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A fatal acute appendicitis with sepsis and pneumonia was caused by melioidosis: a case report

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ABSTRACT

We report anunderdiagnosed fatal case of melioidosis that involved dygestion system which complicated with pneumonia, and sepsis. The case was initially diagnosed as acute appendicitis, and subsequently the patient underwent an exploratory laparatomy and appendectomy. He was discharged afer 3 days of hospitalization. Thirty days afterward, he was admitted to another private hospital to experience another exploratory laparatomy with indication of pancreatitis, intra-abdominal organs adhesions, and postoperative enterocutaneous fistula (ECF), and hospitalized there for 25 days. He eventually suffered from sepsis, pneumonia, unclosed ECF, anemia, hypoalbuminemia, and electrolyte imbalance. He then referred to a tertiary teaching hospital and hospitalized there for a total 134 days until he passed away. His clinical condition was declining, despite a long course of broad spectrum antibiotics. Treatment delay, prolong hospitalization, and complications were the inevitable, although *Burkholderia pseudomallei* was finally identified 2 weeks prior to his death. This case highlight that melioidosis canassociate with acute appendicitis, and that the delay on its diagnosis and treatment may trigger complications and death.

ABSTRAK

Kami melaporkan kasus fatal melioidosis yang melibatkan sistem pencernaan dengan komplikasi pneumonia, sepsis, dan berakibat pada kematian. *Appendicitis* akut adalah diagnosis klinis awal pada kasus melioidosis ini, dan pasien langsung menjalani operasi laparatomi eksplorasi dan appendectomy, kemudian pulang setelah mondok selama 3 hari di sebuah rumah sakit swasta. Tiga puluh hari setelahnya, pasien mondok di rumah sakit swasta lainnya selama 25 hari, dan menjalani operasi laparatomi eksplorasi yang ke dua dengan indikasi pankreatitis, perlengketan organ intra abdomen, dan fistula enterokutan. Kondisi klinis pasien memburuk, dan terjadi sepsis disertai penumonia, luka fistula entero-kutan (FEK) terbuka, anemia, hypoalbuminenia, dan ketidakseimbangan elektrolit. Kemudian pasien dirujuk ke rumah sakit pusat rujukan dan pendidikan dan mondok selama 134 hari sebelum akhirnya meninggal. Kondisi klinis pasien terus memburuk meskipun telah mendapat rangkaian terapi antibiotik berspektrum luas. Keterlambatan terapi, lamanya waktu pemondokan, dan terjadinya komplikasi menjadi tidak terelakkan, meskipun *B. pseudomallei* dapat diidentifikasi pada 2 minggu sebelum kematian. Kasus ini menekankan pentingnya memahami bahwa presentasi melioidosis secara klinis dapat berhubungan dengan appendicitis akut, dan keterlambatan dalam mendiagnosis dan terapi dapat memicu terjadinya komplikasi dan kematian.

Keywords:
melioidosis;
fatal;
delay in diagnosing;
B. pseudomallei;
appendicitis;

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INTRODUCTION

Melioidosis is an infectious disease caused by *Burkholderia pseudomallei.*[1] Clinical feature of melioidosis vary, with major presentation as sepsis, but specific clinical feature and severity depending on the bacterial entry route into host, host immune response, bacterial strain and load.[1] Case fatality rate of melioidosis range from 10% to 50%, with risk of having recurrent infection is 5-28% in patients who survived acute melioidosis.[1]*Burkholderia pseudomallei* infamous with its diverse antimicrobial resistance feature, including resistant to third-generation cephalosporins, penicillins, rifamycins, and aminoglycosides.[2] They also showed relative resistance to quinolones and macrolides which limits therapeutic options.[2] However, most of *B. pseudomallei* show consistent susceptibility to meropenem and ceftazidim that experts and US CDC considered intravenous meropenem and ceftazidim as effective therapy for melioidosis.[3,4]

In Indonesia, melioidosis was scarcely reported although some studies predicted that Indonesia was one of endemic countries in Southeast Asia.[5,6] We describeda fatal melioidosis that occurred in 2015. This case report elucidatedthat melioidosis was rarely accurately and timely diagnosed as its clinical presentation might similar or associated with other infectious diaseases, particularly in limited setting like Indonesia. In this case, melioidosis was associated with acute appendicitis and pancreatitis. In addition, multiple attempts of major operation without a timely identification of the etiology, and long term of empirical broad spectrum antibiotics treatment showed a very limited benefit for the patient. This case report highlight the importance of early diagnoses establishment, and appropriate antibiotic management in melioidosis.

CASE REPORT

A 31 years old male suffered from a chronic post surgical wound, after an appendectomy in a private hospital in May 2015. Two weeks after discharged, he complained of abdominal pain, and fever as infection inflicted on the unhealed surgical wound. He went to another private hospital, where abdominal multi-slice computed tomography (MSCT) scan was conducted and revealed a massive gut adhesion and excessive pus surrounding his pancreas. He then was admitted for exploratory laparotomy. However, 25 days after his second operation, an apparent sepsis finally directed his physician to refer him to Dr. Sardjito General Hospital, a tertiary and teaching hospital in Yogyakarta. He was admitted into Emergency

In the emergency department, he appeared skinny (body weight 55 kg, body mass index: 19.03) and weak, with fever (38.6 °C), tenderness, shortness of breath (respiratory rate: 26 cycles/min), elevated heart rate (148 beat/min), and blood pressure of 107/60 mmHg. The patient chief complain waspain. Pus was continuously dripped from his wound. Laboratory examination supported diagnoses of infection with leucocytosis and neutrophilia (TABLE 1). On physical examination, the attending physicians found consolidation in both side of his lung. A thoracic rontgen photograph showed a prominent right -bilateral pleural effusion (FIGURE 2A). The physicians established diagnosis and management of imminent septic shock complicated with bilateral pneumonia and pleural effusion, anemia, hypoalbuminemia, and surgical site infection of entero-cutaneous fistula (ECF). Resuscitation was conducted in the Emergency Department, and antibiotics (ceftriaxone and metronidazole) were administered in a combination.

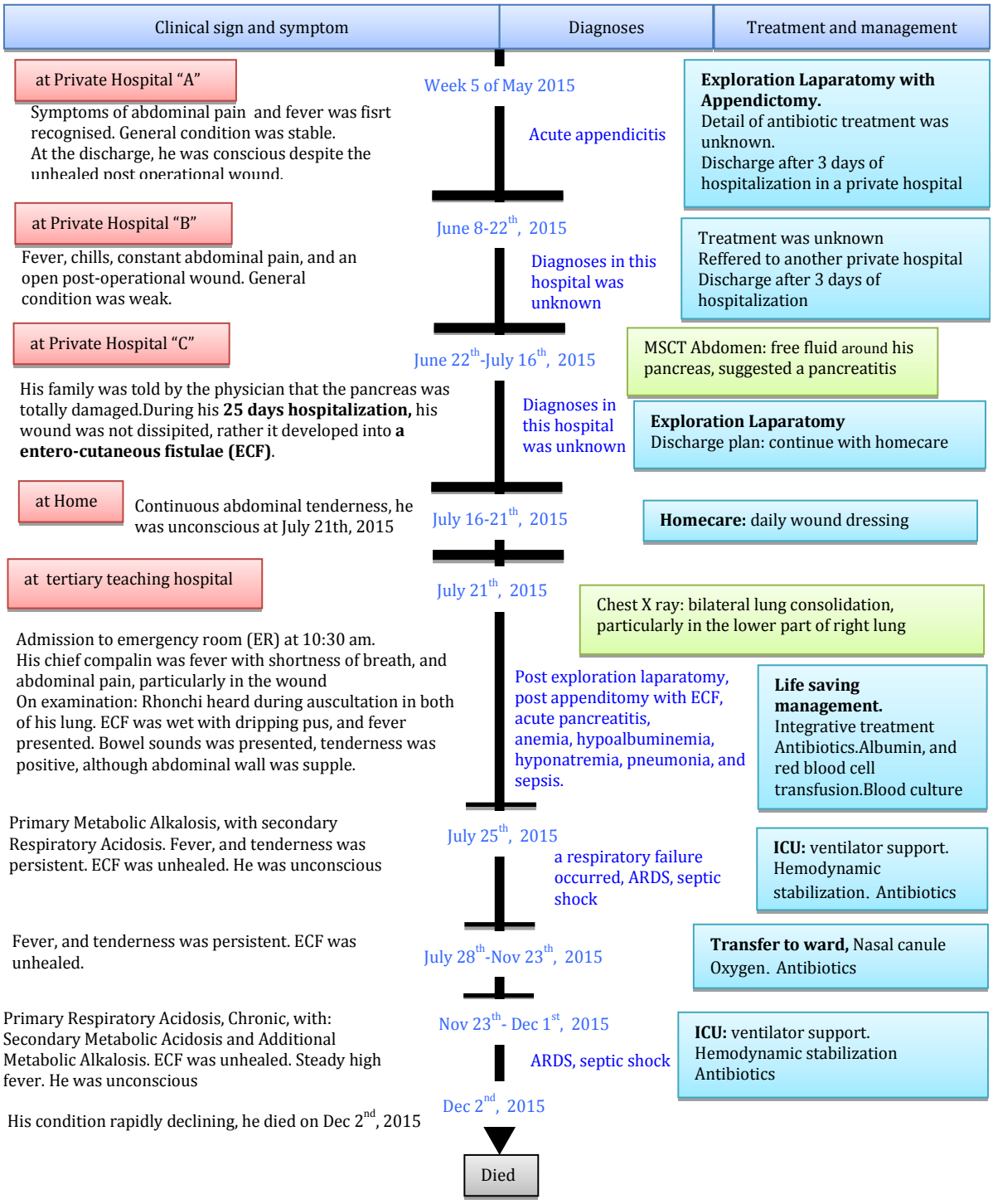

FIGURE 1. A timeline of disease progress, intervention, and outcome of melioidosis.

TABLE 1. Laboratory tests of the melioidosis case during the hospitalization.

Test	July 21th, 2015	July 26th, 2015 (ICU)	Nov 28th, 2015 (ICU)	Dec1st, 2015 (ICU)
Hemoglobine (g/dL)	7.2	7.6	10.4	8.8
Hematocrite (%)	22.9	24.3	32.3	27.9
Leucocyte (/µL)	27,000	19,670	35,160	47,800
Neutrophil (%)	84.4	87	88.7	90.7
Lymphocyte (%)	7.1	6	5.1	4.8
Monocyte (%)	8.4	6.7	3.9	3.7
Basophil (%)	0.1	0.1	0.2	0
Eosinophil (%)	0	0.2	2.1	0.8
Thrombocyte (/µL)	415,000	447,000	281,000	158,000
PH		7.442	7.299	7.295
PO_2(mmHg)		105.7	112.3	101,1
PCO_2(mmHg)		46.6	51.7	53
SO_2(%)		99.6	97.6	96.5
$cHCO_3$(mmol/L)		29.2	24.8	25.2
BE (mmol/L)		6	-1.9	-1.6
BEecf (mmol/L)		7	-1.6	-1.3
$AaDO_2$		484.8	0	336.6
a/AO_2		17.9	100	23.1
FiO_2(%)		0.9	0.21	0.7
Temperature (°C)	38.7	38.3	36.9	37
Albumin (g/L)	1.68	1.65		1.84
Natrium (mmol/L)	131	133	154	153
Chloride (mmol/L)	99	94	114	114
Kalium (mmol/L)	4.3	3.42	3.8	2.9
Amilase	121			
Lipase	180			

After five days of hospitalization, his condition was worsening. Fever and lung consolidation were persisted although broad-spectrum antibiotics have been administered, and transfusion of albumin and blood, as well as resuscitation had been conducted. On July 25th, 2015 he was transferred into inensive care unit (ICU), as he fell to septic shock. During the 3 days of intensive care, a regimen of antibiotics comprised metronidazole, meropenem, and aztreonam, as well as ventilator support were administed. The patient was transferred back to the ward as his condition was stable on July 27th, 2015. However the following4 months of hospitalization were a prolong fluctuation of clinical condition, which was repeat signs of a temporary stable,pre-shock conditions. The ECF was never healed, and the clinical manifestation was exaggerated with pneumonia, electrolyte imbalance, alkalosis, acidocis, and persistent sign of sepsis, tachypnea, tachycardia, leucocytosis, neutrophilia, lymphopenia, and anemia (TABLE 1).

An abdominal MSCT was conducted at August 7th, 2015 suggested a damaged pancreas, with numerous of small size intra-abdominal granuomas (FIGURE 2B). Amylase and lipase were elevated

supported the diagnosis of pancreatitis (TABLE 1), combined with leucocytosis and neutrophilia the suspected etiology was bacterial infection. During the 135 days of hospitalization,nine sets of two sides blood cultures were taken at different days, and the tests were performed with Vitec2, however none of it yielded positive result (TABLE 2). Pus, urine and sputum cultures were also conducted, however it failed to reveal the etiology, until the last wound culture was conducted at day 118 of his hospitalization at another laboratory of microbiology, which revealed *B. pseudomallei* among others bacteria cultivated from the same wound culture (TABLE 2).

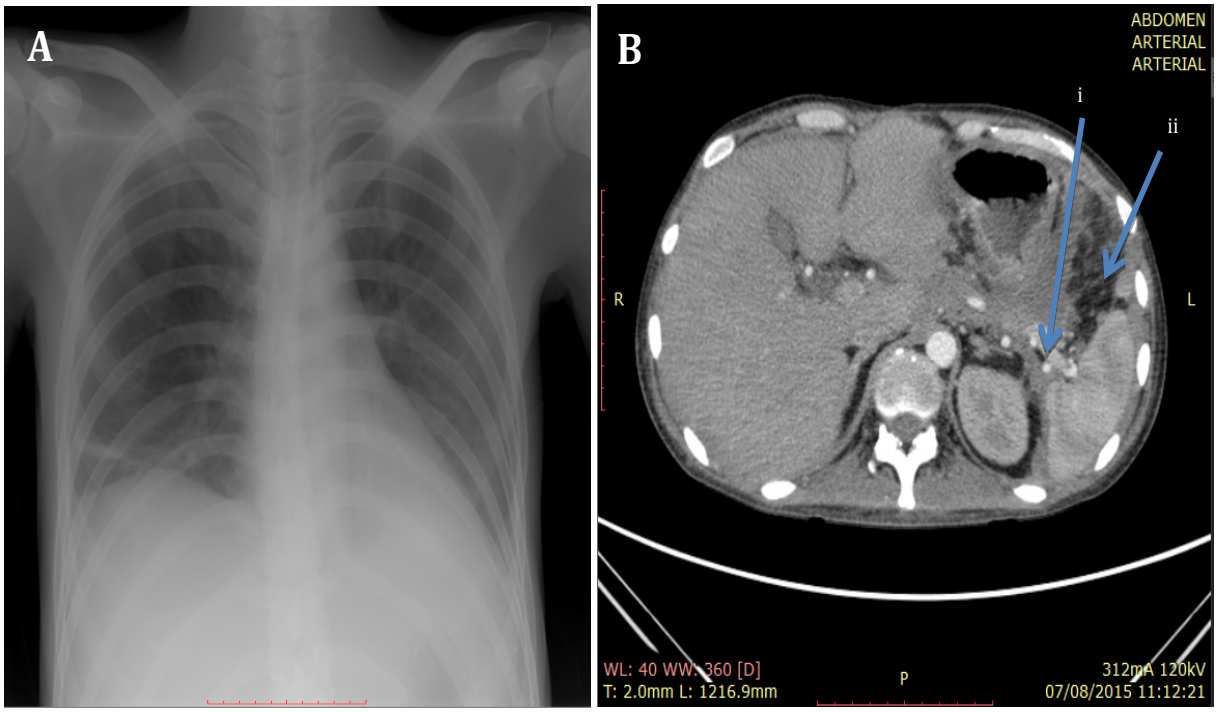

FIGURE 2. Chest X-Ray and abdominal MSCT of the melioidosis. (A). Bilateral lung consolidation was observed from the chest X-ray. (B). MSCT of the abdomen at level of splenic artey (i) and pancreas tail. MSCT showed signs of intra-abdominal adhesion, small granulomas (ii).

Antibiotics regimen, steroid, and antipyretic were continuously changing empirically, following the patient's response during hospitalization. In August 2015, he receive antibiotics combination of gentamycin, metronidazole, ceftazidime, levofloxacin, and amikacin, as swell as antifungal fluconazole. The next month, September, the course of antibiotics were amikacin, imipenem, cefixime, and imipenem-cilastatin, with antifungal of fluconazole. In October 2015, imipenem-cilastatin, levofloxacin, amikacin, and colistin were implemented replaced the previous regimen. In November 2015, the antibiotics regimen comprised imipenem-cilastatin, levofloxacin, cefotaxime, amikacin, ceftazidime, aztreonam, and meropenem. However the clinical condition plunged into septic shock, and at November 24th, 2015 the patient was again transferred to ICU, where he receive intensive care for 8 days before finally he passed away at December 2nd, 2015.

TABLE 2. Culture of blood, pus, urine, sputum, and wound swabs during the 135 days of hospitalization at tertiary teaching hospital.

Date	Material	Result
Jul 23rd, 2015	Blood (2 sites)	Negative
Jul 27th, 2015	Blood (2 sites)	Negative
Aug 3rd, 2015	Pus	Negative
Aug 12th,2015	Pus	*Escherichia coli*, ESBL + (contamination?)
Aug 12th, 2015	Blood (2 sites)	Negative
Aug 16th, 2015	Blood (2 sites)	Negative
Aug 24th, 2015	Blood (2 sites)	Negative
Aug 25th, 2015	Urine	Negative
Aug 29th, 2015	Sputum	Streptococci
Oct 12th, 2015	Blood (2 sites)	Negative
Oct 27th, 2015	Blood (2 sites)	Negative
Nov 3rd, 2015	Pus	Negative
Nov 11th, 2015	Blood (1 sites)	Negative
Nov 15th, 2015	Blood (2 sites)	Negative
Nov 20th, 2015	Wound swab	1. *Enterobacter cloacae* 2. *Klebsiella oxytoca* 3. *Pseudomonas putida* 4. *B. pseudomallei* , with susceptibility pattern: • susceptible to: amikacin, meropenem • resistant to: amoxycillin, clavulanate, ampicillin, eritromycin, gentamycin, levofloxacine, chloramphenicol, penicillin, cefepime, cefixime, ceftriaxone, cefuroxime, ciprofloxacine, and sulfamethoxazole

The research conducted on melioidosis was approved by the Medical and Health Research Ethics Committee, Faculty of Medicine-Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta (Ref.No. KE/FK/1346/EC/2019). Informed consent was obtained from the next of kin.

DISCUSSION

Melioidosis is a severe infectious disease with diverse clinical manifestations and can be difficult to diagnose as it requires microbiologic expertise to examine the suspected case.[7] *Burkholderiapseudomallei*isthecausative agent, a gram negative bacteria which able to survive in both intracellular and extracellular for decades in hosts, and endemic to tropical regions of Asia, South America, Central America, Pacific countries, and Indian ocean islands and some African countries.[7] *Burkholderia pseudomallei*are dubbed as *tropical time bomb* or *Vietnamese bomb*, as they can cause a latent infection with the longest documented interval between exposure and clinical manifestation is 62 years.[8] They are tier 1 select agent by the US government, and the culture required special precaution to reduce exposure risk.[7,8] There is no pathognomonic clinical feature of melioidosis.[7] The current standard diagnostic is culture, however the colony of *B. pseudomallei*

can be miss-identified as culture contaminant or other species, especially by laboratory staff who unfamiliar with this organism.[7] *Burkholderia pseudomallei* colonies are usually non-lactose fermenter with metallic sheen and become pink and become umbonated or rugose on Mac Conkey agar after 48 hours.[7] Under microscope with gram staining, the bacteria appear as bipolar or "safety pin" shaped.[7] However if the specimen obtained from patients received antibiotics before, the appearance rarely seen, instead *B. pseudomallei* may appear highly atypical resembling yeasts or filamentous.[7] The one or two days age of colonies usually erroneously dismissed as contaminant or miss-identified as *Pseudomonas spp* or other organisms when standard diagnosticmethods are used.[7] The performance or commercially systems widely used such as API 20NE (bioMérieux, Craponne, France), Phoenix (Becton, Dickinson, and Company, Franklin Lakes, NJ, USA), and Vitex 2 (bioMérieux, Craponne, France) to correctly identify *B. pseudomallei* were ranging 37-99%, 0-28%, 0-98% respectively.[7] Moreover, currently no specific and sensitive serologic or rapid tests available to identify *B. pseudomallei,* although experienced laboratory staff can identify them with some additional antibiotic tests and specific media (Ashdown), or confirm them with PCR.[7]*Burkholderia pseudomallei* is typically susceptible to amoxicillin/ clavulanic acid, trimethoprim-sulfamethoxazole, and ceftazidime, but resistant to aminoglycosides, colistin and polymyxin.[4,7]

Clinical features of melioidosis vary, comprises acute, chronic, and latent diseases. Acute clinical manifestations of melioidosis vary widely, including sepsis, pneumonia, or internal organ abscesses with or without localized infection, therefore melioidosis should be suspected from every patients in endemic regions with community acquired sepsis or pneumonia, urinary tract infection, upper respiratory tract infection, or abscesses especially for those with predisposing factors such as diabetes mellitus, renal disease or immunosuppression.[7] The chronic manifestations with symptoms usually occur after 2 months of exposure, and are often mimic other diseases such as tuberculosis and cancer.[7] The duration of latent melioidosis takes decades, thus a complete travel history should be obtained accordingly.[7] Relapse or re-infection with the same or different genotype of *B. pseudomallei* may occur after antibiotics treatment.[8] Combination of the aforementioned, the lack of clinicians and laboratory staff awareness, and failure to elicit travel history from patients returning from endemic area are contributed to the difficulties on clinical diagnosis of melioidosis.[7]

The major clinical feature of melioidosis in this case was sepsis, resulted from a prolong misdiagnoses. The reccurent septic shocks were originated from the untreated infection. The unhealed ECF was also a sign of uncontrolled infection. The existed comorbidities and or complication, such as pneumonia, anemia, hypoalbominemia, hiponatremia, andelectrolyte imbalance may contribute significantly to the worsening condition and lead to the mortality after long period of hospitalization.

Bacterial culture is the gold standard for diagnose melioidosis.[7] However, given the persistent sign and symptoms of infection (high fever although anti-pyretic already administered, leucocytosis, neutrophilia, and monocytosis), blood cultures were unable to identify the etiology. In hyperendemic areas such as Thailand, the positive rate of *B. pseudomallei* from blood culture range from 9.1 to16.5% of suspected melioidosis cases.[9-11] A seven-

year study in Thailand analyzed 63,066 blood cultures reported isolation of *B. pseudomallei* in 11% of 7,296 positive blood cultures.[12]

Melioidosis cases may manifest as systemic infection with cause patient fatality, but blood cultures could result false negative.[7] Therefore specific-monoclonal antibody assays were suggested to identify melioidosis, as several study reported high sensitivity and specificity (> 95%).[13,14] In addition, rapid diagnostic tools were also recommended for screening in the area with limited resources where culture is unavailable.[15] Molecular methods are certainly valuable diagnostics tools, which can provide high sensitivity and specificity, as well as rapid identification however the technology is scarcely available in developing countries.[16-18]

The major challenge in establishing diagnosis of melioidosis is the selection of colony from culture prior to conducting further identification whether using biochemical or molecular methods.[19,20] Many bacterial colonies are usually selected after 18-24 h of incubation, since they have produced specific colony features of optimum size of colony.[7,20] In contrast, the colony of *B. pseudomallei* after 18-24 hours of incubation, appears as a contaminant colony.[7,20] Experienced laboratory technician will wait up to 3 days to re-evaluate the colony, so that the colony can be identified.[7,20]

In this case, the problem comprised diagnostic challenges, complications, and the rapid deterioration of patient condition, which unresponsive to the antibiotics treatment. In Yogyakarta where melioidosis was very rarely reported, identification was a big challenge. *Burkholderia pseudomallei* was not identified in the early phase of the patient illness that might cause delay of appropriate infection management, which eventually might lead to patient death. Patient suffered from pneumonia, hypoalbuminemia, electrolyte imbalance, acute pancreatitis, post-operative *colo-cutaneus* fistula with secondary infection, acute kidney injury, melena, sepsis, and prolong hospitalization as the consequences of etiology misidentification. Prolong hospitalization, and immobilization also contributed to hospital-acquired pneumonia with bilateral lung effusion, which finally lead to acute respiratory distress syndrome (ARDS).

The isolated *B. pseudomallei* which susceptible to meropenem and amikacin only, and the presence of other pathogens (TABLE 3) altogether developed into infectious agents package which very difficult to combat. The physicians have struggled to stabilize patient condition, with the available resource. Unfortunately, antibiotic administration management was also challenging since empirical treatment in this case was prone to ineffective to diminish infection, then severe complications accompanied, that made infection even more difficult to be cured. It showed the dynamic of antibiotic treatment and the disease journey. It showed that patient had enduring prolong fever, infection that unresponsive to antibiotic treatment, and recurrent septic shocks before finally he passed away.

CONCLUSION

Lesson learned from this case is the crucial of diagnoses establishment and appropriate antibiotic treatment in melioidosis management. In addition, in the setting where resource are limited, a rapid diagnostic tool will help the clinicians to adjust the empirical treatment prior the culture result.

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