# Nosocomial Outbreak of *Burkholderia pickettii* Infection Due to a Manufactured Intravenous Product Used in Three Hospitals

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**Forty-six cases of nosocomial infection caused by *Burkholderia pickettii* were reported between June and November 1993 in three metropolitan hospitals in Madrid. A case-control study of the outbreak was conducted to identify its cause. Seventy-four percent of the patients were males; the mean age ± SD of the patients was 54 ± 20 years. Sixty-five percent of the patients presented with some gastrointestinal disorder, and 80% had a peripheral catheter; 98% were treated with intravenous fluids, and 96% were treated with intravenous ranitidine. On the basis of results of a descriptive study and knowledge of the epidemiologic features of *B. pickettii*, a provisional causal hypothesis was formulated: intravenous ranitidine was the source of the outbreak. As a control measure, it was advised to stop treatment with this drug. On the basis of results of logistic regression and the microbiological isolation of *B. pickettii* in an ampule of the drug, we concluded that intravenous ranitidine was the cause of the outbreak.**

*Burkholderia pickettii* has been reported as a causal agent of bacteremia, meningitis, osteomyelitis, and urinary and respiratory infections [1]. This microorganism has also been associated with outbreaks of nosocomial infection (bacteremia or colonization of the respiratory tract) due to contamination of intravenously administered products, "sterile" distilled water, chlorhexidine in water, respiratory therapy solutions, and intravenous catheters as well as with pseudooutbreaks due to contamination in the laboratory [2–11]. The aims of the present study were to conduct an epidemiologic investigation of an outbreak, identify the causes, and adopt the appropriate control measures.

## Materials and Methods

*Case descriptions.* An outbreak of 46 cases of nosocomial infection by *B. pickettii* occurred between June and November 1993 in three hospitals in Madrid: Hospital Universitario San Carlos (HUSC; 1,500 beds), Hospital Severo Ochoa (HSO; 425 beds), and Hospital General de Móstoles (HGM; 401 beds).

*Microbiological method.* The clinical samples were processed by means of standard procedures. The drug samples were inoculated in hyperconcentrated nutrient broth, brain-heart infusion broth, or commercial hemoculture bottles. Isolates of *B. pickettii* from clinical or environmental samples were identified on the basis of colony morphology and results of gram staining, the oxidase test, and the API 20 NE identification system (bioMérieux, Marcy l'Etoile, France).

*Identification of the causes.* We conducted a case-control study of this epidemic. Every patient for whom microbiological culture was positive for *B. pickettii* was defined as a case. The controls were randomly selected from patients who were admitted to the same department where a case was detected on the same day (± 2 days) that the sample from which *B. pickettii* had been isolated was obtained. Two controls were selected for each case from a group of possible controls. The information on all cases was gathered 48 hours before the sample positive for *B. pickettii* was taken.

*Statistical methods.* The crude magnitude of the risk (odds ratio) for the possible evaluated factors was estimated. Stratified analysis was performed to determine if there were any biases or interactions. The logistic regression model was adjusted by the forward strategy. The 95% confidence intervals for the odds ratios were calculated.

## Results

*Outbreak description.* A total of 46 cases of *B. pickettii* infection were reported. The infections first developed in HUSC (20 cases). Twenty-one (46%) of the cases occurred in HSO, and five cases (11%) occurred in HGM. There was no history of epidemiologic outbreaks due to *B. pickettii* in any of the three hospitals. The epidemic curve (figure 1) suggested that the cases were produced by a common source in HUSC and HSO. The clinical characteristics of the cases are summarized in tables 1 and 2.

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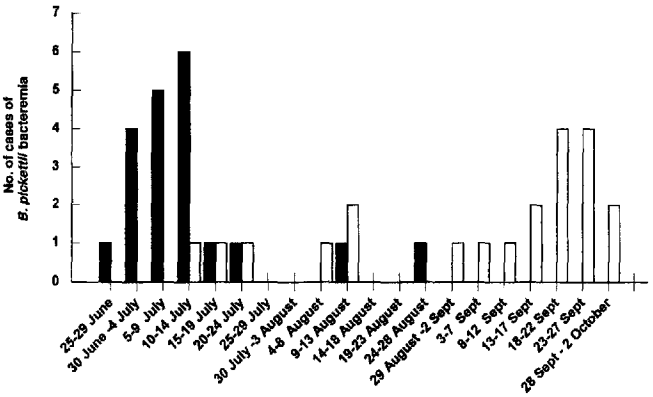


**Figure 1.** Epidemic curve of cases of bacteremia due to *Burkholderia pickettii* in two hospitals in Madrid: Hospital Universitario San Carlos (■; 20 cases) and Hospital Severo Ochoa (□; 21 cases). The five sporadic cases in Hospital General de Móstoles were excluded.

*Clinical/microbiological description.* The 46 cases had 48 infections. The most frequent infection was bacteremia (frequency, 96% [44 cases]). Two (4%) of the cases had catheter infections without associated bacteremia. Thirty-five percent of the cases presented with an infection by another organism. No death was attributed to the infection. Afterward, *B. pickettii* was isolated from six parenteral nutrition samples that contained ranitidine (BBL, Alonga, Madrid). Ranitidine vials were collected again for culture, and *B. pickettii* was isolated from an intravenous ranitidine vial (lot H30; BBL, Alonga) at HUSC. *B. pickettii* was isolated in 47 blood cultures, from three intravenous catheter tips, and from an exudate of surgical drainage of a pancreatic pseudocyst. Thirty-three isolates were analyzed for the biotype.

*Identification of the causes.* The 92 controls were homogeneous with the cases on all studied variables. The crude odds ratios for the risk factors studied are shown in figure 2. When stratified analysis was applied to all variables that were significant in the univariate analysis, intravenous ranitidine remained significant. We also observed that nasogastric tubes behaved as a modifying variable with regard to the effect of intravenous ranitidine (table 3).

**Table 1.** Clinical characteristics of cases of *Burkholderia pickettii* bacteremia and controls.

| Characteristic | Cases ($n$ = 46) | Controls ($n$ = 92) | $P$ value |
|---|---|---|---|
| Mean age (SD) in y | 54 (20) | 56 (22) | >.05 |
| Previous average hospital stay (SD) in d | 10 (13) | | |
| Total average hospital stay (SD) in d | 28 (27) | 16 (18) | .01 |
| Percentage of cases with indicated characteristic | | | |
| Male sex | 74 | 54 | .02 |
| Digestive pathology | 65 | 54 | >.05 |
| Nonfatal basic disease | 74 | 70 | >.05 |
| Department of Medicine | 67 | 43 | |
| Recovery in ICU | 39 | 30 | |
| Parenteral nutrition | 26 | 5 | |

NOTE. ICU = intensive care unit.

**Table 2.** Clinical characteristics of cases of *Burkholderia pickettii* bacteremia according to three hospitals in Madrid.

| Characteristic | HUSC ($n$ = 20) | HSO ($n$ = 21) | HGM ($n$ = 5) |
|---|---|---|---|
| Mean age (SD) in y | 57 (22) | 56 (21) | 49 (5) |
| Previous average hospital stay (SD) in d | 12 (13) | 8 (13) | 13 (13) |
| Total average hospital stay (SD) in d | 40 (33) | 19 (14) | 14 (27) |
| Percentage of cases with indicated characteristic | | | |
| Male sex | 75 | 71 | 80 |
| Digestive pathology | 65 | 71 | 40 |
| Nonfatal basic disease | 70 | 76 | 20 |
| Department of Medicine | 50 | 62 | 20 |
| Recovery in ICU | 55 | 24 | 40 |
| Parenteral nutrition | 40 | 14 | 20 |

NOTE. HGM = Hospital General de Móstoles; HSO = Hospital Severo Ochoa; HUSC = Hospital Universitario San Carlos; ICU = intensive care unit.

## Discussion

There was epidemiologic evidence that *B. pickettii* was the causal agent in our outbreak. Our findings were consistent with those of all other reported outbreaks of *B. pickettii* infection [2–10]. Our outbreak involved a greater number of cases than did any previously documented outbreak. *B. pickettii* variant 2, which was isolated in our outbreak, has been described as the least virulent variant. In our study, this low virulence was confirmed by the absence of death attributed to this microorganism.

The greatest difficulty in the search for the cause of the outbreak was the distribution of the drug in the hospitals. HUSC used three different manufacturer's products for intravenous ranitidine treatment, and the commercial brand of ranitidine

**Table 3.** Effect of intravenous ranitidine and nasogastric tubes on the occurrence of bacteremia due to *Burkholderia pickettii* (logistic regression model).

| Variable | Coefficient | OR | 95% CI | $P$ value |
|---|---|---|---|---|
| Constant | −1.46 | | | .0012 |
| Intravenous ranitidine | 2.16 | 8.66 | 1.28–58.85 | .0027 |
| Nasogastric tube | 0.97 | 2.65 | 0.83–8.47 | .1005 |
| Ranitidine and nasogastric tube | 9.54 | 13,847 | | .7668 |

NOTE. Goodness of fit ($\chi^2$ = 77.021; $P$ = 1.000).

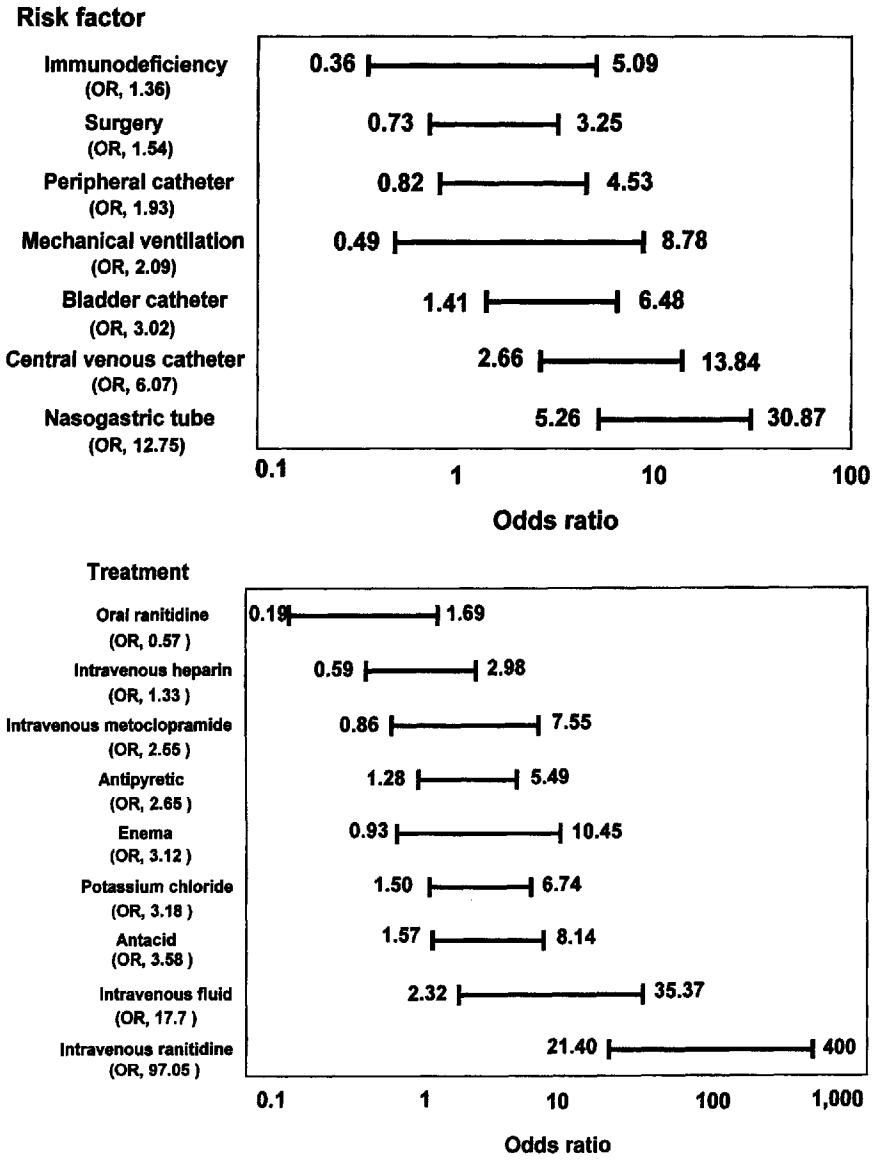


**Figure 2.** Results of a univariate analysis of the risk factors (*top*) and administered treatments (*bottom*) of *Burkholderia pickettii* infection. Crude odds ratios and 95% confidence intervals are shown.

that was administered was not recorded in the nurse's notebook. HSO used only ranitidine from BBL, Alonga; this product was suspected when *B. pickettii* was isolated from the parenteral nutrition containing intravenous ranitidine. All the patients from HSO with *B. pickettii*–induced bacteremia had been treated with intravenous ranitidine within the previous 48 hours. The two patients with nasogastric tubes did not receive intravenous ranitidine during the 48 hours before the specimen for hemoculture was obtained. Therefore, the presence of a nasogastric tube interacts with ranitidine administration. HSO supplied intravenous ranitidine ampules to HGM, where a small outbreak occurred; ranitidine was administered intravenously in all five cases of the outbreak.

As a control measure, the boards of medical directors of the three hospitals were informed when intravenous ranitidine became suspected as the likely source of the outbreak (18 November 1993). The fact that no new cases were detected or reported once the product stopped being dispensed (13 December 1993) supports our hypothesis.

The intravenous ranitidine ampules may have been contaminated during the sterilization process of its production. The usual process consists of filtration through 0.45 or 0.22 micropore filters. Reports have shown that *B. pickettii* may be able to pass through these filters [11]. After the collection of the drug vials, *B. pickettii* was isolated from two lots of the product (H30 and H33).

Epidemiologic analysis and microbiological evidence (the same biotype identified in all the strains studied and isolation of *B. pickettii* from an ampule of the drug [lot H30]) confirmed that intravenous ranitidine was the cause of nosocomial infections by *B. pickettii*. This outbreak highlights the importance of considering manufactured products as a possible cause of

nosocomial infections and offers a sobering reminder of the need to maintain high standards for sterilization techniques and quality control procedures.

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