

## BURKHOLDERIA CEPACIA OUTBREAK IN THE PEDIATRICS WARDS OF THE PHILIPPINE GENERAL HOSPITAL

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### ABSTRACT

**Objective:** To describe an outbreak which occurred at the Pediatric Wards of the Philippine General Hospital.

**Methods:** A cross-sectional study was conducted at the Pediatric Wards of the Philippine General Hospital. Bacteriology records of all pediatric patients from August 2001 to October 2001 were reviewed for identification of all blood isolates of *Burkholderia cepacia* and medical records of those who were positive for the organism were likewise reviewed.

**Results and Conclusion:** Thirty-five patients from the Pediatric Wards of the Philippine General Hospital grew *Burkholderia cepacia* in their blood from August to October 2001. Ages of cases ranged from 3 days old to 17 years old. Sepsis (74.3%) was the most common clinical presentation, followed by pneumonia (17.1%). Conditions found to be associated with *Burkholderia cepacia* infection were prolonged hospitalization (85.7%), malnutrition (37.1%) malignancy (28.6%), and invasive procedures (25.7%). Most of the isolates were sensitive were Metopenem (100%), Imipenem (100%), Cefepime (100%), Piperacillin-Tazobactam (100%), Ciprofloxacin (100%), and Ceftazidime (97%). The isolates were highly resistant to Aminoglycosides, Aztreonam, and Ceftriaxone. Fifty (50%) of patients given Ceftazidime and Piperacillin-Tazobactam did not show improvement and were shifted to other antibiotics. The outcome of patients were generally favorable. Eighty percent of patients were discharged cured, 14.3% expired due to their illness, while 5.7% were lost to follow-up.

The source of *Burkholderia Cepacia* involved in this outbreak remains unknown. Water analysis as well as bacterial cultures of antiseptics used all turned out to be negative. A droplet route of transmission is also unlikely because the patients involved in this outbreak were situated beds apart from each other. The outbreak just resolved spontaneously.

Cefepime as monotherapy was recommended for the treatment of this infection. The importance of rational antibiotic use and strict hand should be emphasized.

### INTRODUCTION

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Keywords: *burkholderia cepacia*, pediatric outbreak

*Burkholderia cepacia* has emerged as a human pathogen causing numerous outbreaks especially in immunocompromised hosts. Although its natural habitat is the soil and water, the hospital environment remains the main source of infection. Because of its resistance to multiple antibiotics, the organisms can be difficult to treat.

In the Pediatric Wards of the Philippine General Hospital *Burkholderia cepacia* became one of the top isolates recovered from the blood from August 2001 to October 2001. The incidence was alarming especially that were no similar reported cases in this institution in the past.

*Burkholderia cepacia* was previously known as *Pseudomonas multivorans*, *Pseudomonas Kingii*, and *Pseudomonas cepacia* and has now been reclassified as new genus *Burkholderia*<sup>1</sup>.

This organism was discovered in 1949 by Walter Burkholder of Cornell University as the phytopathogen responsible for a bacterial rot of onions<sup>2</sup>. *Burkholderia cepacia* is a motile, free-living, non-fermentative Gram negative aerobic bacilli with multitrichous polar flagella. This microorganism can easily be mistaken for *Stenotrophomonas maltophilia*<sup>1</sup>. It is ubiquitous in the environment and can be found in water, soil, plants, and animal sources. The organism has minimal nutritional requirements and is able to survive even in tap and distilled water<sup>1,9</sup>. Although *Burkholderia cepacia* does not appear to survive on dry surfaces for more than a week, it can survive for many months in water<sup>2</sup>. It is also known to be resistant to the commonly used antibiotics, antiseptics and disinfectants<sup>1</sup>. These 2 properties may explain its wide distribution in the environment. Although *Burkholderia cepacia* has low intrinsic pathogenicity for the healthy host, the organism has a particular predilection for the lungs in cystic fibrosis patients and has emerged as an important opportunistic human pathogen in hospitalized and immunocompromised patients<sup>3</sup>. The microorganism's unusually broad metabolic capabilities which enable it to survive and proliferate in water-based environments, probably account for its propensity to cause nosocomial outbreaks<sup>3,6</sup>.

*Burkholderia cepacia* was first discovered as a human pathogen causing endocarditis in the 1950's. In 1971, it was reported as the causative agent of "foot

rot" in U.S. troops on swamp training exercises in Northern Florida; it was also isolated from troops serving in the Mekong Delta, Vietnam<sup>4</sup>.

Although there are a few reported cases of *Burkholderia cepacia* infection in the pediatric age group, most of the reported cases belong to the adult population. Most of the reports of *Burkholderia cepacia* bacteremia in pediatric patients involved those with cystic fibrosis<sup>9,12,13,14</sup>. There were also a few reported neonatal cases of *Burkholderia cepacia* bacteremia in the neonates. Gravel – Trooper et al reported a 3-year outbreak of pseudobacteremia with *Burkholderia cepacia* in 13 neonates. This was later traced to be secondary to a contaminated blood gas analyzer<sup>16</sup>. In 1995, 2 cases of *Burkholderia cepacia* sepsis in premature neonates were reported by Kahyaogly. Prematurity and invasive procedures were the risk factors identified<sup>17</sup>.

Locally, there was a report of increased incidence of *Burkholderia cepacia* bacteremia in the Philippine Children's Medical Center from October 1999 to September 2000<sup>18</sup>. They were able to isolate the organism from the blood of 50 neonates. Eleven (22%) of the cases died. In the said institution, the isolates were resistant to Aminoglycosides, Cefotaxime, Aztreonam, and Imipenem. The isolates were sensitive to Ceftazidime, Ciprofloxacin, and Cotrimoxazole<sup>18</sup>.

The possibility of highly virulent strains of *Burkholderia cepacia* with the potential to survive intracellularly exists if the organism acquires virulence from *Burkholderia pseudomallei*, a very closely related pseudomonad. *Burkholderia pseudomallei* is a soil saprophyte that gives rise to melioidosis, a life-threatening tropical disease seen mostly in Southeast Asia. The disease has a broad clinical spectrum and can remain dormant for years before giving rise to sepsis and death. The pattern of disease produced by *Burkholderia pseudomallei* may vary from a spectrum of clinical consequences from *Burkholderia cepacia* acquisition. The transfer of genetic material between these two closely related organisms in the environment is highly probable, with the subsequent emergence of a hybrid pathogen<sup>2</sup>.

Treatment is a challenge as most of the isolates are resistant to antibiotics commonly used for negative bacterial infections. There are also reported cases of strains that are susceptible in vitro but are not eradicated during therapy.

## OBJECTIVES

**General:** To describe an outbreak which occurred at

the Pediatric Wards of the Philippine General Hospital caused by *Burkholderia cepacia*.

### Specific:

1. To describe the most common clinical presentation of *Burkholderia cepacia* infection among pediatric patients.
2. To describe the common laboratory findings seen in a patient with *Burkholderia cepacia* infection.
3. To determine the most common conditions associated with *Burkholderia cepacia* infection.
4. To determine the antimicrobial susceptibilities of *Burkholderia cepacia* isolated in the pediatric wards of the Philippine General Hospital.
5. To describe the clinical outcome of patients with *Burkholderia cepacia* infection.
6. To determine the source of the outbreak.

## METHODOLOGY

A prospective study was conducted at the Pediatric Wards of the Philippine General Hospital.

Bacteriology records of all patients in the Pediatric Wards from August 2001 to October 2001 were reviewed for identification of all blood isolates of *Burkholderia cepacia*.

The medical records of all patients in the Pediatric Wards admitted during this period with blood isolates of *Burkholderia cepacia* were then reviewed. Information gathered include patients' identification, admitting diagnosis, date admitted, the date when blood culture was taken, identification of blood isolate/s as well as their antimicrobial susceptibility pattern. Other laboratory information obtained were the patients' CBC results, chest x-ray findings, and bacterial culture and susceptibility test results of other sterile sites. Also of importance were the patients' presenting symptoms upon admission, as well as the symptoms during the time when blood culture was done, the type of invasive procedures that the patient has undergone if any, and his/her nutritional status. Included in the data gathered were the kinds of antibiotics that the patients had received prior to and during the isolation of *Burkholderia cepacia* and the number of doses received. Information regarding the outcome of patients were also gathered. Improvement was noted by lysis of fever, improvement of the patients' well-being and respiratory status, improvement of the patients' chest x-ray findings. Cure was defined as clinical improvement and a negative blood culture after 3-5 days of antibiotic therapy.

Bacteriologic analysis were also done on the samples of all water sources of the Pediatric Wards, as well as the antiseptics used prior to blood extraction. This was performed to find the possible source of this outbreak.

## RESULTS

### Patients' Profile:

From August 2001 to October 2001, 35 patients from the Pediatric Wards of the Philippine General Hospital had blood cultures positive for *Burkholderia cepacia*.

Ages of cases ranged from 3 days old to 17 years old (Median 1 year old). (Figure 5) Twenty-two (63%) were males and 13 (37%) were females (Figure 1 & 2).

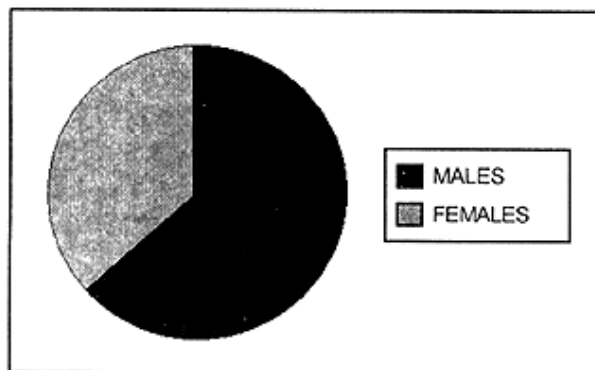


Figure 1. Sex Distribution of Pediatric Patients with *Burkholderia cepacia* Infection August 2001-October 2001, PGH

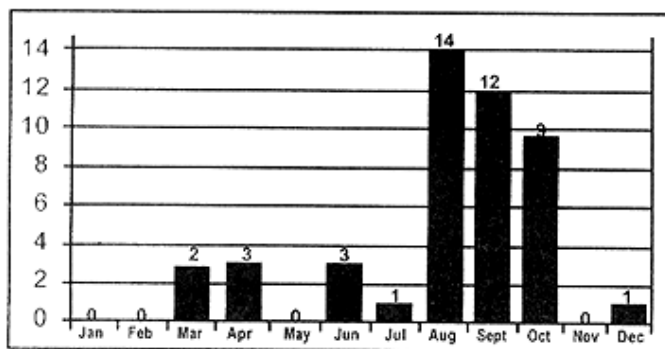


Figure 2. No. of *Burkholderia cepacia* Isolates for the Year 2001 Ward 9 & Ward 11, PGH

### Symptomatology:

Majority of pediatric patients in this study who grew *Burkholderia cepacia* in their blood were not very ill except for the presence of fever. Aside from the 5 (14.3%) patients who needed intensive care and who eventually expired, most of the those who were symptomatic presented with only one or more of the following signs and symptoms: temperature instability, cough, tachypnea, dyspnea, and lethargy. The most common presenting symptom was fever (66.7%),

followed by tachypnea (33.3%), then cough (22.2%). (Figure 8). The degree of fever for those patients who were febrile ranged from low-grade to high-grade. Most of those who had high-grade fever had other concomitant problems like increased intracranial pressure secondary to shunt infection and malfunction, or were undergoing immunosuppressive therapy. Three (8.6%) patients were asymptomatic during the time when *Burkholderia cepacia* was isolated from their blood.

### Associated Factors:

Of the total number of subjects, 10 (28.6%) had malignancies and were undergoing chemotherapy, 8 (22.8%) had problems (congenital anomalies or infections) involving the central nervous system, 8 (22.8%) patients had community-acquired pneumonia, 3 (6.8%) had persistent diarrhea. Malnutrition is another factor that was quite common in this patients. Thirteen (37.1%) patients with *Burkholderia cepacia* infection were moderately to severely wasted.

Prolonged hospital stay was observed common to most patients with *Burkholderia cepacia* infection. The range of hospital stay for these patients was from 4 days to as long as 90 days (mean 26 days). Thirty (85.7%) cases were nosocomially acquired while 5 (14.3%) patients had blood culture (+) for *Burkholderia cepacia* on the day of their admission to the hospital. Those who stayed in the hospital for prolonged periods of time had malignancies of different forms and were undergoing chemotherapy or had shunt malfunction with shunt infection. In these situations, inadequate funds for chemotherapy was the most common reason for prolonged hospital stay.

Ten (28.6%) patients with *Burkholderia cepacia* infection had malignancies of various forms, 9 of these were on chemotherapy during the time when *Burkholderia cepacia* was isolated from their blood.

Another factor which may be associated with *Burkholderia cepacia* infection was the experience of having undergone invasive medical or surgical procedures. Nine (25.7%) of the patients in this study underwent various invasive procedures such as mechanical ventilation, venous cutdown, nasogastric intubation, exploratory laparotomy with appendectomy, surgical repair of gastroschisis, debridement and evacuation of epidermal abscess, and tube ventriculostomy.

### Laboratory Findings:

For the CBC results, 21 (60%) showed

leucocytosis with WBC counts ranging from 12,000 – 30,000/cu.mm., 4 (11.4%) were neutropenic, while 10 (28.6%) had normal WBC counts. These findings did not correlate with the outcome of the patients.

Although there were patients who presented with cough and tachypnea, only 6 (17.1%) of the 35 patients showed radiologic evidence of pneumonia. Twenty-five (71.4%) had normal chest x-ray findings and 1 (2.9%) patient had hyaline membrane disease.

In all the 35 pediatric patients with blood cultures positive for *Burkholderia cepacia*, bacterial cultures of other sterile sites were all negative for the said organism.

**Antimicrobial Resistance**

The isolates were 100% sensitive in vitro to Meropenem, Imipenem, Cefepime, Ciprofloxacin, and Piperacillin-Tazobactam. Thirty out of 31 (97%) isolates were sensitive to Ceftazidime. The isolates were highly resistant to Aminoglycosides (70-95%). Trimethoprim-Sulfamethoxazole (50%), and Ceftriazone (70%).

**Clinical Response to Treatment**

Out of the 35 patients, 24 (68.6%) patients showed improvement after having received 6-8 doses of antibiotics to which the organism was found to be sensitive by Disc Diffusion Method. However, there were 11 (31.4%) patients who, despite being given antibiotics to which the organism was sensitive to still grew the organism in their blood. These were the patients who were given Ceftazidime and Piperacillin-Tazobactam. These patients also did not show clinical improvement. This suggests only in vitro susceptibility of the organism to the antibiotic being given or that the organism can develop rapid resistance to these

**Table 1. Response to Antibiotics of Patients with *Burkholderia cepacia* Infection August 2001 to October 2001, PGH**

ANTIBIOTICS USED	CURED	SHIFTED TO ANOTHER ANTIBIOTIC	EXPIRED
Cefepime+/-Amikacin	9	0	2
Meropenem+/-Amikacin	6	0	0
Imipenem	1	0	0
Ceftazidime+/-Amikacin	5	5	0
Piperacillin-Tazobactam	3	3	2
Trimethoprim-Sulfamethoxazole	0	2	0
Ampicillin+/-Amikacin	2	1	1
Cefuroxime	1	1	0
Ceftriazone	1	1	0

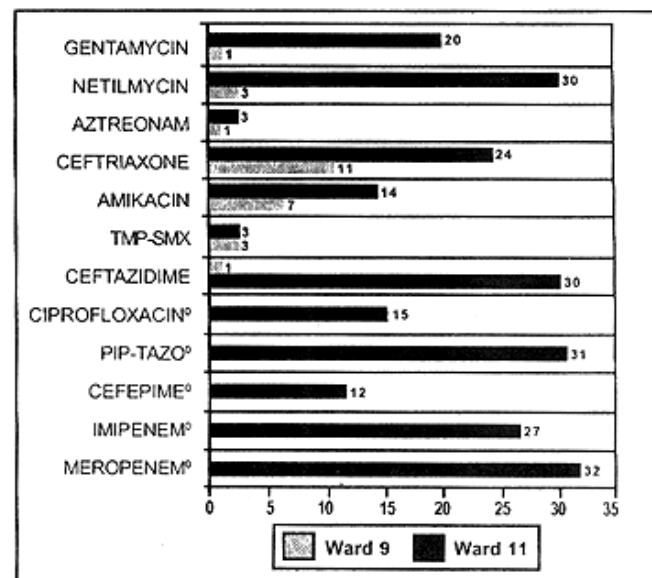
antibiotics. Also, a big factor for treatment failure in some cases was poor compliance to the prescribed antibiotic regimen. All patients who were given Cefepime and Meropenem had negative blood culture results after 3-5 days of treatment.

**Outcome of Patients:**

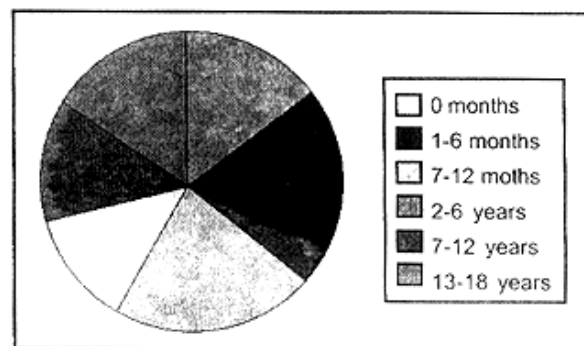
Of the 35 pediatric cases with *Burkholderia cepacia* in their blood 28 (80%) were discharged cured, 2 (5.7%) were lost to follow-up, 5 (14.3%) died of septic shock, and in all of the 5 cases the organism was nosocomially acquired.

**Source of the Outbreak:**

All the 35 patients were admitted in Wards 9 and 11, but they were not located in only one area of the room. These patients were in fact located beds apart from each other. Patients occupying the beds next to the ones with *Burkholderia cepacia* did not grow the



**Figure 4. Antibiotic Resistance Pattern of *Burkholderia cepacia* Isolates, August 2001-October 2001, PGH**



**Figure 5. Age Distribution of Pediatric Patients with *Burkholderia cepacia* Infection August 2001-October 2001, PGH**

organism in their blood nor in any other sterile site. By this observation, a droplet route of transmission for this outbreak is unlikely.

Water analysis as well as bacterial cultures of the antiseptics used in both Pediatric Wards all turned out to be negative.

## DISCUSSION

The incidence of *Burkholderia cepacia* sepsis in the Pediatric Wards of the Philippine General Hospital increased significantly for the months of August 2001 to October 2001.

Although most of the reported cases of *Burkholderia cepacia* bacteremia in pediatrics involved those patients with cystic fibrosis<sup>3,9,12,13,14,15</sup> this is not the case in the Philippine General Hospital because cystic fibrosis is not common in Filipinos.

Result of this study show that sepsis was the most common presentation of the pediatric patients with *Burkholderia cepacia* infection. This is in contrast to the reports that the organism commonly infects the respiratory tract especially in immunocompromised patients<sup>8,9,10,13</sup>. Majority of the patients included in this study had fever as the only sign of infection. Despite the elevation in temperature these patients were not toxic-looking and were still playful even if they were already harboring the organism in their blood.

In this study, *Burkholderia pseudomallei* was isolated from the blood of 2 (5.7%) patients before they grew *Burkholderia cepacia*. The first patient grew *Burkholderia pseudomallei* one month before he grew *Burkholderia cepacia* and the second patient 5 days before *Burkholderia cepacia* was isolated from his blood, these two cases had pneumonia during the time when *Burkholderia pseudomallei* was isolated. In both instances, improvement was noted after two days of giving a 4<sup>th</sup> generation cephalosporin. During the time of isolation of *Burkholderia cepacia* from their blood both cases presented only with fever and there were no symptoms referable to the respiratory system. *Burkholderia cepacia* sepsis in these two cases mentioned did not differ in severity and response to treatment from the other cases in this study. The two patients remained alert and playful despite the elevation in temperature. Fortunately, this finding did not correlate with a report that the possibility of highly virulent intracellularly exists if the organism acquires virulence from *Burkholderia pseudomallei*<sup>2</sup>

*Burkholderia cepacia* is a bacteria which is considered to be of low virulence and rarely causes

invasive disease in healthy human hosts. In this study, malignancy, immunosuppressive therapy, and malnutrition were among the factors associated with the occurrence of *Burkholderia cepacia* sepsis.

The length of hospital stay can also be associated with the nosocomial acquisition of *Burkholderia cepacia*. It has been shown in this study that approximately half of these patients with *Burkholderia cepacia* in their blood has been staying in the hospital for more than seven days. In this case, health care workers may provide a major role in the transmission of this microorganism.

Pediatric patients who underwent invasive procedures also showed an increased chance of infection due to *Burkholderia cepacia*. Cases were more likely to have undergone invasive medical interventions such as venous cutdown, nasogastric intubation, and mechanical ventilation. Two patients also underwent major surgical procedures (exploratory laparotomy with appendectomy and surgical correction of gastroschisis). *Burkholderia cepacia*, being a free-living microorganism can survive in moist sites in the hospital environment. It can be transmitted to patients via equipments such as mechanical ventilators and also through vascular catheters. Outbreaks may thus occur when there is failure in disinfection of the equipments, or when there is a break in the aseptic technique during the performance of an invasive procedure.

*Burkholderia cepacia* is known to be resistant to antiseptics and disinfectants because it has the ability to form an adherent biofilm called glycocalyx. It is responsible for the resistance of the microorganism to iodine<sup>5</sup>. Numerous small focal hospital outbreaks involving non-cystic fibrosis patients have usually been due to a contaminated common source, such as disinfectant preparations or intravenous solutions<sup>6,7,11</sup>. In this study however, bacterial cultures of the antiseptics used in both Pediatric Wards were all negative for *Burkholderia cepacia*.

Studies have shown an association between *Burkholderia cepacia* acquisition and the use of nebulized medications<sup>8,9,10,13</sup>. Nebulized medication devices can become contaminated when non-sterile water is used to rinse nebulizers between use, by extrinsic contamination of nebulized medications, and presumably by the hands of health care workers manipulating the equipments.

Lastly, it has been shown in this study that *Burkholderia cepacia* is often resistant to the commonly used antibiotics. It is usually resistant to



aminoglycosides, antipseudomonal penicillins, and antipseudomonal 3<sup>rd</sup> generation cephalosporins<sup>11</sup>. It is possible that these organisms have adapted to live in soil and water where they are exposed to naturally-occurring antimicrobial substances.

A strong association has been found between *Burkholderia cepacia* colonization and prior aminoglycoside therapy, therefore reemphasizing a need to review guidelines for antimicrobial usage<sup>12</sup>.

*Burkholderia cepacia* possesses all the characteristics needed in order for it to cause nosocomial infection. These properties are the following: ability to establish and survive in hospital environment because of minimal growth requirements, ability to colonize the mucosa and skin of patients and hospital staff, ability to survive on the surfaces of various hospital equipments, and ability to resist antibiotic therapy and killing by antiseptics.

## CONCLUSION AND RECOMMENDATIONS

Despite an extensive investigation, the source of *Burkholderia cepacia* involved in this outbreak remains unknown since it did not seem to originate from a common source. The droplet route of transmission in these cases is also unlikely.

Result of this study show that sepsis was the most common clinical presentation of *Burkholderia cepacia* infection among the pediatric patients of the Philippine General Hospital, followed by pneumonia.

Most of the patients had leucocytosis with shift to the left, although in some cases total white blood cell count can be normal. Chest x-ray results were normal in majority of the cases.

Prolonged hospitalization, malnutrition, malignancy with immunosuppressive therapy, and invasive procedures were the conditions found in this study to be associated with *Burkholderia cepacia* sepsis in the pediatric population.

Most of the isolates were sensitive to anti-pseudomonal 3<sup>rd</sup> and 4<sup>th</sup> generation cephalosporins, ureidopenicillins, carbapenems, and Ciprofloxacin. They were highly resistant to Aminoglycosides, Aztreonam, Trimethoprim-Sulfamethoxazole, and Ceftriaxone. Based on the results of this investigation. Although sensitivity in vitro to Cefazidime and Piperacillin-Tazobactam, many patients did not respond to this treatment as evidenced by persistence of the bacterial in the blood we recommend the use of Cefepime as monotherapy for the treatment of *Burkholderia cepacia* infections.

Outcome of the patients with *Burkholderia cepacia* infection were generally favorable. Five (14.3%) out of the 35 patients expired.

To prevent infection with *Burkholderia cepacia*, the following are recommended: surveillance among high-risk patients, regular and thorough cleaning of hospital equipments, interruption of transmission through strict handwashing, and rational use of antibiotics.

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