Neutropenia during High Dose Intravenous Oxacillin Therapy

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Five patients who developed neutropenia following intravenous administration of high dose oxacillin for serious Staphylococcus aureus infection are described. Neutropenia was reversible with cessation of intravenous oxacillin therapy. Two patients were continued on oral oxacillin without untoward effects.

Although there have been many adverse hematological effects ascribed to the use of penicillin and some semisynthetic penicillins (methicillin (1, 2) and more recently nafcillin (3, 4)), we know of only one previous report which suggests a casual relationship between neutropenia and oxacillin therapy (5). The reasons for this infrequent associated effect have not yet been delineated but may partially involve relationships between the infective agent and host defense, duration of antibiotic use, intravenous administration, or the structural characteristics of oxacillin per se and its interaction with granulocytic bone marrow precursors. The present report describes five patients seen by us during the last 2 years who received high dose intravenous oxacillin therapy for Staphylococcus aureus infection and developed neutropenic leukopenia.

CASE REPORTS

Case 1. (Fig. 1, Table 1). A 13-year-old Negro male was admitted to the Yale-New Haven Hospital with clinical evidence of septic arthritis of the left hip joint. Two days prior to admission he noted the onset of fever, mild rhinorrhea, and left hip pain accentuated by motion. There was no history of trauma. On admission to the hospital the patient had a temperature of 103°F, a pulse of 120, and respirations of 20/min. On physical examination, the left hip revealed limitation of flexion and extension to 15° and limitation of internal and external rotation of 60° with concomitant pain with movement. Admission laboratory work revealed a white blood cell count of 16,000/mm³ with 70% segmented neutrophils, 19% band forms, 3% lymphocytes, and 8% monocytes. The hemoglobin was 13 g/100 ml and the hematocrit was 36%. The sedimentation rate was 36 mm/hr. Urinalysis was normal. Films of the left hip were normal. Surgical exploration of the left hip revealed an inflammatory synovitis. Bacterial cultures of the left hip synovium yielded S. aureus and S. epidermidis, both sensitive to oxacillin. Three sets of blood cultures grew S. aureus sensitive to oxacillin. Intravenous oxacillin in the dosage of 1 g ever 6 hr was begun immediately postoperatively. The dose of intravenous oxacillin was increased to 2 g every 6 hr on the following day. On the 19th day of intravenous oxacillin therapy (Table 1, Fig. 1) the leukocyte count fell to 4000/mm³ with a differential count of 40% neutrophils, 19% band forms, 2% eosinophils, 30% lymphocytes, and 7% monocytes. The temperature rose slightly to 38°C. On the 20th day of
intravenous oxacillin therapy, the leukocyte count was 2000/mm³ with no segmented neutrophils and 11% band forms. Intravenous oxacillin was discontinued on the 21st day of therapy. During the next 4 days, the white blood cell count rose to normal range with a normal differential count. The patient received no other medication during his hospital admission. He was discharged on the 23rd hospital day. A leukocyte count 13 days following cessation of intravenous oxacillin therapy was 8100/mm³ with 59% segmented neutrophils, 15% band forms, 21% lymphocytes, 3% monocytes, and 1% eosinophils.

Case 2. (Fig. 2, Table 2). On February 18, 1974, a 54-year-old male was admitted to Yale-New Haven Hospital with the diagnosis of osteomyelitis of the lumbosacral spine. The patient previously had a history of lower back pain and was treated in another hospital with ampicillin, 500 mg every 6 hr orally for a staphylococcal urinary tract infection. He was on oral ampicillin at the time of admission to the Yale-New Haven Hospital. Admission white blood count was 5800/mm³ with 68% segmented neutrophils, 0% bands, 17% lymphocytes, 6% eosinophils, and 9% monocytes. The sedimentation rate was 32 mm/hr. The urinalysis was normal. The patient was afebrile. Lumbosacral spine films revealed osteomyelitis of the second and third lumbar vertebrae. A bone biopsy of the third lumbar vertebrae taken during surgical exploration on the sixth day of admission grew S. aureus resistant to

| Table 1 | Patient Number 1 |
|---------|------------------|
| Days of | Antibiotic       | Total         | Neutrophils (%) | Lymphocytes (%) | Monocytes (%) | Eosinophils (%) | Others (%) |
| therapy | therapy         | leukocyte     | Segmented       | Band forms      | (%)           | (%)           | (%)        |
| 1       | Oxacillin,      | count (per mm³) | neutrophils     | neutrophils     | (%)           | (%)           |            |
|         | 4 g/day iv      | 16,000        | 70              | 19              | 3            | 8            | 0          | 0          |
| 2       | Oxacillin,      | —              | —               | —               | —            | —            | —          | —          |
|         | 8 g/day iv      | 4,000         | 40              | 19              | 30           | 7            | 2          | 2          |
| 19      | —              | 2,000         | 0               | 11              | 74           | 8            | 4          | 3          |
| 20      | Oxacillin       | —              | —               | —               | —            | —            | —          | —          |
|         | discontinued    | 3,900         | 12              | 19              | 51           | 11           | 4          | 3          |
| 22      | —              | 4,600         | 44              | 10              | 26           | 10           | 7          | 3          |
| 25      | —              | 8,100         | 59              | 15              | 21           | 3            | 1          | 1          |

Fig. 1. Case report number 1, antibiotic therapy and hematological profile during therapy (see Table 1).
OXACILLIN-INDUCED NEUTROPENIA

[Graph showing leukocyte counts over days of therapy]

FIG. 2. Case report number 2, antibiotic therapy and hematological profile during therapy (see Table 2).

Penicillin and ampicillin and sensitive to oxacillin. The pathological report of the lumbar bone revealed acute and chronic inflammation with focal necrosis, infiltration with plasma cells, lymphocytes, monocytes, polymorphonuclear cells, and a few giant cells. Immediately postoperatively, the patient was begun on intravenous oxacillin, 2 g every 4 hr in addition to Probenicid, 500 mg orally twice a day. Intravenous oxacillin was decreased to 10 g/24 hr on the 22nd day of therapy. On the 26th day of intravenous oxacillin therapy, the leukocyte count fell to 2900/mm³ with 14% segmented neutrophils, 1% bands, 47% lymphocytes, and 17% monocytes with 18% eosinophils (Fig. 2, Table 2). The intravenous oxacillin was discontinued and the patient was started on therapy with oral dicloxacillin, 500 mg every 6 hr with continuation of the Probenicid. The white blood cell count returned to normal 8 days after discontinuing intravenous oxacillin. There was no depression of the white blood cell count over a period of 8 months of oral therapy with dicloxacillin. Representative white blood cell counts and differential cell counts during therapy were: 6900/mm³ with 71% segmented neutrophils, 23% lymphocytes, 4% monocytes, and 2% eosinophils at 6 weeks, and 6500/mm³ with 58% segmented neutrophils, 29% lymphocytes,

| TABLE 2 | Patient Number 2 |
| Days of therapy | Antibiotic therapy | Total leukocyte count (per mm³) | Neutrophils (%) | Lymphocytes (%) | Monocytes (%) | Eosinophils (%) | Others (%) |
|--------------|-------------------|-------------------------------|-----------------|-----------------|---------------|----------------|------------|
| 1            | Oxacillin, 12 g/day iv | 9,400                        | —               | —               | —             | —              | —          |
| 7            |                    | 10,100                       | 84              | 7               | 3             | 5              | 0          | 1          |
| 10           |                    | 9,900                        | 77              | 6               | 9             | 6              | 2          | 0          |
| 18           |                    | 6,700                        | 64              | 14              | 11            | 6              | 4          | 1          |
| 22           | Oxacillin, 10 g/day iv | —                            | —               | —               | —             | —              | —          |
| 26           | Oxacillin discontinued Dicloxacillin 2 g/day po | —                            | —               | —               | —             | —              | —          |
| 34           |                    | 2,900                        | 14              | 1               | 52            | 11             | 18         | 4          |
|              |                    | 6,100                        | 67              | 0               | 26            | 2              | 5          | 0          |
AHERN, HICKS AND ANDRIOLE

FIG. 3. Case report number 3, antibiotic therapy and hematological profile during therapy (see Table 3).

TABLE 3
Patient Number 3

| Days of therapy | Antibiotic therapy | Total Leukocyte count (per mm³) | Neutrophils (%) | Lymphocytes (%) | Monocytes (%) | Eosinophils (%) | Others (%) |
|-----------------|--------------------|---------------------------------|----------------|----------------|---------------|----------------|------------|
|                 |                    | Segmented                      | Band forms      |                |               |                |            |
| A. First febrile episode | 1 Oxacillin, 6 g/day iv* | 9,200                          | 82             | 10             | 7             | 1              | 0          | 0          |
|                  | 2                   | 10,100                         | 77             | 4              | 17            | 2              | 0          | 0          |
|                  | 3                   | 4,600                          | 74             | 1              | 20            | 5              | 0          | 0          |
|                  | 5                   | 4,400                          | 71             | 8              | 18            | 3              | 0          | 0          |
|                  | 6 Oxacillin discontinued | 3,000                          | 50             | 0              | 47            | 2              | 1          | 0          |
| B. Second febrile episode | 1 Oxacillin, 12 g/day iv | 20,500                         | 73             | 21             | 3             | 3              | 0          | 0          |
|                  | 2                   | 13,700                         | 70             | 23             | 1             | 6              | 0          | 0          |
|                  | 8                   | 14,900                         | 57             | 11             | 17            | 9              | 4          | 2          |
|                  | 11                  | 10,500                         | 66             | 13             | 13            | 5              | 1          | 2          |
|                  | 16                  | 7,200                          | 61             | 5              | 29            | 4              | 1          | 0          |
|                  | 18                  | 5,400                          | 57             | 4              | 26            | 9              | 4          | 0          |
|                  | 23                  | 4,300                          | 37             | 3              | 44            | 9              | 7          | 0          |
|                  | 28 Oxacillin discontinued | 3,400                          | 22             | 3              | 44            | 26             | 3          | 2          |
|                  | 32 Dicloxacillin, 1 g q.d.i.d. po | 5,300                        | 4              | 6              | 65            | 21             | 3          | 1          |
|                  | 35                  | 5,600                          | 40             | 12             | 34            | 10             | 1          | 3          |
|                  | 39                  | 9,900                          | 57             | 6              | 25            | 4              | 2          | 6          |
|                  | 49 Dicloxacillin discontinued | 8,800                          | 69             | 5              | 18            | 5              | 1          | 2          |
| C. Third febrile episode, 2 weeks after discontinuation of dicloxacillin | 1 Oxacillin, 12 g/day iv | ——                             | ——             | ——             | ——            | ——             | ——        | ——        |
|                  | 2                   | 11,000                         | 89             | 4              | 6             | 1              | ——         | ——        |
|                  | 6                   | 6,500                          | 66             | 8              | 16            | 9              | 1          | 0          |
|                  | 16                  | 8,100                          | 56             | 3              | 34            | 5              | 1          | 1          |
|                  | 41                  | 6,500                          | 63             | —              | 25            | 6              | 6          | 0          |

*Gentamicin, 80 mg iv x 1 dose; and ampicillin, 2 g iv x 1 dose.
11% monocytes, and 1% eosinophils at 5 months. Two months after discontinuing oral oxacillin, the white blood cell count was 6800/mm³ with 66% segmented neutrophils, 26% lymphocytes, and 8% monocytes.

Case 3. (Fig. 3, Table 3). A 71-year-old white male was admitted to the West Haven Veterans Administration Hospital on January 10, 1975. The patient was confused and unable to give a history of his illness. He had previously been admitted to a nearby hospital for a seizure presumed secondary to alcoholic withdrawal. On his January 10, 1975, admission to the West Haven Veterans Administration Hospital, the temperature was 103°F, the blood pressure was 125/80 mm Hg, respirations were 20/min, and the pulse was 100. On physical examination, there were a few rales in the left lower lobe posteriorly. The patient’s left pupil was greater in size than the right pupil, but both were reactive to light. There was a question of mild left facial weakness.

Laboratory data on admission to the hospital revealed a total white blood cell count of 9200/mm³ with 82% segmented neutrophils, 10% bands, 7% lymphocytes, and 1% monocytes. The sedimentation rate was 42 mm/hr. A culture of the urine grew more than 10,000 cocci. The cerebrospinal fluid was clear and analysis revealed a glucose content of 77 mg%, and a protein content of 45 mg%, and contained no cells. Gram stain and culture were negative. The sputum grew 2+ S. epidermidis. Blood cultures were negative. A film of the chest revealed atelectasis or infiltrate in the left lower lobe.

Course in the hospital: The patient experienced three febrile episodes while in the hospital. The first febrile episode (Table 3A) was on admission when the patient had a temperature of 103°F. The patient was empirically started on intravenous oxacillin in the dose of 1 g every 4 hr and was also given one 80 mg dose of gentamicin intravenously and one 2-g dose of ampicillin intravenously for possible sepsis. On the sixth day of therapy, the white blood cell count dropped to 3300/mm³ with 50% segmented neutrophils, 47% lymphocytes, 2% monocytes, and 1% eosinophils. Intravenous oxacillin was discontinued. Five days after discontinuing the intravenous oxacillin, the leukocyte count rose to 6000/mm³ with 69% segmented neutrophils, 2% band forms, 28% lymphocytes, and 1% eosinophils. Nine days after cessation of the oxacillin therapy, the temperature rose to 103°F, and the patient was begun on a course of oral ampicillin therapy. The following day a temperature of 105°F was recorded. A grade III/VI systolic murmur was heard at the apex of the heart and radiated into the axilla. At that time, the white blood cell count was 25,000/mm³ with 73% segmented neutrophils, 21% band forms, 3% lymphocytes, and 3% monocytes (Table 3, Fig. 3). The erythrocyte sedimentation rate was 62 mm/hr. Intravenous oxacillin at a dose of 2 g every 4 hr was reinstated. Six sets of blood cultures drawn during the second febrile episode and prior to the initiation of oxacillin therapy grew S. aureus, coagulase positive. On the 23rd day of intravenous oxacillin therapy, the white blood cell count had fallen to 4300/mm³ with 37% segmented neutrophils, 3% band forms, 44% lymphocytes, 9% monocytes, and 7% eosinophils. On the 28th day of therapy, the white blood cell count was 3400/mm³ with 22% segmented neutrophils, 3% band forms, 44% lymphocytes, 26% monocytes, and 2% eosinophils. Intravenous oxacillin therapy was discontinued and oral dicloxacillin, 250 mg four times daily, was initiated. Four days later the white blood cell count was 5300/mm³ with 4% segmented neutrophils, 6% band forms, 65% lymphocytes, 21% monocytes, and 3% eosinophils. By the seventh day of oral therapy, the white blood cell count and differential had returned to normal (i.e., 5600/mm³ with 40% segmented neutrophils, 12% band forms, 34% lymphocytes, 10% monocytes, and 1% eosinophils). Oral
dicloxacillin was discontinued after 20 days of therapy. Fourteen days later the patient’s temperature again rose to 103°F and the white blood cell count was 20,000/mm³ with 65% segmented neutrophils, 18% band forms, 16% monocytes, and 1% eosinophils. Blood cultures were again positive for S. aureus, and intravenous oxacillin, 2 g every 4 hr, was reinstituted. The patient was treated intravenously for 41 days without the development of neutropenia and leukopenia.

Case 4. (Fig. 4, Table 4). A 24-year-old juvenile-onset diabetic was admitted to the Yale–New Haven Medical Service on August 18, 1974, with complaints of persistent ketonuria, fever, and left flank pain of 3 days duration. The patient’s diabetes mellitus was no longer controlled with his usual insulin dose. Initial physical examination revealed a temperature of 101°F rectally and mild left costovertebral angle tenderness. Initial urinalysis contained 25–30 white blood cells per high powered field.

| Days of therapy | Antibiotic therapy | Total leukocyte count (per mm³) | Neutrophils (%) | Lymphocytes (%) | Monocytes (%) | Eosinophils (%) | Others (%) |
|-----------------|--------------------|--------------------------------|-----------------|-----------------|---------------|-----------------|-----------|
|                 |                    |                                | Segmented       | Band forms      |               |                 |           |
| 1               | Oxacillin,         | 6000                           | 72              | 13              | 4             | 10              | 1         | 0         |
|                 | 12 g/day iv        |                                 |                 |                 |               |                 |           |
| 6               |                     | 8700                           | 61              | 12              | 15            | 6               | 5         | 0         |
| 10              |                     | 7900                           | 82              | 4               | 10            | 3               | 0         | 1         |
| 14              |                     | 5100                           | 52              | 3               | 35            | 6               | 2         | 2         |
| 28              |                     | 2700                           | 26              | 5               | 41            | 8               | 17        | 3         |
| 29              | Oxacillin          |                                 |                 |                 |               |                 |           |
|                 | discontinued       |                                 |                 |                 |               |                 |           |
|                 | Clindamycin,       |                                 |                 |                 |               |                 |           |
|                 | 2.7 g/day po       |                                 |                 |                 |               |                 |           |
| 30              |                     | 3000                           | 14              | 2               | 52            | 22              | 3         | 7         |
| 33              |                     | 3800                           | 28              | 18              | 24            | 22              | 6         | 2         |
|                 |                     | 3900                           | 25              | 20              | 27            | 22              | 6         | 0         |
| 1 week after    |                     |                                 |                 |                 |               |                 |           |
| cessation of    |                     |                                 |                 |                 |               |                 |           |
| therapy         | None               | 6800                           | 46              | 1               | 36            | 14              | 3         | 0         |
| 6 weeks post-   |                     |                                 |                 |                 |               |                 |           |
| cessation of    | None               | 7600                           | 73              | 7               | 15            | 5               | 0         | 0         |

*Clindamycin therapy was continued after discharge from the hospital for a total course of 10 days.

FIG. 4. Case report number 4, antibiotic therapy and hematological profile during therapy (see Table 4).
and was 1+ positive for protein and 4+ positive for glucose and ketones. Initial white blood cell count was 14,900/mm³ with 69% segmented neutrophils, 18% band forms, 8% lymphocytes, and 3% monocytes. He was begun empirically on ampicillin, 1 g intravenously every 6 hr, and cephalothin, 1 g intravenously every 4 hr. Culture of the admission urine grew coagulase-positive S. aureus. Multiple blood cultures were negative. The erythrocyte sedimentation rate obtained 10 days after admission was 50 mm/hr. When results of the urine culture were available on August 21, 1974, the antibiotic coverage was changed to oxacillin, 2 g intravenously every 4 hr, because the organism was resistant to ampicillin. His subsequent hospital course included development of a left pleural effusion noted on physical examination and chest film on August 20, 1975, associated with splinting of the left hemithorax. This physical finding, in association with persistence of his fever, led to an extensive urological evaluation which included an intravenous pyelogram, ultrasound of the left kidney, and renal arteriography, the results of which led to a diagnosis of a left perinephric abscess. On the 28th day of intravenous oxacillin therapy (September 18, 1974) the white blood cell count was noted to be 2700/mm³ with a differential count of 26% segmented neutrophils, 5% band forms, 41% lymphocytes, 8% monocytes, 17% eosinophils and 3% atypical lymphocytes; the erythrocyte sedimentation rate was 21 mm/hr. Intravenous oxacillin was discontinued and clindamycin, 300 mg every 8 hr orally, was instituted and continued for 10 days, during which time the leukocyte cell count and differential count improved rapidly. His white blood cell count 1 week after cessation of all therapy was 6800/mm³ with 46% segmented neutrophils, 1% band forms, 36% lymphocytes, 14% monocytes, 3% eosinophils, and 1% atypical lymphocyte. Follow-up renal arteriography approximately 3 months after diagnosis of the perinephric abscess and 6 weeks after cessation of therapy showed only minimal narrowing of the vessels in the area of previous infection.

Case 5 (Fig. 5, Table 5). A 9-month-old infant was admitted to the Yale-New Haven Hospital Pediatric Service on August 27, 1975, with a 2-day history of fever, vomiting, irritability, and limitation of movement of the left leg. He had been seen by a physician 2 days prior to admission and was begun on oral penicillin for the fever. The symptoms had not improved and the child was admitted to the pediatric ward when the mother noted warmth over the left knee and brought him to the Emergency Room. Positive physical findings at that time were limited to a temperature of 102° F., a pulse of 100, and a tender, warm, erythematous, left knee with evidence of effusion and limitation of flexion. His white blood cell count was 13,300/mm³ with 35% segmented neutrophils, 51% lymphocytes, 12% monocytes, and 1% eosinophils. The erythrocyte sedimentation rate was 59 mm/hr. Aspiration of the left knee joint yielded 6 ml of purulent fluid. The protein content was 5.7 g%. Total nucleated cells were 89,000/mm³, 95% of which were neutrophils. Gram stain of the material revealed sheets of neutrophils and a few gram-positive cocci. No organisms grew on culture. Blood and cerebrospinal fluid cultures were negative. Films of the left hip and knee were normal. Surgical exploration of knee joint, on the day of admission, revealed no communication with the metaphysis of the femur. Oxacillin, 350 mg every 4 hr, and ampicillin, 350 mg every 4 hr, was begun intravenously on the day of admission (August 27, 1975). He became afebrile on the fourth hospital day. On September 16, 1975, after 14 days of antibiotic therapy with both agents, it was noted that his white blood cell count had fallen to 5,600/mm³ with a differential of 1% segmented neutrophils, 1% band forms, 88% lymphocytes, 5% monocytes, and 2% eosinophils. The sedimentation rate had fallen to 42 mm/hr. Oxacillin was discontinued on September 17 and cephalothin substituted, 80 mg intravenously every 4
hr. Five days later the white blood cell count had returned to 13,300/mm³, with a differential count of 18% neutrophils, 1% band forms, 67% lymphocytes, 11% monocytes, and 3% eosinophils. All antibiotics were discontinued on September 23, 1975, after 25 days of therapy. A white blood cell count one week later was 9400/mm³, 24% neutrophils, 58% lymphocytes, 8% monocytes, and 2% eosinophils. The erythrocyte sedimentation rate was 30 mm/hr.

### Table 5

| Days of therapy | Antibiotic therapy                      | Total leukocyte count (per mm³) | Neutrophils (%) | Lymphocytes (%) | Monocytes (%) | Eosinophils (%) | Others (%) |
|-----------------|----------------------------------------|--------------------------------|-----------------|-----------------|---------------|----------------|------------|
| 1               | Oxacillin, 6 g/day iv Ampicillin, 2 g/day iv | 13,300                         | 35              | 51              | 12            | 1              | 1          |
| 5               | Oxacillin, 2.1 g/day iv Ampicillin, 2.1 g/day iv | 11,200                         | 38              | 56              | 6             | 0              | 0          |
| 7               |                                        | 14,200                         | 21              | 60              | 13            | 5              | 1          |
| 13              |                                        | 7,300                          | 28              | 57              | 6             | 4              | 3          |
| 20              |                                        | 5,600                          | 1               | 88              | 5             | 2              | 3          |
| 21              | Ampicillin, 2.1 g/day iv Cephalothin, 480 mg/day iv Oxacillin discontinued | 7,100                          | 4               | 85              | 10            | 1              | 0          |
| 22              |                                        | 7,700                          | 2               | 90              | 7             | 0              | 1          |
| 24              |                                        | 8,100                          | 7               | 80              | 8             | 5              | 0          |
| 26              |                                        | 13,300                         | 18              | 67              | 11            | 3              | 0          |
| 27              | All antibiotics discontinued            |                                |                 |                 |               |                |            |
| 30              | None                                   | 11,800                         | 20              | 65              | 7             | 7              | 1          |
| 34              | None                                   | 9,400                          | 24              | 58              | 8             | 2              | 8          |
OXACILLIN-INDUCED NEUTROPENIA

DISCUSSION

Reversible adverse hematological reactions following the administration of the semisynthetic penicillins, nafcillin and methicillin, for the treatment of $\beta$-lactamase-producing staphylococcal infections have been infrequently reported (1-4, 6). Bone marrow examination in two recent studies involving nafcillin therapy demonstrated a maturation arrest of the myeloid series at the myelocyte stage without depression of the megakaryocytic or erythroid series (3, 4). Our review of the literature has revealed only one case of apparent oxacillin-induced neutropenia and leukopenia associated with eosinophilia (5). In that case report, the antibiotic was oral sodium oxacillin (5-methyl-3-phenyl-4-isoxazolyl penicillin). However, the patient had previously demonstrated clear evidence of penicillin hypersensitivity with angioneurotic edema, while receiving penicillin and eosinophilia and pruritus during methicillin therapy. Bone marrow aspirate obtained after cessation of oxacillin therapy for persistent neutropenia revealed a maturation arrest of the myeloid series with relative hypoplasia of the erythroid series. One week after discontinuation of the oxacillin, prednisone therapy was initiated since there had been no evidence of spontaneous bone marrow recovery. After 3 days of steroid therapy, the total leukocyte counts and differential counts had returned to normal values. This author also reported evidence of hepatocellular damage, in that the serum transaminase and urinary urobilinogen levels rose in this patient during oxacillin therapy and spontaneously improved with cessation of the drug prior to the institution of prednisone, a finding also noted by Huang et al., in children with cystic fibrosis (6). No clinical or laboratory evidence of liver involvement was found in four of our patients. Patient number 3 developed abnormal liver function tests after admission with a markedly increased alkaline phosphatase and mild transaminase (SGOT) and lactic dehydrogenase elevations. The values returned to normal while on oxacillin therapy. The etiology of the abnormalities was unknown but a biliary stone was implicated. Consequently, we have no evidence of oxacillin-related hepatotoxicity in our patients.

In our series of five patients receiving intravenous oxacillin therapy, three demonstrated a leukopenia and all five developed a transient neutropenia. All of our patients had received at least 2 weeks of intravenous therapy prior to the observation of the peripheral white blood cell dyscrasias. Cessation of intravenous therapy alone brought prompt recovery of the peripheral leukocyte and differential cell counts within 1 week. In our experience, we have seen many patients with similar degrees of osteomyelitis on oxacillin therapy who did not develop leukopenia. Therefore, this leukocyte dyscrasia is not felt to be related to the infection per se. Similar reversion of neutropenia towards normal has been observed to occur within 72 hr following discontinuation of methicillin (8). Institution of oral dicloxacillin in two of our patients did not impede the return of the peripheral white blood cell count to normal values.

An eosinophilia reaction has previously been described with oxacillin (9). Eosinophilia in the range of 18% occurred in two of our five patients, and a range of 4 to 7% was seen in the remaining patients. The eosinophils regressed with cessation of intravenous therapy. No other systemic manifestations of drug hypersensitivity were noted in our patients. Erythrocyte sedimentation rates were elevated in all five patients at the time of admission. These values continued to improve during the time of the neutropenic leukopenia. Four of the five patients remained afebrile during this time period. Patient number 3 developed a severe left arm phlebitis at his intravenous infusion site and was febrile to 102°F during the neutropenia. He defervesced within 24 hr, with the changing of the intravenous site and the application of warm soaks.
Furthermore, while all the patients presented with an anemia of varying severity, this hematological abnormality improved spontaneously in three of the patients (1, 2, 4). Patient number 3 was evaluated for his anemia 2 weeks after admission and was found to have both folate deficiency and an anemia compatible with chronic disease with a bone marrow showing abundant iron stores. He received 2 units of packed red blood cells which increased the hematocrit to 27%, a value which he maintained throughout the remainder of his hospital course. Patient number 5, the infant, was found to be iron deficient and responded rapidly to oral iron therapy with a brisk reticulocytosis which persisted throughout the period of leukopenia.

The mechanism of the selective bone marrow suppression by the semisynthetic penicillins is as yet undefined. A direct toxic effect on the white blood cell precursors is suggested by the improvement occurring merely with cessation of antibiotic administration. The associated eosinophilia seen in two of our patients and observed by others in association with drug allergy, i.e., fever (3) and rash (4) and prior reactions to penicillin (4), suggests a hypersensitivity reaction to oxacillin leading to a marrow arrest. However, further studies are needed to support this hypothesis.

Transient neutropenia and leukopenia appear to be complications of high dose intravenous oxacillin therapy in certain patients and warrant clinical alertness and monitoring of the hematological profile of patients when this antibiotic is employed. Continued oral therapy with dicloxacillin [3 (2, 6-dichlorophenyl)-5-methyl-4-isoxazolyl penicillin], ranging from 1 week to 8 months in two of our patients, did not perpetuate the hematological abnormalities noted during high dose intravenous oxacillin therapy. Thus, oral dicloxacillin may be a suitable alternative should these side effects be observed and should intravenous therapy no longer be required.

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