THE 1990 - 1991 OUTBREAK OF MELIOIDOSIS IN THE NORTHERN TERRITORY OF AUSTRALIA : CLINICAL ASPECTS

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Abstract. From November 1990 to June 1991, 33 cases of acute melioidosis were diagnosed in tropical Northern Territory, Australia during an exceptionally wet monsoon. Eighteen (55%) were alcoholic, 16 (48%) diabetic and only 4 (12%, all survivors) had no risk factors. Twenty-seven (82%) were considered recent infection, with an incubation period of 3 - 21 days (mean 14) documented in eight cases with presumed cutaneous inoculation. Fourteen patients presented with pneumonia (4 septicemic) and of 11 others with septicemia 4 had genitourinary foci. Three of 4 with splenic abscesses required splenectomy. Three had only skin/soft tissue infection. One patient with brainstem encephalitis needed prolonged ventilation. Overall mortality was 36% (12 cases, including three relapses), despite therapy with ceftazidime and intensive care facilities. *Pseudomonas pseudomallei* is the commonest diagnosed cause of fatal bacteremic pneumonia at Royal Darwin Hospital and emphasis is placed on early appropriate antibiotic therapy and compliance with maintenance therapy for at least three months.

INTRODUCTION

Human melioidosis was first described in Australia from north Queensland in 1950 (Rimington, 1926), and the first reported case in the Northern Territory (NT) was from 1960 (Crotty *et al,* 1963). From January 1984 to November 1990 there were 54 melioidosis cases confirmed at Royal Darwin Hospital (RDH) (Woods *et al,* 1992), and melioidosis is now recognized as the commonest cause of death from community-acquired pneumonia at RDH (Anstey *et al,* 1992). Between November 1990 and June 1991, during an exceptionally wet monsoon, 33 melioidosis cases (12 deaths) were diagnosed at RDH (Merianos *et al,* 1993). We report here the clinical aspects of the 33 patients.

MATERIALS AND METHODS

All 33 cases in this study were confirmed bacteriologically (n = 29) or serologically (n = 4). Clinical and laboratory data were recorded prospectively, and survivors were usually followed for at least 12 months. Concurrent epidemiological and environmental studies are reported in the accompanying article (Merianos *et al,* 1993).

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Laboratory investigations

Standard biochemical and hematological tests were performed. *Pseudomonas pseudomallei* was cultured from blood using tryptic soy broth bottles (Roche) incubated at 35°C, and from sputum, urine and tissue samples using Ashdown's medium that contains gentamicin for selection (Ashdown, 1979). Confirmation of *P. pseudomallei* was made biochemically by the API 20E system (API System SA, Lyon, France). Sensitivity testing was by agar dilution method using defined breakpoint concentrations for inhibition of bacterial growth (NCCLS, 1990).

P. pseudomallei serology was performed using indirect hemagglutination (IHA), enzyme immuno-assay (EIA) for IgG and IgM, and immunofluorescence (IF) for IgG and IgM, methods being as described elsewhere (Ashdown *et al,* 1989).

Statistical analysis

The two-tailed Fisher's exact test was used for comparing proportions.

RESULTS

Clinical features

The presentation of the 33 cases in relation to rainfall is shown in Fig 1 in the accompanying article; 14 cases (42%) occurred in January, the

wettest month (922mm rainfall). Apart from a three year old Aboriginal boy, cases were aged 20 - 80 years (mean 40 years). Twenty-five (76%) were males and eleven (33%) were Aboriginal. Twenty-two (67%) were from Darwin city, eight (24%) from rural Darwin region and three from elsewhere in tropical NT.

Predisposing risk factors for disease are summarized in Tables 1 and 2, and further analysed in the accompanying article. Of the 16 diabetics only one was Type 1 (juvenile onset, insulin dependent). One of the adult onset diabetics was insulin dependent; the rest were controlled by diet or oral hypoglycemics. One diabetic was diagnosed as a result of the melioidosis admission.

Three of the cases were considered probable reactivations of latent disease and three were acute exacerbations of chronic disease which preceded the wet season. The remaining 27 (82%) were considered likely recent acquisition. Of these 27, 13 (48%) had specific events thought to cause infection. In eight cases a significant penetrating skin injury with soil exposure occurred, with five of these developing local infection. Only one of these five actually presented with confirmed ongoing melioidosis skin infection, with the others all presenting with systemic illness. Five other patients had events of intense exposure to mud from heavy rain, with cutaneous or respiratory exposure to *P. pseudomallei* possible. Accurate documentation allowed incubation period calculation in eight cases, with a range of 3 - 21 days (mean 14 days). There was no correlation between incubation period and severity of illness on presentation.

Table 3 summarizes the clinical presentations and outcomes. All presentations were septic in nature, although no patient had strictly defined septic shock on admission (blood pressure below 90 mm Hg systolic and signs of vital organ dysfunction). Septicemic melioidosis cases all had severe febrile illness (duration before admission 2 - 18 days; median 4 days), except for one patient with 21 days of fever without constitutional features. Blood culture negative cases were generally less ill (duration 1 - 65 days; median 8 days), although fevers were prominent.

Overall, 14 (42%) cases presented with pneumonia (4 septicemic), and five (15%) with genitourinary infection (4 septicemic). All genitourinary infections had non-specific abdominal pain as the prominent feature in addition to fever, with diarrhea, dysuria, urinary frequency and incontinence in various combinations. The case of encephalitis is one of seven neurologic melioidosis patients recently reported from the NT (patient 6; Woods *et al,* 1992) with profound motor weakness, brainstem encephalitis and prolonged respiratory failure requiring ventilation. Another patient with neurologic melioidosis (patient 7; Woods *et al,* 1992) acquired infection during the same wet season while a tourist in the NT, but presented to hospital outside the NT.

Table 1

Risk factors (n = 33)

	No.(%)
Alcohol*	18 (55)
Diabetes	16 (48)
Chronic lung disease+	5 (15)
Malignancy	3 (9)
Steroid therapy	2 (6)
Chronic renal disease	1 (3)
TB/leprosy	0 (0)

* males > 60g/day
females > 40g/day

+ 21 (64%) smokers

Table 2

Risk factor combinations (n = 33)

	No.(%)
4 risk factors	1 (3)
3 risk factors	2 (6)
2 risk factors	9 (27)
1 risk factor	17 (52)
Nil risk factor	4 (12)

Serology and bacteriology

Diagnosis was by serology alone in two cases with pneumonia and two cases with splenic abscess (Table 4).

Table 3

Clinical presentation.

	No.	Died (%)
Blood culture positive		
Pneumonia with septicemia	4	2 (50)
Septicemia with secondary pneumonia	3	3 (100)
Septicemia with genitourinary focus	4	2 (50)
Septicemia with peritonitis	1	1 (100)
Septicemia with splenic abscesses	1	0
Septicemia with no focus or collections	2	1 (50)
Total blood culture positive	15	9 (60)
Blood culture negative		
Pneumonia	8	1 (13)
Splenic abscesses	2	0
Peritonitis, splenic and subphrenic abscesses	1	0
Genitourinary infection	1	0
Skin ulcers	2	0
Soft tissue abscess	1	0
Brainstem encephalitis	1	0
Total blood culture negative	16	1 (6)
Blood culture not done		
Pneumonia	2	2 (100)
Overall total	33	12 (36)

Table 5 shows the antibiotic sensitivity pattern seen for 27 of the 29 initial *P. pseudomallei* isolates. One initial isolate showed primary resistance to ceftriaxone and amoxycillin/clavulanate, but was still sensitive to doxcycline, co-trimoxazole (sulphamethoxazole/trimethoprim), chloramphenicol and ceftazidime. Another isolate had primary co-trimoxazole resistance. Four of five isolates from relapse episodes had the same common sensitivity pattern as initial isolates. One isolate from a fatal relapse which occurred during amoxycillin/clavulanate maintenance therapy had newly acquired resistance to ceftazidime, ceftriaxone and amoxycillin/clavulanate, but remained sensitive to doxycycline, co-trimoxazole and chloramphenicol.

Management and outcome

Twelve patients (36%) died (Table 3), eight during initial admission at 1 - 16 days (four within 48 hours), three on relapse of disease and one was dead on arrival at RDH. Deaths were septicemic in nature, usually with multi-organ failure and despite ventilation and inotrope support in four cases.

All 15 bacteremic melioidosis cases were treated with a third generation cephalosporin except for one patient with disseminated lung cancer who died the day after admission. Empirical therapy with ceftriaxone was usually changed to ceftazidime after *P. pseudomallei* was isolated. Additional parenteral therapy in most cases included one of co-trimoxazole, rolitetracycline or chloramphenicol. Nonbacteremic cases were mostly given similar initial parenteral therapy. Usually after 7 to 14 days of parenteral therapy maintenance oral therapy was begun with doxycycline or co-trimoxazole for 3 months. Two patients,

Table 4

Serological diagnosis.

	IHA	EIA IgG	EIA IgM	IF IgG	IF IgM
Splenic abscess	1 : 160	+	+	1 : 160	1 : 20
Splenic abscesses	> 1 : 5120	−	borderline +	1 : 160	1 : 160
Pneumonia	> 1 : 5120	+	borderline +	1 : 160	1 : 80
Pneumonia	> 1 : 5120	+	−	1 : 80	1 : 80
Normal reference Range	< 1 : 40	−	−	< 1 : 10	< 1 : 10

Table 5

P. pseudomallei antibiotic sensitivities (27 out of 29 initial isolates).

Sensitive (breakpoints mg/l)			
ceftazidime	(8)	imipenem	(4)
ceftriaxone	(8)	piperacillin	(32)
cotrimoxazole	(19/1)	chloramphenicol	(8)
doxycycline	(4)	amoxycillin/clavulanic acid	(8/2)
Resistant			
penicillin	(0.06)	gentamicin	(4)
erythromycin	(0.5)	tobramycin	(4)
cephalexin	(8)	ciprofloxacin	(1)
amoxycillin	(8)	trimethoprim	(2)

one with mild pneumonia and one with a buttock ulcer, had resolution of infection without antibiotics active against *P. pseudomallei.* Another ulcer case and another with mild pneumonia were treated entirely as outpatients with oral agents.

Surgery was necessary in five cases because of persisting febrile illness despite antibiotics; three of the four patients with splenic abscesses required splenectomy, one septicemic genitourinary case required prostatectomy at 24 days for multiple prostatic abscesses which still cultured *P. pseudomallei,* and a patient with a large soft tissue shoulder abscess required drainage. In addition, one of the splenectomy cases had a perforated gastric ulcer at laparotomy, as did one of the fatal cases on relapse.

There were six relapse episodes. One fatal relapse occurred after the patient absconded during acute therapy and three (one fatal mentioned above) were after failure to continue maintenance therapy. The only patient to relapse twice had a fatal second relapse after being given amoxycillin/clavulanate maintenance outside the NT following treatment of his first relapse. The isolate from this fatal relapse had acquired amoxycillin/clavulanate resistance. One 74 year old diabetic patient, apparently compliant with doxycycline maintenance, had a blood and urine culture positive relapse seven months after his initial, similar presentation. Extensive imaging revealed no evident genitourinary collection, and the relapse isolates showed standard sensitivities (Table 5). He was given parenteral therapy with ceftazidime and rolitetracycline followed by six months of maintenance oral co-trimoxazole, and he remained well six months later.

On three fatal cases autopsies were performed. A 60 year old male alcoholic with septicemia and secondary pneumonia had multiple lung abscesses bilaterally, liver cirrhosis and a congested spleen. *P. pseudomallei* grew from lung tissue, spleen and a midle ear collection. A 20 year old male insulin--dependent diabetic with septicemic pneumonia and ketoacidosis had a severe upper lobar pneumonia with microabscesses. A 56 year old alcoholic who was dead on arrival had extensive unilateral purulent pneumonia and pleuritis.

Correlates with mortality

Rainfall appeared to correlate with disease severity as well as with case numbers. Of the 14 cases in January seven (50%) died, and three others were septicemic. Although all four patients with no underlying risk factors were blood culture negative and survived, there was no statistically singificant correlation between risk factor combinations and mortality. Age, sex, ethnicity, incubation period (where ascertained) and duration of symptoms did not significantly correlate with mortality, although excluding relapse deaths and one with acute on chronic disease, all fatal cases presented within 10 days of illness onset. Pyrexia was not predictive of survival, with all but one fatal case presenting with fever above 37.5°C.

Nine (60%) of the 15 blood culture positive cases died compared with one (6%) of 16 blood culture negative cases ($p = 0.002$). The one fatal blood culture negative case died after 16 days, with progressive pneumonia following a 3 day delay in initiation of appropriate antibiotics. Table 6 presents the prognostic indices on admission. Admission lymphopenia, hyponatremia, hypoalbuminemia, low bicarbonate and elevated urea, creatinine, aspartate aminotransferase and bilirubin were all predictive of mortality. Nine of the ten fatal cases had more than two abnormal predictive parameters on admission, compared with only one of seventeen (6%) survivors ($p < 0.001$). The fatal case with only one abnormal parameter (sodium 127 mmol/l) was the blood culture negative patient mentioned above, and the survivor with four abnormal parameters had septicemia and spleen abscesses requiring splenectomy. All six blood culture positive survivors had at least one abnormal parameter, compared with three of eleven (17%) blood culture negative survivors ($p = 0.009$).

DISCUSSION

Melioidosis is now recognized as the commonest cause of fatal bacteremic community-acquired pneumonia at RDH (Anstey *et al,* 1992), with only *Streptococcus pneumoniae* responsible for more bacteremic pneumonia admissions. Over the last six years the bacteremic pneumonia mortality rate has been 26% for *S. pneumoniae* and 55% for *P. pseudomallei* (Currie, unpublished data). RDH empirical therapy for severe community-acquired pneumonia has been ceftriaxone, with gentamicin added to cover especially *Acinetobacter baumannii* (the third commonest cause of fatal bacteremic pneumonia) if underlying risk factors are present (Anstey *et al,* 1992).

In the 19 years after the first reported NT melioidosis patient in 1960 (Crotty *et al,* 1963) there were 36 further cases diagnosed at RDH, with 10 in the five years 1975 to 1979 (Rode *et al,* 1981). The 33 cases described here occurred over seven months, compared with 4.5 years for the preceding 33 cases at RDH. The correlation of melioidosis with rainfall is well recognized in the NT and elsewhere (Chaowagul *et al,* 1989; Guard *et al,* 1984; Rode *et al,* 1981) and is evident in this series which occurred during an extremely wet monsoon. A direct correlation has been shown between rainfall and increased presence of *P. pseudomallei* in surface water in Malaysia (Strauss *et al,* 1969).

The prospective nature of this study enabled clarification of several aspects of melioidosis in tropical Australia. The predominance (82%) of recently acquired disease was confirmed, with documented incubation periods from 3 days to 3 weeks. The majority of infections were considered to originate from skin penetration, either by direct injury or by contamination of a pre-existing wound. Inhalation or ingestion of *P. pseudomallei* remain possible as sources of infection (Chaowagul *et al,* 1989; Guard *et al,* 1984), although not confirmed in this study.

The association of melioidosis with pre-existing illness is well recognized (Chaowagul *et al,* 1989; Guard *et al,* 1984; Leelarasamee *et al,* 1989) and is confirmed in this study (Tables 1, 2). Particularly at risk are diabetics and alcoholics. In the NT males, Aboriginals and those 50 years old and over were also over-represented (Merianos *et al,* 1993). In Thailand, renal impairment was

present in 27% of septicemic cases and diabetes in 32% (Chaowagul *et al,* 1989). Disease is unusual in children (Guard *et al,* 1984; Tanphaichitra, (1989), but is seen occasionally (Chaowagul *et al,* 1989; Rode *et al,* 1981; Leelarasamee *et al* (1989) as with the three year old reported here.

The clinical features of our cases (Table 3) are similar to previous reports (Chaowagul *et al,* 1989; Guard *et al,* 1984; Rode *et al,* 1981; Tanphaichitra, 1989; Leelarasamee *et al,* 1989) with a spectrum of disease as follows:

1. subclinical;
2. local cutaneous and soft tissue infection;
3. septicemia without or with abscess formation in any organ (especially lung, spleen and liver);
4. residual active foci without life-threatening systemic illness *(eg* lung, subcutaneous, genitourinary, joint, bone and lymph node);
5. recrudescence of disease from latent residual foci.

The encephalitis case in this series is possibly exotoxin induced. This distinct syndrome has been recognized in the NT and posibly occurs also in Australian animals (Woods *et al,* 1992).

Despite no patient presenting in defined septic shock, usually no delay in beginning third generation cephalosporins and availability of intensive care therapy, the overall mortality in septicemic melioidosis cases was 60% (9/15). This shows little improvement over the 1960 - 1979 NT septicemic mortality of 70% (14/20) (Rode *et al,* 1981), or the north Queensland septicemic mortality of 75% (6/8) [but bacteremic mortality 46% (6/13)] (Guard *et al,* 1984), both where "conventional" melioidosis therapy was used. Series from Thailand (Chaowagul *et al,* 1989; Tanphaichitra, 1989) in which a mixture of "conventional" antibiotics and third generation cephalosporins was used had septicemic mortality rates of 68% (42/62) and 48% (14/29). In one of the Thai studies (Chaowagul *et al,* 1989) only 17/62 (27%) had initial therapy with drugs active against *P. pseudomallei* and 18/19 (95%) patients presenting with septic shock. A more recent open randomized study of severe melioidosis in Thailand showed a mortality rate with ceftazidime of 43% (12/28) in the bacteremic cases compared with 76% (19/25) ($p = 0.03$) for "conventional" therapy with chloramphenicol, doxycycline, trimethoprim and sulphamethoxazole (White *et al,* 1989). Of interest is that ceftazidime did not reduce the mortality in the first 48 hours, suggesting that early deaths may reflect irreversible pathological abnormalities. Four deaths in our study were within 48 hours and two other patients were maintained on ventilation till death at 4 and 16 days. Over half the septicemic melioidosis deaths in Thailand were within 48 hours (Chaowagul *et al,* 1989), as were five of six deaths in Queensland (Guard *et al,* 1984).

Three of the deaths in our series were on relapse, making acute septicemic mortality 40% (6/15). The one death in the 16 blood culture negative cases followed a delay in beginning appropriate therapy, which is recognized as an important contributor to mortality in severe melioidosis.

For empirical sepsis therapy we generally prefer ceftriaxone (2 g daily) over ceftazidime dime because of its better gram positive coverage, especially *S. pneumoniae* and *Staphylococcus aureus,* and also because it can be given intramuscularly in rural areas. Ceftazidime is used when *P. pseudomallei* is confirmed or strongly suspected.

At present we add tetracycline or co-trimoxazole to ceftazidime for acute therapy of melioidosis (Sookpranee *et al,* 1992). The importance of subsequent maintenance therapy is well documented (Guard *et al,* 1984; Leelarasamee *et al,* 1989; Sookpranee *et al,* 1992) and we aim for at least three months of doxycycline or co-trimoxazole.

The often slow response to therapy and the persistence of positive cultures despite 14, 20 and 22 days of ceftazidime in three non-fatal cases in this series reflects the disseminated nature of the disease, with often deep-seated tissue involvement including visceral abscesses. It remains unclear to what extent toxin production and host immune activation contribute to pathogenesis and mortality in addition to the disseminated pyogenic infection; corticosteroid therapy has been unhelpful (Leelarasamee *et al,* 1989). The abnormal admission laboratory parameters predictive of mortality (Table 6) are of interest and have been noted in Thailand (Chaowagul *et al,* 1989). They reflect both the severity of disease and the multi-organ involvement in fatal cases.

Table 6

Prognostic indices on admission.

Parameter	Died (%)	Survied (%)	Significance P
White cells > 11.0 × 10^9/l	8/10 (80)	13/16 (81)	NS
Lymphocytes < 1.2 × 10^9/l	6/8 (75)	4/15 (27)	0.039
Sodium < 130 mmol/l	7/10 (70)	6/16 (38)	NS
Urea > 8 mmol/l	6/10 (60)	1/17 (6)	0.004
Creatinine > 120 µmol/l	6/9 (69)	0/15 (0)	< 0.001
Bicarbonate < 22 mmol/l	4/7 (57)	0/13 (0)	0.007
Bilirubin > 22 µmol/l	6/9 (67)	3/17 (18)	0.028
AST > 45 units/l	6/9 (67)	2/17 (12)	0.008
Albumin < 33 g/l	8/9 (89)	2/17 (12)	< 0.001

AST = serum aspartate aminotransferase
NS = not significant

While much remains to be learnt about pathogenesis and optimal therapy of melioidosis, emphasis in tropical Australia must be placed on :

1. prevention and control of the two major risk factors, diabetes and alcoholism;
2. decreasing exposure to wet season soils by use of protective footwear and gloves where appropriate;
3. preventing delay in beginning appropriate therapy for suspected melioidosis;
4. encouraging compliance with maintenance therapy to minimize relapse.

ACKNOWLEDGEMENTS

We would like to thank our physician colleagues Drs David Lo, Jim Burrow and Vicki Krause for their support; Dr Leslie Ashdown in Townsville for performing the serological tests for melioidosis; the Department of Microbiology, Fremantle Hospital, Western Australia for performing sensitivity testing; and Jill Albion and Gaby Falls for help preparing the manuscript. This study received fiancial support from the Menzies School of Health Research and the Department of Health and Community Services, Northern Territory, Australia.

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