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Complications of Melioidosis: A Systematic Review

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Abstract

Introduction: Melioidosis, also known as Whitmore disease, is caused by the gram-negative bacillus, *Burkholderia pseudomallei* and remains a public health concern in Southeast Asia and northern parts of Australia. This study attempts to identify all possible complications of melioidosis and its outcomes.

Methods: Literature search was conducted from databases such as PubMed, Science Direct and Scopus from 1st January 2000 to 31st August 2019. Medical Subject Headings (MeSH) search strategy was used with the terms 'Melioidosis' or '*Burkholderia pseudomallei*' and 'Complications'.

Results: A total of 162 titles were identified and 22 articles were included in the review. Findings showed that among the 22 articles, the ratio of male to female melioidosis incidence was 2.3 to 1, with most cases (86.4%) aged older than 14 years old and showed a mean age of 46 years old. A third (7/22) of the papers reported the involvement of the nervous system as a complication of melioidosis followed by cardiovascular complications. Among the 23 cases reported, 13 had underlying medical conditions with most of them (84.6%) having diabetes mellitus or newly diagnosed with diabetes mellitus. Overall, only one case (4.3%) had resulted in mortality, while 17.4% developed complications and 78.3% managed a full recovery after undergoing treatment for melioidosis.

Conclusion: The most commonly found complication of melioidosis involved the nervous system but patient outcomes were favourable. Rare complications included mycotic aneurysm that can be fatal. Melioidosis can affect almost any organ leading to various complications.

Keywords: Melioidosis, *Burkholderia pseudomallei*, complications, encephalitis, brain

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Introduction

Melioidosis also known as Whitmore disease is caused by the gram-negative bacillus, *Burkholderia pseudomallei*. The disease is endemic in Southeast Asia, Papua New Guinea, most of the Indian subcontinent, Southern China, Hong Kong, and Taiwan. It is observed to be highly endemic in northeast Thailand, Malaysia, Singapore and northern Australia. Sporadic cases have also been reported in parts of South America, West and East (Birnie et al., 2019; Currie, Dance, & Cheng, 2008). Person to person contact is rare but potentially may occur through direct contact (Currie, Ward, & Cheng, 2010).

The incubation period for melioidosis is generally 1-21 days however with a high inoculum, symptoms may develop after a few hours. Although melioidosis may remain latent from months to years before symptoms develop (Currie et al., 2000). The disease generally occurs in individuals with impaired immunocompetence whose non-intact skin has had contact with contaminated soil or surface water. Among the known clinical risk factors associated with melioidosis are diabetes mellitus, pre-existing liver and renal diseases, chronic lung diseases, thalassemia, malignancies and hazardous alcohol consumption (Chaowagul et al., 1989; Currie et al., 2010; Suputtamongkol et al., 1999).

The clinical manifestation is broad spectrum, ranging from acute fulminant sepsis to chronic infection mimicking tuberculosis. The lungs are the primary organ affected where patients are presented with acute or subacute pneumonia (Currie et al., 2010; Meumann, Cheng, Ward, & Currie, 2012). In children, the disease may present as acute febrile illness or in less virulent forms ranging from chronic localised skin infection to the formation of abscess in organs where the most common organs being affected are the lung, spleen, and liver (Sanderson & Currie, 2014).

In some regions, for instance in Thailand and Cambodia , one third of children with melioidosis develop complications such as parotid abscess or acute suppurative parotitis which is in contrast to Australian children who rarely develop such complications (Sanderson & Currie, 2014; White, 2003). A previously published case report found that melioidosis could lead to uncommon complications such as mycotic aneurysm despite undergoing aggressive antibiotic therapy (Anunnatsiri, Chetchotisakd, and Kularbkaew, 2008). In Sri Lanka, Guillain-Barre syndrome was found to be a rare complication of melioidosis and should be suspected in patients who develop lower limb weakness (Wijekoon, Bandara, Kailainathan, Chandrasiri, and Hapuarachchi, 2016).

Although melioidosis is endemic in Southeast Asia and northern parts of Australia, it is still considered uncommon and exotic in most parts of the world. Currently, there is a gap in knowledge on the specific melioidosis complications found in the human body. This review attempts to provide a comprehensive overview of all complications, and outcomes of melioidosis among children and adults from the available literature and case reports seen globally.

Methodology

Literature Search Strategy

Extensive search of literature was obtained from electronic databases such as PubMed, Science Direct and Scopus from 1st January 2000 to 31st August 2019. For PubMed, Medical Subject Headings (MeSH) and the title terms 'Melioidosis' 'or' '*Burkholderia pseudomallei'* 'and' in combination with the term 'Complications' were used. Similar literature search strategy with the other electronic databases were used as well. Two investigators (MG and MM) conducted the systematic review of the literature independently by assessing the study eligibility from the extracted data. A third investigator (ET) was consulted in case of disagreements or discrepancies so that a final decision could be made based on mutual consensus.

Study selection and eligibility criteria

Titles and abstracts were extracted from the extensive search via electronic databases. Duplicate research papers were then removed, and the relevant papers were screened based on the titles and abstracts. Research papers that were irrelevant were excluded. Full texts of the selected research papers were then retrieved and assessed for eligibility. Inclusion criteria for the eligibility study comprised articles that reported complication of melioidosis while excluding systematic reviews and editorial reviews. The studies selected also had to be in the English language. Studies in which the full article was not accessible were excluded. Among the results, 114 articles were excluded since their title and abstract did not match the criteria, 19 articles were excluded after they were found to be irrelevant based on a full text review or if researchers were unable to retrieve the full text. Irrelevant here means that the article did not provide in depth explanation of melioidosis complications.

Data extraction

This review extracted information regarding the first author's name, country, year of publication, age of studied participants, complication(s), system affected and outcome(s).

Study selection process

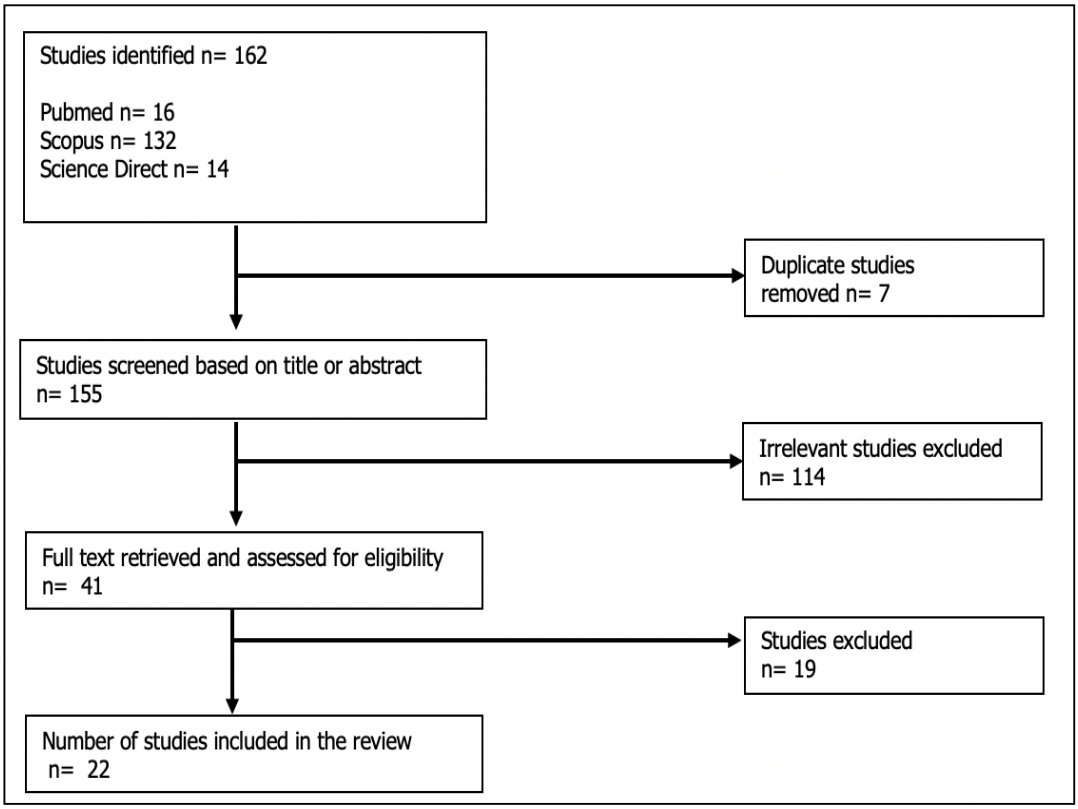

Figure 1: Flow chart of the study selection process

Results

Study selection and characteristics of the published studies

Figure 1 demonstrates the flowchart for the conducted systematic review following the PRISMA-P guidelines. A total of 162 titles were identified through the search. A total of 22 articles were deemed appropriate for inclusion.

This systematic review showed that the ratio of male to female melioidosis incidence is 2.3 to 1 (Table 1), with most cases (86.4%) aged older than 14 years old (adults). The mean age of cases in this review is 46 years old. Only 4.3% (1 case) resulted in mortality, while 17.4% developed complication and 78.3% had full recovery after undergoing treatment for melioidosis.

Table 1: Summary of reviewed articles

Author, Year, Country	Age (years), Sex	Complication	Systems Affected	Treatment	Outcome
Maytapa et al., 2018, Thailand	52, Male	Gastrosplenic fistula	Gastrointestinal	IV Ceftazidime, splenectomy with gastrosplenic fistula repair, oral Trimethoprim/ Sulfamethoxazole	Recovery
Wijekoon et al., 2016, Sri Lanka	46, Female	Guillaine-Barre Syndrome	Nervous	IV Meropenem, plasmaphoresis, IV Cotrimoxazole, IV Co-amoxyclav	Recovery
Lu et al., 2018, Malaysia	38, Male	Constrictive Pericarditis	Cardiovascular	IV Ceftazidime, IV meropenem, oral Bactrim, IV Ciprofloxacin	Complication
Direksunthorn, 2017, Thailand	54, Male	Portal Vein Thrombosis	Cardiovascular	IV Ceftazidime, IV Metronidazole, oral Amoxicillin-Clavulanic acid	Recovery
Morelli et al., 2015, Netherlands	63, Male	Acute Renal Failure	Renal	IV Ceftazidime, oral Trimethoprim/Sulfamethoxazole, oral doxycycline	Complication
Li et al., 2015, Hong Kong	82, Male	Mycotic Aneurysm of aortic arch/left subclavian artery	Cardiovascular	IV Amoxicillin-clavulanate and Azithromycin, IV Ceftazidime, oral Amoxicillin-clavulanate and Doxycycline, IV Meropenem and Doxycycline, IV Minocyclin and Moxifloxacin	Mortality
Ng et al., 2015, Malaysia	62, Male	Acute Parkinsonism	Nervous	IV Imipenem, Levodopa/Benserazide, oral Co-trimoxazole and Doxycycline	Recovery
Abidin et al., 2007, Malaysia	65, Male	Pacemaker infection	Others	IV Ampicillin-sulbactam, IV Meropenem, IV Ceftazidime, Oral TMP-SMX and Doxycycline	Recovery
Chen et al., 2007, Taiwan	51, Male	Endophthalmitis	Ophthalmic	IV Cefazolin and Gentamicin, IV Ceftazidime, oral Trimethoprim/Sulfamethoxazole, Intravitreal	Complication

				Vancomycin and Ceftazidime, Topical Vancomycin, Ceftazidime and 1% prednisolone acetate	
Wang et al., 2003, Singapore	61, Male	Necrotising Fasciitis	Integumentary	Wound debridement and split thickness skin grafting, IV Ceftazidime and Doxycycline, IV Imipenem, oral Amoxicillin-clavulanate and Doxycycline	Recovery
Kumar et al., 2016, India	10 months, Female	Brainstem microabscesses	Nervous	IV Amoxicillin-clavulanic acid, IV Meropenem and Cotrimoxazole	Recovery
Porter et al., 2018, Australia	35, Female	Chorioamnionitis	Reproductive	IV Meropenem, IV Ceftazidime, oral amoxicillin-clavulanic acid	Recovery
Saravu et al., 2015, India	39, Male	Encephalitis and empyema	Nervous	IV Ceftazidime, oral Cotrimoxazole and Doxycycline	Recovery
Saravu et al.,2015, India	45, Male	Encephalitis and Transverse Myelitis	Nervous	IV Meropenem and Cotrimoxazole, oral Cotrimoxazole and Doxycycline	Complication
Wijewickrama and Weerakoon, 2017, Sri Lanka	33, Female	Thrombotic thrombocytopenic purpura	Hematopoietic	IV Ceftriaxone and Clarythromycin, plasmapheresis, IV Meropenem, oral Cotrimoxazole	Recovery
Chen et al., 2018, China	55, Male	Splenic abscess	Lymphatic	Laparoscopic exploration and splenectomy, IV Cefmenoxime and Pieracillin-Tazobactam, IV Ceftazidime, oral Trimethoprim/Sulfamethoxazole,	Recovery
Nernsai et al., 2018, Thailand	31, Female	Left Tubo-ovarian abscess	Reproductive	IV Gentamicin and Clindamycin, exploratory laparotomy, left salpingo-oophorectomy and pus drainage, IV Ceftazidime and oral Cotrimoxazole	Recovery
Kogilavaani et al., 2014, Malaysia	11, Female	Bilateral orbital abscesses with subdural empyema	Ophthalmic and Nervous	IV Cloxacillin, Cefepime, and Metronidazole, IV Ceftazidime and Ceftriaxone, IV Meropemen and	Recovery

		and cavernous sinus thrombosis		Metronidazole, oral Trimethoprim/Sulfamethoxazole	
Mohammad and Ghazali, 2017, Malaysia	64, Male	Venous thrombo-embolism and cavitary pneumonia	Cardiovascular and Respiratory	IV Ceftazidime and IV Heparin	Recovery
Pelerito et al., 2016, Portugal	62, Female	Gluteal abscesses and left ileum osteomyelitis	Musculoskeletal	IV Meropenem, oral Amoxicillin-clavulanic acid	Recovery
Schindler et al., 2002, United Stated of America	58, Male	Infected intrathoracic subclavian artery pseudoaneurysm	Cardiovascular	Coronary artery bypass grafting procedure and pseudoaneurysm repair, femofemoral bypass graft, IV Ceftazidime, oral Doxycycline and Amoxicillin clavulanic acid	Recovery
Andersen et al.,2016, Australia	4, Male	Acute flaccid paralysis	Nervous	IV Meropenem and Cotrimoxazole, oral Cotrimoxazole	Recovery
Martin et al., 2016, Philippines	44, Male	Liver abscess	Hepatobilliary	IV Ceftazidime, oral Trimethoprim/Sulfamethoxazole	Recovery

Discussion

This review attempt to identify all the various complications of melioidosis to further improve the management of patients with melioidosis. Since all the reviews were obtained via case reports the inclusion of novelties or rare complications are included in this systematic review. The results of the systematic review revealed that the incidence of melioidosis is approximately two times higher in males than females, which is similar to the global burden of melioidosis in 2015, showing cases twice as high for men as for women (Birnie et al., 2019).

Melioidosis is known to cause sepsis in adults with underlying conditions that impair immune function, such as diabetes, chronic renal failure, alcoholism and prolonged steroid use (Cheng & Currie, 2005). In this current review 84.6% of the cases had diabetes mellitus. This corresponds with the findings reported by Birnie et al. (2019), where diabetes or newly diagnosed hyperglycaemia were among the top four risk factors for melioidosis globally.

One third of the papers (7/22) reported the involvement of the nervous system as a complication of melioidosis despite the rare occurrences of neurological melioidosis. It is notable that in this current systematic review, encephalitis is the most common neurological manifestation which correlates with a 20-year prospective study of melioidosis conducted in Northern Australia. Therefore, melioidosis should always be suspected in a patient with superficial or deep seated abscess formation with neurological presentation that presents as clinical features of meningo-encephalitis (Wijekoon et al., 2016) .This is crucial as previous studies have reported that patients with neurological melioidosis have a mortality rate of 25% (Andersen, Mackay, & Ryan, 2016).

In adults, cardiac complications due to melioidosis is usually rare compared to other more common outcomes such as pneumonia and intra-abdominal abscess. Among the papers reviewed, five cases (22%) showed a breakdown of the cardiovascular system as a complication of melioidosis. The case of melioidosis reported from Hong Kong showed relapsing melioidosis which was further complicated by mycotic aneurysm. The report disclosed that the patient had succumbed to the disease despite treatment (Li, Chau, & Wong, 2015). Melioidosis presenting as mycotic aneurysm is very uncommon and has been found to be associated with high morbidity, high mortality and relapse rates (Low, Quek, Sin, & Ang, 2005). Therefore, physicians should be attentive to the development of mycotic aneurysm especially when treating for persistent or recurrent melioidosis and should consider early surgical intervention (Li et al., 2015).

Apart from that, most of the cases reported favourable outcomes (survival) which have resulted in full recovery of the patients after treatment (78.3%) as opposed to the survival outcomes reported by the global burden of melioidosis in 2015, which revealed 93.6% of melioidosis survivors ended up with some sort of complication such as post-sepsis, ongoing CNS or musculoskeletal impairment, while only 6.4% include consolidated treatment (Birnie et al., 2019).

In terms of public health intervention, even when the current risk factors are well known, active public health intervention is still lacking. Even though protective footwear is frequently suggested for individuals at risk of melioidosis, the practicality and effectiveness of this advice is unknown (Cheng & Currie, 2005).

Conclusion

Melioidosis, a known opportunistic pathogen, is a disease that needs to be understood by public health authorities especially in Southeast Asia and parts of Australia since it has the potential to spread to other parts of the world. From this systematic review, it was revealed that the most common complication involved the nervous system, however outcomes were favourable for a majority of patients. Despite advancement in antibiotic therapy, there are patients that can succumb to this emerging disease due to rare and severe complications such as mycotic aneurysm. Melioidosis can involve almost any organ and can cause the human body to deteriorate rapidly. Therefore, strengthening surveillance and medical diagnostics are crucial especially in countries endemic with the disease.

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