

# SYSTEMATIC REVIEW: CHARACTERISTICS OF METHICILLIN- RESISTANT *STAPHYLOCOCCUS AUREUS* (MRSA) INFECTION IN DIABETES MELLITUS

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**Abstract:** Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a serious and common problem in patients with diabetic predisposition. *S. aureus* was the most common pathogen among the gram-positive bacteria isolated from ulcers, and almost 50% of *S. aureus* isolates are MRSA. Research shows 24.4% patients carried MRSA in three academic hospitals in Indonesia. Objective is to assess the characteristic of MRSA infection in diabetes mellitus. Method used is systematic review with inclusion and exclusion criteria through search engines obtained 236 journals that were reviewed. 8 journals is used as main references in writing this review. The data obtained are in the form of qualitative and quantitative data which are then arranged systematically and according to each topic discussed so that a conclusion is obtained that represents the entire content of the review. Patient with MRSA infection in diabetes mellitus are predominantly male, with obesity as a predominantly risk factor, nephropaty as the most common complication, and treated with diabetic ulcer predominantly in grade 3-5 based on Wagner's classification. One of diabetic ulcer first therapies is to use antibiotics, which type of antibiotic that is commonly used is Clindamycin. In conclusion, the characteristics of MRSA infection in diabetes mellitus can vary between patients due to environmental demographic, social, cultural, internal factors and other external factors.

**Keywords:** Methicillin-resistant *Staphylococcus aureus* (MRSA), Diabetes mellitus.

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## I. INTRODUCTION

Diabetes mellitus is a chronic hyperglycemia which is associated with long-term damage, dysfunction, and failure of different organs. There are two types of diabetes type 1 diabetes and type 2 diabetes. Type 1 diabetes which is an autoimmune disease that leads to the destruction of the insulin-producing pancreatic beta cells.<sup>13</sup> Type 2 is the most common form of diabetes mellitus characterized by hyperglycemia, insulin resistance, and relative insulin deficiency.<sup>15</sup> Type 1 diabetes is characterized by autoimmune destruction of insulin producing cells in the pancreas. The autoimmune destruction of pancreatic  $\beta$ -cells, leads to a deficiency of insulin secretion. The loss of insulin secretion causes the function of pancreatic  $\alpha$ -cells is also abnormal and there is excessive secretion of glucagon. Type 2 diabetes has two main pathological defects in type 2 diabetes which are impaired insulin secretion through a dysfunction of the pancreatic  $\beta$ -cell, and impaired insulin action through insulin resistance.<sup>3</sup>

*Staphylococcus aureus* is divided into sensitive *Staphylococcus aureus* (MSSA) and methicillin-resistant *Staphylococcus aureus* (MRSA).<sup>21</sup> Methicillin-resistant *S. aureus* strains have acquired resistance to methicillin and other beta lactam antibiotics such as penicillin and cephalosporin. MRSA is usually spread by contact with infected people or things that are carrying the bacteria.<sup>2</sup> The mode of transmission of MRSA is mainly from colonized or infected patients to others. The

portal of entry of MRSA can be a hair follicle, break in the skin, or the respiratory tract. The incubation period between the transmission of the bacteria and the onset of signs and symptoms of infection is 1–10 days on average<sup>1</sup>. Infection in patients with diabetes causes many pathophysiological changes. The complement system contains plasma proteins and cell surface proteins which promote bacterial phagocytosis by leukocytes. This system is activated and may increase the lysis of microorganism and mediates a B-cell antibody production.<sup>12</sup>

## II. METHODOLOGY

A comprehensive summary in the form of a systematic review: characteristics of methicillin-resistant *Staphylococcus aureus* (MRSA) infection in diabetes mellitus. The protocols used in this study are The Center for Review and Dissemination and The Joanna Briggs Institute Guideline as a guide in evaluating the quality of the collected studies. Systematic review assessment uses the PRISMA checklist to determine the completion of studies that have been found and adjusted to the objectives set.<sup>19</sup> Literature searches conducted during November-December 2020 against literature obtained from previous researchers or secondary data in the form of international journals using the PubMed database and Embase. Based on the results of a literature search through the database that was previously mentioned using keywords and filters, 236 articles were obtained. Furthermore, a selection was carried out in the form of screening based on the title and abstract so that there were 70 articles. A total of 70 articles were then analyzed thoroughly using inclusion and exclusion criteria so that there were 8 articles that could be used in this systematic review. The characteristics of methicillin-resistant *Staphylococcus aureus* (MRSA) infection in diabetes mellitus was the main variable evaluated in this systematic review. The result synthesis used in this systematic review is a descriptive method, namely an explanation in the form of a narrative description in describing the results obtained. The narrative explanation used aims to gather evidence about the effectiveness of the intervention and develop a coherent and systematic textual narrative. The data were evaluated by review questions namely background, theoretical framework, research objectives, research content, research design, sample size, sampling method, sample description, validity and reliability, instruments used, statistical analysis, and analysis of results.

## III. RESULT AND DISCUSSION

### 3.1 Characteristics of the Study

The characteristics of the articles used are 8 study articles consisting of cross sectional and cohort studies taken in the period 2000-2020. The population in the study of the articles used in this systematic review is a population of 16 countries. Age in population > 18 years and length of patient with diabetes >10 years. The therapy was administered medically including antibiotics or gels and the surgical approach and duration of wound healing varied as shown in table 1.

**TABLE 1: Characteristics of the Study Used**

Study (year)	Type of Study	Location	Total Patient	Age (years)	Duration of diabetes (years)	Treatment	Wound Healing Time
Dang et al. (2003)	Cross sectional	United Kingdom (UK)	63	≥18	NR	Antibiotic therapy (clindamycin amoxicillin/clavulanic acid)	12 weeks (all ulcers of the study)
Hartemann-Heurtier et al. (2004)	Prospective cohort	France	180	65±12	21±12	Antibiotic therapy (amoxicillin/clavulanic acid and aminoglycoside)	4.6 ± 8.4 months (MDRO+) 6.7 ± 13 months (MDRO-)
Cavallini (2007)	Prospective cohort	Italy	10	45-76	NR	Surgical debridement, antibiotic therapy and dermal graft with meshes of autologous fibroblasts	7 patients healed at 14.2 weeks

Kim et al. (2008)	Prospective cohort	South Korea	52	62.3 ± 11.2	15.4±5.1	Modified resection arthroplasty	25.6 ± 6.2 days
Richard et al. (2008)	Prospective cohort	France	188	68	17	Antibiotic therapy (fluoroquinolone, rifampicin and clindamycin)	14 weeks (MDRO+) 10 weeks (MDRO-)
ElMakki Ahmed et al. (2010)	Prospective cohort	Sudan	122	57.9±9.2	>10	Surgical debridement and. Antibiotic therapy (amoxicillin/clavulanic acid)	16 ± 8 weeks
Nagoba et al. (2010)	Retrospective cohort	India	115	>20	NR	3% citric acid gel daily	106 cases healed with 16-34 applications
Eckmann et al. (2015)	Retrospective cohort	UK, Ireland, France, Germany, Italy, Spain, Portugal, Austria, Greece, Poland, Slovakia and the Czech Republic	485	≥18	NR	Antibiotic (vancomycin, linezolid)	linezolid-treated patients (17.8 ± 14.0 days) shorter duration compared with vancomycin-treated patients (20.3 ± 11.6 days)

Table 2 shows the gender of the patient as stated in 6 articles shows that the patient is predominantly male. The predominant diabetes risk factors as listed in the 3 articles indicate that most of them are obesity. The complication of diabetes patient majority listed in the 3 articles that mentioned nephropathy. Wagner grade is a classification system used to determine the degree of ulcers in diabetic foot. The majority of patients exhibiting grade 3-5 as summarized in 3 articles. A total of 8 articles showed that first line treatment of ulcer is antibiotic which clindamycin ranks first as the most frequently used antibiotic.

**TABLE 2: Symptom Frequency and Characteristics of Findings**

Characteristics	Total Studies	Number of Patients with Characteristics	Number of Patients Checked
Females	6	196	552
Males	6	471	552
<b>Daibetic risk factors</b>			
Obesity	3	154	795
Hypertension	3	41	795
Smokers	3	47	795
Positive family history	3	90	795
<b>Diabetic complication</b>			
Nephropathy	3	263	490
Neuropathy	3	172	490
Osteomyelitis	3	125	490
Retinopathy	3	118	490
Cardiovascular disease	3	199	490
Infection	3	52	490
Impotence	3	67	490
<b>Wagner diabetic ulcer grading</b>			
1	3	34	305
2	3	52	305
3-5	3	219	305
<b>Treatment of ulcer</b>			
Antibiotic	8	1177	1215

Surgical debridement	8	80	1215
Dermal graft	8	62	1215
Antibiotic treatment			
Clindamycin	8	307	1215
Amoxicillin	8	185	1215
Clavulanic acid	8	63	1215
Fluoroquinolone	8	188	1215
Rifampicin	8	188	1215
Ceftriaxone	8	17	1215
Ciprofloxacin	8	33	1215
Vancomycin	8	258	1215
Linzolid	8	227	1215

### 3.2 Risk of Study Bias

The study quality of each article that was determined as the source of systematic review was determined based on the quality analysis of The JBI Critical Appraisal Tools Cross Sectional Studies and The JBI Critical Appraisal Tools Cohort Studies, so that 8 articles were obtained according to the systematic review. Table 3 shows the results obtained are 1 articles of cross-sectional prevalence study and 7 articles cohort consist of 5 prospective cohort study and 2 retrospective cohort. After performing critical appraisal using The JBI critical appraisal tools, cross-sectional or prevalence studies are given a quality score of six while cohort studies are given a varied total quality score from eight to nine on the checklist. Based on the overall study summarized, all research on average contains variable characteristics that are ready to be observed. The assessment bias in the study shows that the results of articles that are assigned to systematic reviews are at risk of confounding factors that can effect the results and are not described in the article in detail regarding strategies for overcoming possible confounding factors.

**TABLE 3: Study Assessment Results Using The JBI Critical Appraisal Tools**

Reference	The JBI Critical Appraisal Tools Cross Sectional Studies Criteria								Result
	1	2	3	4	5	6	7	8	
Dang et al. (2003)	v	v	v	v			v	v	6/8 (75%)

Reference	The JBI Critical Appraisal Tools Cohort Criteria											Result
	1	2	3	4	5	6	7	8	9	10	11	
Hartemann-Heurtier et al. (2004)	v	v	v			v	v	v	v		v	8/11 (72%)
Cavallini (2007)	v	v	v			v	v	v	v		v	8/11 (72%)
Kim et al. (2008)	v	v	v			v	v	v	v		v	8/11 (72%)
Richard et al. (2008)	v	v	v			v	v	v	v	v	v	9/11 (81%)
ElMakki Ahmed et al. (2010)	v	v	v			v	v	v	v	v	v	9/11 (81%)
Nagoba et al. (2010)	v	v	v			v	v	v	v		v	8/11 (72%)
Eckmann et al. (2015)	v	v	v			v	v	v	v		v	8/11 (72%)

### 3.3 Summary of Evidence

This review suggests that the characteristic may be influenced by location of research implementation and so on. In addition, the results of data collection from several studies indicate that the most commonly used treatments for MRSA infection manifest as ulcer include antibiotic, surgical debridement, and dermal graft. Based on the distribution of sociodemographic data, most of the literature states that complaints in the form of MRSA infection in diabetes mellitus patient are higher in the male sex than in female.<sup>16</sup> Most of research found that obesity was important risk factors for diabetes mellitus. In people with MRSA infection in diabetes mellitus, the pancreas produces insulin in sufficient quantities for maintains blood glucose levels at normal levels, but the insulin could not work to the maximum help the body's cells absorb glucose because plagued by complications obesity, one of which is fat content especially high blood cholesterol and triglycerides.<sup>20</sup> One of the most common complication of diabetes is nephropathy. Research reveals that there is a relationship between duration of diabetes and the incidence of kidney failure or nephropathy. Usually occurs 5 - 15 years since diagnosis of DM. It can still be prevented by glucose control and tight control of blood pressure. Histopathologically, it is seen too thickening of the glomerular basement membrane.<sup>18</sup> Research reveals patients treated with diabetic ulcer predominantly in grade 3-5 based on Wagner classification. Increasing in grade indicates increasingly uncontrolled blood glucose levels. The severity of diabetic foot ulcers is more common in patients with risk factors neuropathy.<sup>22</sup> One type of antibiotic that is commonly used is clindamycin which inhibits streptococci, staphylococci, and pneumococci. Clindamycin inhibits protein synthesis by interfering with the formation of the aminoacyl initiation and translocation complex and is indicated for the treatment of anaerobic infections caused by aerobic gram-positive cocci, gram-negative bacilli, protozoa, and MRSA. Clindamycin penetrates well into ulcers and is actively taken up and concentrated in phagocytic cells. The location of the drug binding is the 50S subunit of the bacterial ribosome which will produce a bacteriostatic effect.<sup>6</sup> Pharmacological therapy is carried out by administering antibiotics. Empiric antibiotics are usually given as therapy pending the results of culture and sensitivity tests. Empiric therapy is also given if culture and sensitivity tests are not performed. Definitive therapy is given based on the results of culture and sensitivity tests obtained from wound specimens. In general, the duration of use of antibiotics should be as minimal as possible. Antibiotic therapy is only used to treat infections, not to heal wounds which usually take longer.<sup>9</sup>

### 3.4 Limitation

The dominant cohort study has limitations on the limited research sample in some literature. In prospective cohort studies, loss of follow-up may occur, giving rise to selection bias. Loss of follow-up bias is caused by the loss of individuals from one or more exposure groups. In retrospective cohorts, already existing medical records may be used. In that case, there could be missing data due to poor registration quality or due to variables that were not considered to be registered in advance.

## IV. CONCLUSION

Patient with MRSA infection in diabetes mellitus are predominantly male, with obesity as a predominantly risk factor, nephropathy as the most common complication, and treated with diabetic ulcer predominantly in grade 3-5 based on Wagner's classification. One of diabetic ulcer first therapies is to use antibiotics, which type of antibiotic that is commonly used is Clindamycin. Characteristics of MRSA infection in diabetes mellitus can vary between patients due to environmental demographic, social, cultural, internal factors and other external factors.

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