Prevention of wound sepsis in amputations by peri-operative antibiotic cover with an amoxycillin-clavulanic acid combination

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Summary

In a series of 44 patients with lower limb ischaemia requiring amputation for major limb sepsis, the performance of a new antibiotic combination with ß-lactamase-inhibiting properties, amoxycillin plus clavulanic acid (A-CA) (Augmentin; Beecham), was compared with that of penicillin in the prevention of wound infection. The sepsis rate of 12,9% in the group of patients receiving peri-operative A-CA was significantly lower than the 76,9% in the penicillin control group ($x^2 = 14,48$; $P < 0,001$). It is concluded that there is a need for peri-operative antibiotic cover in this situation and that A-CA appears to be highly effective. No statistical difference was found as regards development of sepsis in wounds closed primarily or left open while under A-CA cover.

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Postoperative wound infection after amputation for septic limb lesions is a source of considerable morbidity.[1-3] In the presence of distal sepsis, the tissue at the amputation site contains lymphatic and vascular channels carrying micro-organisms. Any surgical procedure undertaken through such tissue is liable to produce wound infection. This is more likely to occur in poorly perfused limbs in patients with diabetes than in patients with an otherwise healthy limb. Cross-infection during operation is another important factor in the development of stump sepsis.[4] Prolonged hospital stay and delay in rehabilitation procedures are factors worth considering, in addition to the inherent morbidity of amputation stump sepsis. The vascular unit at King Edward VIII Hospital, Durban, is confronted with a large number of patients presenting with septic complications of lower limb ischaemia. In many instances reconstructive vascular surgery is not feasible and an ablative procedure is the only alternative means of treatment. Because an adequate antimicrobial agent is needed in the peri-operative period, a new antibiotic

combination of amoxycillin and clavulanic acid (A-CA) (Augmentin; Beecham), was studied and its efficacy in preventing amputation wound sepsis determined. In this combination the amoxycillin is supplemented by clavulanic acid, which is a ß-lactamase enzyme inhibitor protecting amoxycillin from degradation. This combination has a broad spectrum of activity against a range of Gram-positive and Gram-negative aerobic organisms as well as certain anaerobes, including bacteroides and clostridial species. We would have preferred to compare an A-CA series with a 'no antibiotic' control series, but because of the risk of clostridial contamination and gas gangrene we felt obliged to give penicillin to all the patients in the control series. The performance of the antibiotic is therefore compared with that of penicillin as a control.

Patients and methods

A total of 44 patients was available for study. They were subdivided into two groups, one group receiving A-CA and the control group receiving penicillin.

A-CA group. Thirty-three patients were entered into this trial group but 2 were withdrawn because of sampling errors, leaving 31 patients for analysis. Most patients were Black males and the mean age was 55,6 years (range 22-77 years). Diabetes was present in 13 instances (Table I). Wet gangrene or gangrene with cellulitis was the usual limb lesion and the commonest site was the forefoot (Table II). The lymph nodes in the groin appeared clinically involved in 24 cases. Below-knee amputation was performed in 15 patients, above-knee amputation in 13 and other procedures in 3 (Table III).

Control group. In this group of 13 patients, 12 were male and 4 had diabetes. The mean age was 53,4 years (range 38-79 years) (Table I). Wet gangrene was present in 7, gangrene and cellulitis in 5, and ulceration and cellulitis in 1 patient. The site of sepsis was the forefoot in 8 patients and the foot and leg in 5 (Table II). Below-knee amputation was performed in 8 instances and above-knee amputation in 5 (Table III).

TABLE I. AGE AND SEX DISTRIBUTION AND INCIDENCE OF DIABETES

Group	Total	Male	Female	Age range (mean)	No. of diabetics
A-CA	31	25	6	22-77 (55,6)	13
Control	13	12	1	38-79 (53,4)	4
Total	44	37	7		17

TABLE II. NATURE AND SITE OF LIMB SEPSIS

Group	Wet gangrene	Ulcer + cellulitis	Gangrene + cellulitis	Toes	Fore-foot	Leg
A-CA	15	1	15	6	19	6
Control	7	1	5	—	8	5
Total	22	2	20	6	27	11

Methods

All procedures were done under general or spinal anaesthesia. The level of ablation was decided beforehand by clinical judgement and limb blood pressure measurements with the Doppler ultrasound probe, and the feasibility of the elected site determined intra-operatively by obtaining free muscle bleeding. No tourniquet was used and the skin was prepared with iodine. Care was taken to protect the operation site against contamination from the septic area or perineum. In the A-CA group the wounds were left open in 25 patients and were closed in 6. No drains were used. The open wounds were covered with a non-medicated Vaseline gauze.

Bacteriological examination. Two swabs were taken from the area of sepsis before operation and submitted for anaerobic and aerobic culture.

Antibiotic administration. In the A-CA group 750 mg of the antibiotic was administered orally 2 hours before operation and this dose was repeated 8-hourly for a total of 48 hours. The patients in the control group received one million units of benzyl penicillin intravenously with the premedication and thereafter 500 000 U 6-hourly for 48 hours. The dressing was left undisturbed until the 5th postoperative day when the wound was inspected and assessed on its macroscopic appearance, i.e. the presence of frank pus, cellulitis or slough. The dressing would be removed earlier, however, if increasing local pain, fever, soiling or smell dictated this. Two wound swabs were taken and submitted for microbiological study. The antibiotic was deemed effective if there was no reappearance of the original pathogenic organisms at the amputation site. Possible side-effects of the antibiotic such as rash, diarrhoea or nausea were noted.

TABLE III. TYPE OF AMPUTATION

Group	Toe-ectomy	Transmeta-tarsal	Below-knee	Above-knee
A-CA	1	2	15	13
Control	—	—	8	5
Total	1	2	23	18

Results

A-CA group

A clinically good result was obtained in 28 patients (90,3%), while in the remaining 3 patients sepsis was visibly present. In 1 of these the below-knee amputation was converted to an above-knee amputation. Another of these patients had a ray amputation of a toe and the third a transmetatarsal amputation. In both of these cases a direct field contamination seems likely. The preoperative swabs yielded a variety of aerobic and anaerobic organisms. Most frequently isolated in the aerobic group were *Proteus mirabilis* and *Pr. vulgaris* (19), *Streptococcus faecalis* (14), *Escherichia coli* (8) and *Staphylococcus aureus* (5), whereas in the anaerobic group *Bacteroides fragilis* (12), *Bact. melaninogenicus* (10), *Clostridium* sp. (8) and *Peptococcus magnus* (8) were most common. The postoperative wound swabs were negative in 27 cases, representing a bacteriological success rate of 87,1% and a sepsis rate of 12,9% (Table IV). The 4 failures included the 3 patients previously referred to, and another in whom an A-CA-sensitive *Pr. mirabilis* was isolated from the amputation site. Sepsis occurred in 1 out of the 6 patients whose wounds were closed primarily and in 3 out of the 25 patients whose wounds were left open.

Control group

In the original isolates *Strept. faecalis* (9), *Pr. morgani* (5), *Pr. mirabilis* (6) and *Pr. vulgaris* (4) were the most frequent aerobes, and *Bact. melaninogenicus* (4), *Pept. asaccharolyticus* (4), and a *Clostridium* sp. (5) the commonest anaerobes. Nine of the 13 patients in this group had clinical evidence of wound sepsis, and in a total of 10 patients wound swabs were positive for pathogenic organisms. This represents a sepsis rate of 76,9% (Table IV).

Statistics

The chi-square test with Yates' correction was used for statistical analysis. The sepsis rate in the A-CA group (12,9%) was found to be much lower than that in the control group (76,9%)

TABLE IV. INCIDENCE OF WOUND SEPSIS

Group	Total	Clinical signs: Absent No.	Absent %	Present No.	Present %	Bacteriological examination: Negative No.	Negative %	Positive No.	Positive %	
A-CA	**31**	**28**	**90,3**	**3**	**9,7**	**27**	**87,1**	**4**	**12,9**	$\chi^2 = 14,48$
Con-trol	**13**	**4**	**30,7**	**9**	**69,3**	**3**	**23,1**	**10**	**76,9**	$P < 0,001$

and this difference was shown to be highly significant ($x^2 = 14,48$; $P < 0,001$). No statistical difference was found as regards the occurrence of infection in the wounds which were closed primarily and those left open while under peri-operative A-CA cover ($x^2 = 0,14$).

Discussion

Several factors contribute to delay in wound healing after amputation. Malnutrition, ischaemia, haematoma formation and sepsis all play an important role. Amputation-related mortality ranges from 2% to 37%.[1-3, 5, 6] This is undoubtedly due to the poor risk many of these patients present because of age and generalized vasculopathy. Huston *et al.*[2] quote a 15% mortality among 100 patients who underwent above-knee amputation, of which 54% was sepsis-related. Robinson[5] reported a 7% mortality for below-knee, 17% for through-knee and 30% for above-knee amputations. Potts *et al.*[6] mentioned 11 infections in below-knee and 11 in above-knee amputations out of 83 operations in patients with diabetes and peripheral vascular disease. Sepsis accounted for 3 deaths of the total of 10. No mention was made of peri-operative antibiotics, but in a large series of 283 amputations[1] these were not routinely used and sepsis was the cause of death in 9 patients.

Most of the deaths must be ascribed to cardiovascular and pulmonary complications, and these symptoms should be carefully monitored in the immediate pre- and postoperative period. Wound infection might be caused by operating through tissues with blood and lymphatic vessels carrying bacteria, cross-infection occurring in the operating theatre (either from the patient or another source), or secondary infection occurring postoperatively.[4] Many organisms originate from the patient's own gastro-intestinal tract, and attempts have been made to lower the amputation wound sepsis rate by reducing the intestinal flora.[7] In our group of 44 patients we encountered a *Clostridium* species which occurred pre-operatively (from the devitalized limb) in 13 instances, and from the amputation wounds in 2.[8] In his review of 85 clostridial wound infections, Parker[8] found 47 in lower limb amputations for ischaemia and 13 of these in diabetics. He therefore advocated penicillin prophylaxis and non-suturing of muscles.

In order to reduce the postoperative incidence of these infections, attention should be paid to meticulous skin preparation and draping before operation. Amputation at an ischaemic site certainly predisposes to sepsis, and the choice of the amputation site is an important one. The aim is to preserve as much length of limb as possible without compromising its viability. Below-knee amputation is preferable to the above-knee procedure because of a lower associated mortality rate, preservation of the knee joint with better prospects of rehabilitation to ambulation, less stump pain and fewer demands on the energy reserves of the patient. We use the Doppler ultrasound probe to measure peripheral arterial pressure and the pressure index (below-knee pressure/brachial systolic pressure). Ankle pressure measurements correlate well with the calf blood flow, and the pressure index reflects the degree of arterial disease in the leg. Healing after a below-knee amputation can be predicted with pressure readings >70 mmHg and a pressure index >0,3,[9-11] although patients with marked vessel calcification might have pressure indices >1.[12] Other techniques measure skin blood flow (isotope clearance, thermography, photopletysmography), as skin circulation correlates better with wound healing than does muscle blood flow.[13,14]

Clinical judgement depends on appearance at operation and the amount of free bleeding obtained. However, successful healing has taken place when little bleeding has occurred.[9] Wound infection has also been associated with the use of drains, notably the corrugated Penrose or sump drains. Berardi and Keonin[15] had a 27,6% incidence of stump sepsis in a series of 163 amputations, the majority in stumps that were drained (82,5% *v.* 17,5% for non-drained stumps). We do not use drains, but it has been our practice not to close amputation wounds in the presence of distal sepsis. As this has the disadvantage of requiring a second procedure, a direct primary closure was performed in a group of 6 patients receiving A-CA. One of them developed a wound infection compared with 3 patients of the 25 whose wounds were left open. Although these numbers are small, it appears that antibiotic cover might obviate the need for delayed primary closure; this is promising. Few studies have been published on the need for and choice of prophylactic antibiotics. Parker[8] and Jamieson and Hill[12] advise the routine use of penicillin against clostridial infection, although this is ineffective against most Gram-negative organisms. Hares *et al.*[7] used pre-operative oral metronidazole and neomycin. In our series we have shown the need for an effective antibiotic with a broad spectrum of activity against organisms commonly found in septic ischaemic lower limb lesions. From our results we conclude that the combination of amoxycillin and the ß-lactamase inhibitor, clavulanic acid, is a highly effective formulation, and its use as a peri-operative antibiotic for amputations is recommended.

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REFERENCES

1. Hall R, Shucksmith HS. The above-knee amputation for ischaemia. *Br J Surg* 1971; **58:** 656-659.
2. Huston CC, Bivins BA, Ernst CB, Griffen WO. Morbid implication of above-knee amputation. *Arch Surg* 1980; **115:** 165-167.
3. Finch DR, MacDougal M, Tibbs DJ, Morris PJ. Amputation for vascular disease: the experience of a peripheral vascular unit. *Br J Surg* 1980; **67**: 233-237.
4. Weaver PC, Chattopadhya B, Angel J. An investigation into the spread of bacterial infection in lower limb amputation. *Br J Surg* 1973; **60**: 723-729.
5. Robinson K. Amputation in vascular disease. *Ann R Coll Surg Engl* 1980; **62**: 87-91.
6. Potts JR, Wendelken JR, Elkins RC, Peyton MD. Lower extremity amputation: review of 110 cases. *Am J Surg* 1979; **138**: 924-928.
7. Hares MM, Downing R, Marsh J. Failure of metronidazole/penicillin oral prophylaxis to prevent amputation stump infection. *Lancet* 1980; **i**: 1028-1029.
8. Parker MT. Postoperative clostridium infections in Britain. *Br Med J* 1969; **3**: 671-676.
9. Barnes RW, Shanik GD, Slaymaker EE. An incidence of healing in below-knee amputation: leg blood pressure by Doppler ultrasound. *Surgery* 1976; **79**: 13-20.
10. Pollock SB, Ernst CB. Use of Doppler measurements in predicting success in amputation of the leg. *Am J Surg* 1980; **139**: 303-306.
11. Creaney MG, Chattopadhya DK, Ward AS, Morris-Jones W. Doppler ultrasound in the assessment of amputation level. *J R Coll Surg Edinb* 1981; **26**: 278-281.
12. Jamieson CW, Hill D. Amputation for vascular disease. *Br J Surg* 1976; **63**: 683-690.
13. Holstein P, Sager P, Lassen NA. Wound healing in below-knee amputations in relation to skin perfusion pressure. *Acta Orthop Scand* 1979; **50**: 49-58.
14. Roon AJ, Moore WS, Goldstone J. Below-knee amputation: a modern approach. *Am J Surg* 1977; **134**: 153-158.
15. Berardi RS, Keonin Y. Amputations in peripheral vascular occlusive disease. *Am J Surg* 1978; **135**: 231-234.