gastro-oesophageal surgery we found that the lowest rate of infection was with the use of intravenous cefuroxime. We also advocate the use of metronidazole in combination with cefuroxime to reduce the risks of anaerobic infection.

INFECTION FOLLOWING BILIARY SURGERY

The most common organism isolated from infected bile is *Escherichia coli,* followed by enterococcus and then *Klebsiella aerogenes.* Anaerobic bacteria are rare in bile and are usually associated with *Clostridium perfringens* and anaerobic streptococci. Obligate anaerobes such as *B. fragilis* are very rare in bile.

When bile is infected, the counts of bacteria are very high, usually exceeding 1×10^7 organisms per ml, a similar bacteria inoculum to those found in gastric juice. A high incidence of bacteria in bile was found in patients requiring emergency cholecystectomy for acute fulminating cholecystitis with perforation. In elective operations on the biliary tract without antibiotic cover, the incidence of infection in bile was found to be 72% in jaundiced patients, particularly in patients with jaundice due to stones, whereas in malignant bile duct obstruction, the incidence was much lower.

We have correlated the aetiology of infection in biliary surgery and have found that approximately 64% of wound infections are due to an organism previously identified from the bile at the time of operation. Patients developing septicaemia as a complication of biliary disease almost always have an organism in the blood stream which is also present in the biliary tract. Hence the incidence of wound infection in patients receiving no antibiotic cover is a relatively low 10% in patients having cholecystectomy alone, but is 31% in patients having exploration of the bile duct, and higher still in patients requiring emergency operations for acute biliary disease.

Only one-third of patients undergoing biliary surgery have organisms in the bile at the time of the operation so they do not need a prophylactic antibiotic. If we provide no antibiotic cover, however, there is an unacceptably high incidence of infection to the majority of patients. Therefore, it would be advisable to identify patients with infected bile pre-operatively so that selective administration of antibiotics could be used. In a multivariate analysis of factors associated with bile infection, we identified several factors which were associated with a high risk of infection. These were: age (over 70 years); patients jaundiced at operation; patients requiring an emergency operation or operations less than four weeks after an acute episode of cholecystitis or cholangitis; patients having previous biliary operations; patients with a history of cholangitis less than one week before operations; and two operative findings – bile duct obstruction and stones in the common bile duct. Thus it is now our policy to provide antibiotics to such patients using a single dose of pre-operative cephalosporin. We found that gentamicin is successful, cephazolin is more successful but, in our own experience, cefuroxime is as good as cephazolin and is much cheaper, so we also use this agent in biliary surgery.

INFECTION FOLLOWING APPENDECTOMY

We surveyed the medical literature regarding wound infection rates in patients having appendectomy without any form of antibiotic therapy. We found that even when a normal appendix is removed, there may be a 15% incidence of infection. The rate is almost as high as that for patients having acute appendicitis. Therefore it is our policy always to give a single dose of antibiotic in patients having an appendectomy. Of course if the appendix is gangrenous or perforated, this administration is not for prophylaxis but for an established infection. In this case, I always prolong the antibiotic course for five days.

INFECTION FOLLOWING COLO-RECTAL SURGERY

Patients with cancer of the colon present a real problem in terms of preventing infection. Analysis of infection rate in a group of patients in 1973, when we were not using antibiotics, showed that over 50% developed a wound infection and that 8% died as a direct consequence of severe infection occurring post-operatively. When we analysed the organisms responsible we determined that *E. coli* was the commonest aerobic organism and that *B. fragilis* was the commonest anaerobe.

Indeed, the isolates of *B. fragilis* exceeded the isolation rate of the more usually recognised aerobic Gram-negative organisms.

I believe that prophylaxis begins by getting the colon clean. We used to starve and purge our patients and we would then wash out their rectums. This is still important because when we analyse the rate of intra-abdominal abcess or anastomotic breakdown in colo-rectal surgery according to the quality of mechanical bowel preparation, we find that in patients with a poor mechanical bowel preparation, the rate of post-operative breakdown or abcess is very high. When the mechanical bowel preparation is good, few patients have anastomotic breakdowns with serious intra-abdominal sepsis. It is impossible to determine, by rectal examination alone on the evening before the operation, whether the mechanical bowel preparation is satisfactory. We give our patients 50 small radio-opaque markers to take orally two days before operation when we commence our mechanical preparation. We then x-ray the patient on the evening before the operation and if many of the discs are apparent, we either cancel the operation or insist upon repeated rectal washouts to get the colon clean. If, however, there are just one or two markers in the rectal ampulla, we can continue with the operation the following day.

We use the intra-cavity end-to-end stapling device in colo-rectal operations to an increasing extent. This undoubtedly reduces the incidence of colostomy, both permanent and temporary, but the passage of this instrument through a dirty rectal ampulla is associated with a very high bacterial inoculum into the operation site. I therefore place our patients in the Lloyd-Davis position and use a rectal catheter so that the rectal ampulla can be washed with antiseptic solutions at the time of the operation. We have shown that, in this way, we can substantially reduce the bacterial flora of the rectal ampulla. The best results are achieved with sodium hypochlorite. The counts of *E. coli* and *B. fragilis* after washouts have been reduced drastically.

In colo-rectal surgery, it has been traditional for surgeons to use oral drugs such as phalasulphathiazole neomycin. More recently, combinations of neomycin with metronidazole or neomycin with erythromycin have been used for the prophylaxis of infection. In 1976, we conducted a randomized prospective clinical trial using kanamycin and metronidazole given either orally for two days pre-operatively, or intravenously at the time of the operation, giving three doses in the first 24 hours only. The purpose of oral antimicrobial prophylaxis was to reduce the colonic microflora without achieving serum concentrations of the drug, and the purpose of systemic antimicrobial prophylaxis was to achieve high blood and tissue levels without substantially influencing colonic microflora. Our results clearly demonstrated that only when the drugs were

systemically administered was there any significant reduction in the incidence of infection. In fact, we discovered a very high infection rate in the group receiving oral antimicrobial prophylaxis. We analysed the bacterial isolates in the infections of this group and found the commonest organisms responsible for infection were *E. coli* and *Staphylococcus aureus.* Infection from *B. fragilis* was also very common. In 12 isolates of *E. coli,* nine were resistant to kanamycin, as were five of seven isolates of *S. aureus.*

There have been other trials, and I know of at least one in Korea, which have also demonstrated that systemic antimicrobial prophylaxis was at least as good as the oral regimen and in two other centres, in England and Switzerland, advantages were shown when systemic agents were used for prophylaxis. Therefore in colonic surgery drugs should be given intravenously. Clearly, in a patient with a large intestinal obstruction, it is quite inappropriate to give agents orally or to use a mechanical preparation. Indeed, in all emergency operations, it is essential to use intravenous antimicrobials immediately prior to the operation, just before the skin incision is made.

One occasional complication of antimicrobial agents, particularly in colonic surgery, is the development of pseudomembraneous entercolitis. In our comparison of oral versus systemic antibiotic prophylaxis, we found that there was a much higher incidence of antibiotic-associated colitis in the group receiving oral antibiotics where the normal microflora of the colon were disturbed. In a series of experiments in healthy volunteer subjects who received only one dose of intravenous antibiotics, we demonstrated that the emergence of *Clostridium difficile* never occurred in patients receiving penicillins, but that there was an increasing emergence of *C. difficile* in patients receiving cephalosporins. This problem became particularly acute in patients receiving broad spectrum third-generation cephalosporins. Three of six volunteers receiving only one dose of latamoxef or moxalactam developed *C. difficile*, as did two of six receiving ceftriaxone and four of six receiving ceftazidime.

Over the past ten years, I have been able to audit the results of antimicrobial prophylaxis in colo-rectal surgery. Lincomycin produced reasonable results but we had to discontinue it because of pseudomembraneous entercolitis. Cefoxitin was associated with a high incidence of infections from the obligate anaerobes, and latamoxef or moxalactam was associated with serious problems from bleeding. Metronidazole and mezlocillin were associated with a high staphylococcal infection rate. Metronidazole and cefuroxime were unfortunately associated with infection from *Pseudomonas* spp. The best results have been with metronidazole and kanamycin, but here we had

to use three doses. With metronidazole (1.5 g) and ceftriaxone, a protein-bound cephalosporin which achieves very high blood levels over 24 hours, we were able to achieve high antibiotic concentrations, not just at the operation, but even 24 hours after surgical treatment.

Therefore, for prophylaxis in colo-rectal surgery, we should be using long-acting drugs as single dose peri-operative cover. In complicated colo-rectal surgery, such as a patient with fistulas from the colon to the skin, we do not consider antibiotics as prophylaxis, for we found in a clinical trial that, under these circumstances, it was necessary to give antibiotics for five days. In our experience, by using metronidazole and gentamicin for five days we were able to achieve a significant reduction in infection.

The choice of antibiotic for blind treatment of the new-born

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INTRODUCTION

For a number of reasons it is imperative that premature babies receive antibiotics at the first clinical sign of sepsis. The signs and symptoms of sepsis in the premature new-born baby are often subtle and obscure. Because of this it is not possible to diagnose infection clinically and babies who are subsequently shown to be infected cannot be distinguished from those who are not infected.

Bacteraemia is a common event amongst premature babies and meningitis is more common in this age group than at any other time of life; therefore, the consequences of any delay in initiation of chemotherapy may be disastrous. Because the progress of neonatal infection is so rapid, the introduction of antimicrobial chemotherapy cannot be delayed until culture results are available. In the absence of quick and reliable alternative methods for the diagnosis of infection, blind antibiotic treatment must be started at the first suspicion of infection.

CHANGES IN TREATMENT

Twenty years ago in Europe, the practice was to administer a mixture of ampicillin and cloxacillin to infants with clinical signs of sepsis. During the 1970s, the rate of infection caused by *Staphylococcus aureus* decreased while the number of coliforms resistant to ampicillin increased. Ampicillin and cloxacillin, therefore, became inappropriate therapy. Like many units throughout the world, the neonatal units in the U.K. turned to gentamicin combined with either ampicillin or penicillin as first-line treatment. Prior to that, gentamicin had been reserved for life threatening infections or diagnosed infection with a known sensitive organism. This change to the routine use of gentamicin in the1970s was perfectly reasonable, because at that time there was no

suitable alternative. During the last 10 years a number of new agents have become available and it is appropriate to reconsider whether the aminoglycosides are still the best antibiotics for the initial treatment of premature babies.

IDEAL CHARACTERISTICS

A number of characteristics are required of an antibiotic for use in the new-born. It should be *non-toxic,* not only because of the possibility of increased susceptibility of new-born babies to toxic drugs but also because a significant percentage of babies who receive treatment are subsequently shown not to be infected. The range of bacteria that affect the new-born baby is very wide and therefore the agent must have a *broad spectrum of activity*. So many infecting organisms produce β-lactamase enzymes that an agent must be *resistant to β-lactamase degradation.* The agent should also have a *high level of antibacterial activity,* i.e. a small amount of drug should inhibit microbial growth.

Ideally, an antibiotic would *penetrate into the cerebrospinal fluid* to control meningitis, which is more common in neonates than in any other patient group. An antibiotic should also *penetrate into soft tissue* and ought to be *bactericidal* in action because of the diminished immune responses of the premature neonate. Finally, since so little is known about the oral absorption of antibiotics in very small babies, coupled with the problems of regurgitation and aspiration, antibiotics should be *administered parenterally*.

VARIATIONS IN PATHOGENS

There is wide variety in the distribution and incidence of neonatal infection in different parts of the world. It is very apparent that the problems with infection that are encountered in Southeast Asia are quite different from those in Western Europe. For example, *Flavobacterium* spp., which are a frequent cause of neonatal infection in Southeast Asia, are almost unheard of in England. This serves to emphasize that in any discussion about antibiotics in a neonatal unit it is essential that the paediatricians and microbiologists collaborate so that their antibiotic policy reflects the local situation and experience. It is clearly a dangerous practice to simply copy a policy that has proved successful in another unit.

The organisms that are of concern in the U.K. are listed in Table 1. Because of its increased resistance to antibiotics, *Pseudomonas aeruginosa* will cause problems from time to time. A few neonatal units

TABLE 1

Common neonatal pathogens in the U.K.

Escherichia coli	*Streptococcus agalactiae*
Klebsiella spp.	*Staphylococcus aureus*
Enterobacter spp.	*Staphylococcus epidermidis*
Serratia spp.	Enterococci
Pseudomonas aeruginosa	*Listeria monocytogenes*
Salmonella spp.	

have a resident strain of pseudomonas and therefore have continuing problems. In the U.K., there is relatively little infection due to *Salmonella* spp., whereas in other parts of the world it is more common. Group B streptococci together with *Escherichia coli* are responsible for 70% of the cases of neonatal meningitis in England. Serious *Staphylococcus aureus* infection in neonates is not common in the U.K., but there are increasing problems with infection due to *Staphylococcus epidermidis,* complicated by the difficulty in differentiating between infection and colonization with this organism. *Listeria monocytogenes,* which is a common organism in France, is relatively uncommon in England. The enterococci as neonatal pathogens are particularly pertinent in the context of cephalosporins because they are all uniformly resistant to this group of antibiotics.

REGIMEN REVIEW

Because of concern about the potential toxicity of the aminoglycosides and, in particular, the very unpredictable pharmacokinetics of these drugs on very small babies, we have looked at a number of alternative antibiotics during the last seven years. Bearing in mind that the nature and antibiotic sensitivity of the infecting organisms are rarely known, we need an antibiotic in this situation that is active against the majority of frequently encountered neonatal pathogens. The activity of ampicillin against Gram-negative organisms can no longer be relied upon because of its susceptibility to β-lactamase degradation. The same, to a slightly lesser extent, is true for the ureidopenicillins (azlocillin, mezlocillin and piperacillin). For this reason these antibiotics cannot be recommended for blind therapy in units where infection with coliforms is common.

In the U.K., there has been a great deal of publicity about netilmicin as an alternative to gentamicin for the treatment of neonates on the grounds that it is less toxic. There are, however, no published data on

the actual toxicity of gentamicin in neonates. We have determined mathematically that a study population in excess of 3,000 patients would be required to show whether or not netilmicin is less toxic than gentamicin.

It has also been claimed that netilmicin is more active than gentamicin – unfortunately the early studies did not test the two antibiotics under the same conditions. Subsequent studies have failed to support the original claim. The third claim for netilmicin is that it is active against gentamicin-resistant bacteria. This is true, in some cases. Unfortunately, the converse is also true and there has been a tragic example in England where a neonatal unit changed from gentamicin to netilmicin on the basis of possibly lower toxicity. Within three months, there was an outbreak of infection with a netilmicin-resistant Gram-negative rod that killed six babies. Ironically, the organism was sensitive to gentamicin. For these reasons, we do not consider netilmicin to be a reasonable alternative to gentamicin and we would rather look for a non-aminoglycoside alternative.

Regarding Gram-positive bacteria, it is still the case that enterococci are most sensitive to ampicillin and that *L. monocytogenes* is most appropriately treated with ampicillin with or without gentamicin. Arguments have been made against the use of cephalosporins for the Gram-positive organisms. It is true that for *Streptococcus agalactiae* and *S. aureus* and, to a lesser extent, *S. epidermidis,* the minimal inhibitory concentration (MIC) of the cephalosporins for these organisms is higher than those of penicillin or ampicillin. There is, however, a dramatic difference between the earlier penicillins and the new cephalosporins in the response curves following a standard intramuscular or intravenous dose. Levels range from 40 mg/l to 150 mg/l (Table 2). And at the end of the treatment regimens, the concentrations are in excess of 10 mg/l for cefuroxime, cefotaxime, ceftazidime, moxalactam and the long-acting cephalosporin, ceftriaxone. Thus the apparent decreased activity of the cephalosporins against Gram-positive cocci compared to that of the penicillins is countered by their higher serum concentrations.

A useful way of comparing peak and trough serum concentrations is by means of the therapeutic ratio (TR) of the drugs (the drug concentration at the end of dosage interval divided by the mean MIC for the organisms concerned). Thus the therapeutic ratio of gentamicin with penicillin or ampicillin is 4-8 against the common coliforms at the end of a 12-hour dosage interval. This compares favourably with cefuroxime although the activity of cefuroxime against the group B streptococcus (TR 200) is lower than that for the penicillins (TR 800). The therapeutic ratio against Gram-negative rods progressively increases with the new cephalosporins. Their activity against *S. aureus* is now comparable to

TABLE 2

Pharmacokinetic data on new antibiotics in neonates

	Dose (mg/kg)	Route	Peak serum level (mg/1)	Trough serum level (mg/1)	Serum half life (hours)	Volume of distribution (ml/kg)	Total clearance (ml/min/kg)
Ceftazidime	25	IM/IV	73	17	8.6	450	0.8
Cefuroxime	25	IM/IV	45	10.5	5.8	671	1.6
Cefotaxime	50	IM/IV	87	8	3.1	559	1.7
Ceftriaxone	50	IM/IV	149	54	15.5	325	0.3
Moxalactam	50	IM/IV	100	28	6.8	503	0.9
Gentamicin	2.5	IM	8	2	7.9	637	1.0