Microbiological profile of diabetic foot infection in the Middle East and North Africa: a systematic review

Diabetic foot infection (DFI) is associated with high medical and economic burden. This systematic review investigated the microbiological profile of DFI in Middle East and North African (MENA) countries. A literature search was performed and 39 studies conducted between 1999 and 2016 in 10 countries. Gram-negative rods (GNR) were more prevalent than Gram-positive cocci (GPC) in 58% of studies. GNR were more common in hospitalised patients and GPC in outpatient settings. Isolates found in most studies included *Enterobacteriaceae* (18–66%); anaerobes (0–21%); methicillin-resistant *Staphylococcus aureus* (0–26%); *Pseudomonas* (<20%); fungi, mainly *Candida* spp (1–9%); and *Acinetobacter* (5%). The prevalence of methicillin-resistant *Staphylococcus aureus* appears to be stable. Extended spectrum beta-lactamase enzyme production in GNR ranged from 11% to 53%. There is a high prevalence of GNR in DFI in MENA countries, which could be related to late presentation with high-grade ulcers. Raising awareness among patients with diabetes to seek early medical care is highly important. The results of this review could be used to establish regional guidelines for antibiotic treatment of DFI.

Authors:
Lamia Jouhar, Mohammad Minhem, Elie Akl, Nesrine Rizk and Jamal Hoballah

In 2015, more than 35 million people in the Middle East and North Africa (MENA) had diabetes, and this number is expected to double by 2040 (Ogurtsova et al, 2017). This alarming increase in prevalence will result in an increase in related complications, such as diabetic foot ulcers. A systematic review of the diabetic foot in many MENA countries showed that it is more prevalent, less well managed and is associated with worse health outcomes compared to developed countries (Al-Wahbi, 2006). Foot wounds are frequent in people with diabetes and half of such wounds are complicated by infection (Lavery et al, 2007). Infection imposes an additional economic and medical burden on patients and society as it increases the rate of hospitalisation and leads to poor health outcomes, such as amputation (Lavery et al, 2006). A multidisciplinary team is required to treat diabetic foot infection (DFI) as metabolic, vascular and infectious aspects of health need to be addressed (Lipsky et al, 2006). Positive outcomes depend on proper wound care and appropriate surgical interventions in addition to the timely and adequate use of appropriate antibiotic therapy (Lipsky et al, 2005).

The Infectious Diseases Society of America (IDSA)'s clinical guidelines recommend treating clinically-infected diabetic foot ulcers with empiric antibiotics until the results of microbiological culture are available. Empiric antibiotics should be selected according to the infection severity, clinical presentation, the prevalence of microorganisms in the local area and their antibiotic susceptibility. The IDSA recommends starting with a narrow-spectrum antibiotic covering Gram-positive cocci (GPC) in mild DFI and keeping wide-spectrum antibiotics for severe, moderate chronic and extensive infections (Lipsky et al, 2012).

While GPC are the most common pathogens isolated from DFI in developed countries, where most guidelines were developed, reports from developing countries — including MENA countries — show a higher prevalence of Gram-negative rods (GNR) (Uçkay et al, 2014). Such a

Lamia Jouhar (LJ) *is Postdoctoral Research Fellow;* ***Mohammad Minhem (MM)*** *is Postdoctoral Research Fellow, both at Department of Surgery, American University of Beirut Medical Center, Beirut, Lebanon;* ***Elie Akl*** *is Associate Professor;* ***Nesrine Rizk*** *is Instructor;* ***Jamal Hoballah*** *is Professor; all at Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon*

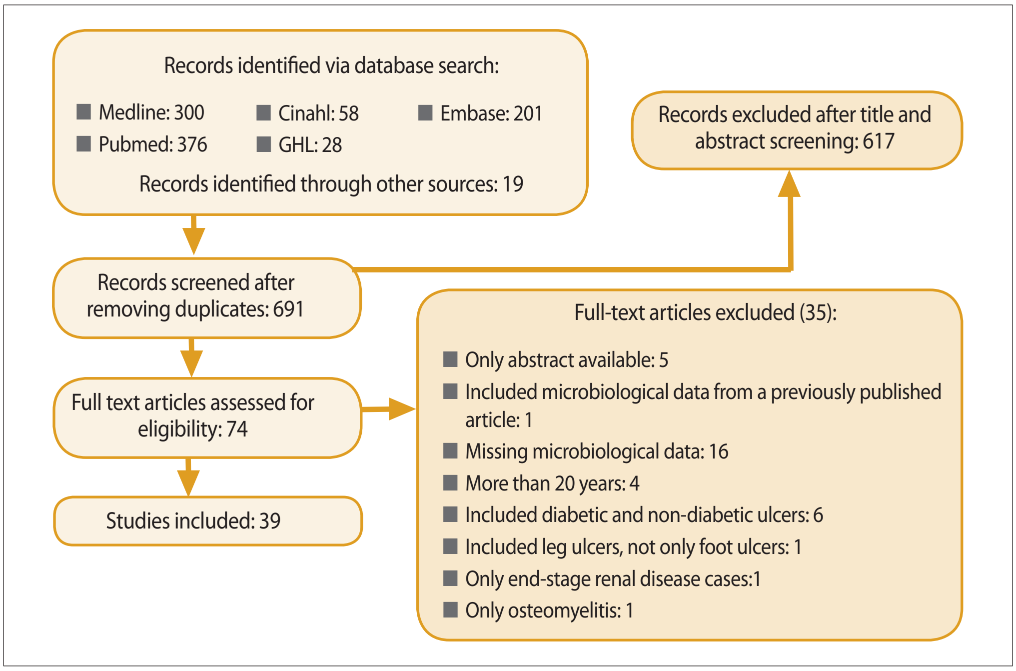

Figure 1. PRISMA flow diagram for the inclusion and exclusion of studies relating to the analysis of organisms present in diabetic foot infections in the Middle East and North Africa.

difference has been attributed to geographical, cultural and climate-related factors (Lipsky et al, 2012; Uçkay et al, 2014). This discrepancy may make using international guidelines in developing countries impractical. The objective of this systematic review was to investigate the microbiological profile of DFI in MENA countries.

Methods

Ovid Medline, PubMed, Cinahl, Embase, the Global Health Library, Google Scholar and World Cat databases were searched on November 30, 2017 to identify retrospective and prospective observational studies of diabetic foot ulcers conducted in MENA countries (including Turkey) published after January 1, 1997. The search strategy included both free text words and MESH terms for the following concepts: diabetic foot AND microbiological profile or antimicrobial susceptibility AND the MENA countries. The references of the articles included were manually screened for additional relevant studies. Case reports, case series, reviews and abstract posters were excluded.

After combining the search results from the databases and removing duplicate records, two authors (LJ and MM) worked in duplicate and independently to screen titles and abstracts for potential eligibility. Full texts of papers judged potentially eligible by at least one author were obtained. Subsequently, LJ and MM screened in the full texts duplicate and independently for eligibility. They compared their results and resolved disagreements through discussion or with the help of the third author when unsuccessful.

LJ and MM used a standardised data abstraction form, in duplicate form and independently, to extract the following information:

- Name of the first author and year of publication
- Context: country, date of sample collection, setting (inpatient *versus* outpatient)
- Methodology: sampling method
- Clinical data: number of patients, mean age, classification of ulcer grade and infection severity using classification systems such as Wagner (Jeon et al, 2017), the International Working Group for Diabetic Foot/ Infectious Diseases Society of America classification (Lavery et al, 2007) and PEDIS (Chuan et al, 2015)
- Statistical findings: the total number of isolates and percentage of each pathogen.

Any disagreement was resolved through discussion or with the help of a third author.

Data analysis

Descriptive analysis of the studies included was conducted. The demographics and clinical data were summarised using percentages, median and interquartile range (IQR). The prevalence of each organism was calculated as a percentage of the total number of isolates in each study.

Results

Studies included

Suitable studies were selected using the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) diagram *[Figure 1]*. The search strategy captured 691 citations. Seventy-four full texts were assessed, of which 39 studies met the eligibility criteria. Reasons for the exclusion of 35 full-text studies are given in *[Figure 1]*.

The studies included were performed between 1999 and 2016. Seventy-two per cent were conducted in Iran, Egypt and Turkey. Only one-fifth were conducted before 2008. Over 70% of the studies were conducted in an inpatient setting. Demographic and clinical data from the 39 studies are given in *Table 1*.

Microbiological profile:

The prevalence of polymicrobial infections ranged between 15% and 90% (median: 53%). The mean number of pathogens isolated per sample ranged from 1.1 to 4.4 (median: 1.6). The microbiological profile of DFI and percentages of the pathogens found is given in *Table 2*. The prevalence of each pathogen is summarised in *Table 3*.

Two studies assessed methicillin-resistant *Staphylococcus aureus* (MRSA) prevalence only and one study assessed fungi only. Of the 36 studies with a full microbiological profile, GNR were more prevalent than GPC in 21 (58%) studies. A comparable prevalence was noted in six (17%) studies. GPC were more common in nine (25%) studies.

Enterobacteriaceae represented between 18% and 66% of the total isolates, with *E coli* and *Proteus* being the most common (Qari and Akbar, 2000; Esmat et al, 2012; Hadadi et al, 2014; Kamel et al, 2014; HajiAbdolbaghi et al, 2015; Ben Moussa et al, 2016). Other genera isolated included *Klebsiella*, *Enterobacter*, *Citrobacter*, *Morganella* and *Serratia*. *S aureus* was the most common isolate in 18 studies. *Enterococcus* was the most commonly isolated genus in two studies in Iran (Rouhipour et al, 2012; Anvarinejad et al, 2015).

Pseudomonas was reported to be present in almost all studies (<10% of isolates in 19 studies; 11–19% of isolates in 15 studies). It was the most commonly isolated organism in six studies (Quari and Akbar, 2000; Ozer et al, 2010; Ertugrul et al, 2012; Turhan et al, 2013; Parsa and Samani, 2015). A very high prevalence of 30% and 35% was reported by Turhan et al (2013) and Parsa and Samani (2015). The authors attributed these high rates to chronicity and recurrence of the DFI in addition to susceptibility to hospital-acquired infection.

Table 1. Demographic and clinical data from studies included (*n*=39).

Characteristic	Number (%) of studies
Country:	
Iran	12 (31)
Egypt	9 (23)
Turkey	7 (18)
Saudi Arabia	2 (5)
Kuwait	2 (5)
Morocco	2 (5)
Israel	2 (5)
Algeria	1 (2.5)
Libya	1 (2.5)
Tunisia	1 (2.5)
Number of participants:	
Median	82
IQR	49
Period during which the study was conducted:	
1999–2008	7 (18)
2009–2012	14 (36)
2013–2016	13 (33)
Not reported	5 (13)
Setting:	
Inpatient	27 (69)
Out-patient	4 (10)
Both	5 (13)
Not reported	3 (8)
Study design:	
Prospective	18 (46)
Retrospective	12 (31)
Cross-sectional	5 (13)
Not reported	4 (10)
Sampling method:	
Swab	16 (41)
Swab and tissue	9 (23)
Tissue only	5 (13)
Swab and tissue and bone	5 (13)
Not reported	4 (10)
Classification of ulcer grade or severity of infection:	
Wagner	12 (31)
PEDIS	4 (10)
IWGDF/IDSA	2 (5)
Not reported	21 (54)

IQR: interquartile range; IWGDF/IDSA: International Working Group for Diabetic Foot/ Infectious Diseases Society of America; PEDIS: Perfusion, Extent, Depth, Infection and Sensation.

Acinetobacter was reported in 23 studies. A high prevalence (10% and 11%) was only reported by two studies (Hefni et al, 2013; Alikhani et al, 2015).

Table 2. Microbiological profile (percentages of total isolates) in each study (*n*=39).

Study	Poly-microbial %	Number of isolates	Mean number of isolates per sample	Gram-positive (%)	Gram-negative (%)	Anaerobes (%)	Fungi (%)	*Staphylococcus aureus* (%)	*Methicillin-resistant Staphylococcus aureus* (%)	Coagulase negative *Staphylococcus* (%)	*Enterococcus* (%)	*Streptococcus* (%)	*Enterobacteriaceae* (%)	*Pseudomonas* (%)	Acinetobacter (%)
Djahmi et al, 2013	50	277	1.8	45	55	0	-	31	26	11	3	1	43	8	3
Esmat et ak, 2012	39	167	1.4	31	69	-	-	16	11	8	7	-	52	13	3
Ahmed et al, 2013	76	254	2.5	31	46	13	9	15	4	9	-	7	37	9	0
Hefni et al, 2013	40	98	1.4	30	67	-	1	17	7	-	-	12	33	19	10
Ahmed et al, 2014	-	-	-	-	-	-	-	-	17	-	-	-	-	-	-
El-Sheikh et al, 2014	18	31	1.4	61	32	6	-	42	3	10	-	6	26	6	-
Kamel et al, 2014	77	206	2.3	34	66	-	-	13	4	12	-	2	54	9	-
Dwedar et al, 2015	51	148	1.9	28	56	8	8	22	10	1	4	1	43	11	2
Ali et al, 2016	45	86	1.4	33	47	21	-	26	17	-	-	6	40	7	-
El-Naggar et al, 2016	63	65	1.6	57	43	-	-	37	15	-	-	5	25	18	-
Alavi et al, 2007	50	42	1.6	43	55	0	2	26	24	14	-	-	50	5	-
Dezfulian et al, 2011	56	109	1.6	55	40	5	-	19	19	22	6	5	33	6	2
Rouhipour et al, 2012	90	546	3.3	62	36	2	-	19	6	15	21	6	25	5	5
Amini et al, 2013	22	104	1.2	58	42	0	-	35	23	-	19	4	28	10	-
Hadadi et al, 2014	20	119	1.2	29	71	-	-	21	-	-	3	4	50	8	4
Akhi et al, 2015	53	92	1.7	61	35	4	-	28	11	17	15	-	24	7	4
Alikhani et al, 2015	-	200	-	43	54	-	4	29	-	10	3	2	26	15	11
Anvarinejad et al, 2015	21	122	1.4	64	30	-	6	7	6	23	28	1	26	2	2
HajiAbdolbaghi et al, 2015	-	61	-	52	44	-	-	16	2	13	13	10	39	2	5
Parsa and Samani, 2015	-	68	1.3	29	62	6	3	25	6	-	-	3	26	35	-
Akhi et al, 2017	-	119	1.5	-	-	-	-	-	11	-	-	-	-	-	-
Slater et al, 2004	-	150	2.5	57	35	8	-	20	1	15	8	10	28	4	3
Katz et al, 2016	52	131	3.3	26	53	21	-	5	1	-	7	8	35	7	5
El-Tahawy, 2000	37	161	1.5	40	47	7	5	19	6	5	7	9	30	15	-
Qari and Akbar, 2000	-	42	1.2	24	67	10	-	-	-	-	-	10	50	17	-
Abdulrazak et al, 2005	64	140	1.6	46	44	6	4	24	4	-	8	10	31	11	-
Benwan et al, 2012	75	777	1.8	32	51	15	1	19	8	1	6	7	28	17	-
Irhuma et al, 2006	64	235	4.4	41	59	-	-	11	-	-	-	24	43	11	6
Zemmouri et al, 2015	42	137	1.7	53	47	-	-	26	7	-	9	9	35	9	2
Belefquih et al, 2016	54	310	1.8	51	48	-	1	14	1	8	9	13	34	9	4
Ben Moussa et al, 2016	33	136	1.2	18	82	-	-	9	0	-	-	10	66	8	1
Ozkara et al, 2008	34	60	1.2	47	42	7	5	33	13	-	-	10	18	12	-
Ozer et al, 2010	19	74	1.3	38	58	-	4	11	-	5	15	7	36	19	3
Bozkurt et al, 2011	-	86	1.1	51	47	2	-	24	6	9	7	9	36	10	-
Ertugrul et al, 2012	-	115	1.6	48	48	4	-	14	7	7	12	15	27	18	3
Turhan et al, 2013	15	312	1.2	39	61	-	-	17	7	5	12	3	23	30	3
Saltoglu et al, 2015	-	208	-	44	55	1	-	23	5	9	-	7	33	17	5
Hatipoglu et al, 2016	-	387	1.1	36	60	-	3	11	2	6	10	7	40	12	3

Table 3. Prevalence of each pathogen as a percentage out of the total number of isolates in each study.

Pathogen	Median prevalence	Interquartile range	Range
Staphylococcus aureus	20	11	5–42
Coagulase-negative *Staphylococcus*	9	7	1–23
Enterococcus	8	6	3–28
Streptococcus	7	5	1–24
Gram-positive rods	4	3	1–9
Enterobacteriaceae	34	14	18–66
Pseudomonas	10	8	2–35
Acinetobacter	3	2	0–11
Anaerobes	6	6	0–21
Fungi	4	2	1–9

Anaerobes were found in 22 studies. They made up between 0% and 21% of the total number of isolates. *Bacteroides* spp and *Peptostreptococcus* were the most commonly isolated anaerobes. Anaerobes were isolated in combination with aerobic organisms in all 22 studies.

Meanwhile, fungi were identified in 14 studies (1–9% of the total isolates). *Candida* was the most common genus in all studies.

Multidrug-resistant organisms (MDROs)

Extended-spectrum beta lactamase (ESBL) producers were reported in six studies conducted between 2012 and 2014 in Egypt, Iran and Morocco, and their prevalence ranged between 11% and 53% (Ahmed et al, 2013; Kamel et al, 2014; Anvarinejad et al, 2015; Dwedar et al, 2015; Belefquih et al, 2016). ESBL enzymes were produced by 11% and 20% of *Enterobacteriaceae* isolates cultured by Katz et al (2016) and Saltoglu et al (2015), respectively.

The proportion of MRSA varied widely between studies performed in different countries and in different years, ranging from 0% to 100% (median: 31%) *[Figure 2]*. There was no chronological trend in MRSA prevalence except for studies conducted in Egypt, where there was an increase in methicillin resistance over time.

Enterococcus were susceptible to vancomycin in 12 studies. Seven reported that all isolated *Enterococcus* spp were sensitive to this antibiotic (El-Tahawy, 2000; Slater et al, 2004; Abdulrazak et al, 2005; Benwan et al, 2012; Amini et al, 2013; Dwedar et al, 2015; Belefquih et al, 2016). In one study, 3% of *Enterococcus* spp were resistant to vancomycin (Turhan et al, 2013). High rates of vancomycin-resistant *Entercoccus* (21–46%) were reported in four studies conducted in hospitalised patients in Iran (Rouhipour et al, 2012; Akhi et al, 2015; Anvarinejad et al, 2015; HajiAbdolbaghi et al, 2015).

Discussion

In developed countries, mild community-acquired DFIs are caused by aerobic GPC, mainly *S aureus*, *streptococci* and coagulase-negative *staphylococcus*. A narrow-spectrum antibiotic covering these organisms is usually sufficient to start treatment with. However, studies from countries with a warm climate have found a higher prevalence of GNR in DFI (Lipsky et al, 2012; Uçkay et al, 2014) and the real cause of this discrepancy is not clear. There was a high prevalence of GNR in severely infected and in previously treated DFIs (Citron et al, 2007; Roberts et al, 2012). GNR were more prevalent than GPC in many studies included in this systematic review.

On further inspection, 50% of studies reporting a high GNR prevalence had a high proportion of patients with high-grade ulcers and moderate to severe infections (Alvi et al, 2007; Ozkara et al, 2008; Ozer et al, 2010; Bozkurt et al, 2011; Benwan et al, 2012; Ertugrul et al, 2012; Ahmed et al, 2013; Djahmi et al, 2013; Hefni et al, 2013; Hadadi et al, 2014; Irhuma et al, 2006; Saltoglu et al, 2015; Hatipoglu et al, 2016). GPC were more prevalent in studies conducted on patients presenting to outpatient clinics with low-grade ulcers, in those who had not previously received antibiotics, and in studies excluding deep and extensive ulcers (Slater et al, 2004; Abdulrazak et al, 2005; Rouhipour et al, 2012; Amini et al, 2013; El-Sheikh et al, 2014).

Half of the studies did not report the grade of ulcer or severity of infection. The difference in microbiology, according to Wagner grade, was assessed in two studies (Ahmed et al, 2013; Anvarinejad et al, 2015). Both showed a high prevalence of GPC in low-grade ulcers and GNR in high-grade ulcers. As such, the high prevalence of GNR in DFI in MENA countries could be attributed to a delay in seeking medical care and patients presenting with more advanced ulcers, rather than geographical factors.

The role of anaerobic pathogens in DFI is not fully understood. Anaerobes are more common in severely infected and ischaemic wounds, which form a suitable environment for these organisms to grow. A worldwide review of anaerobe prevalence in DFI showed a very wide variation of 0–79% (Charles et al, 2015). This variation could be related to the fact that anaerobe isolation is dependent on the sampling

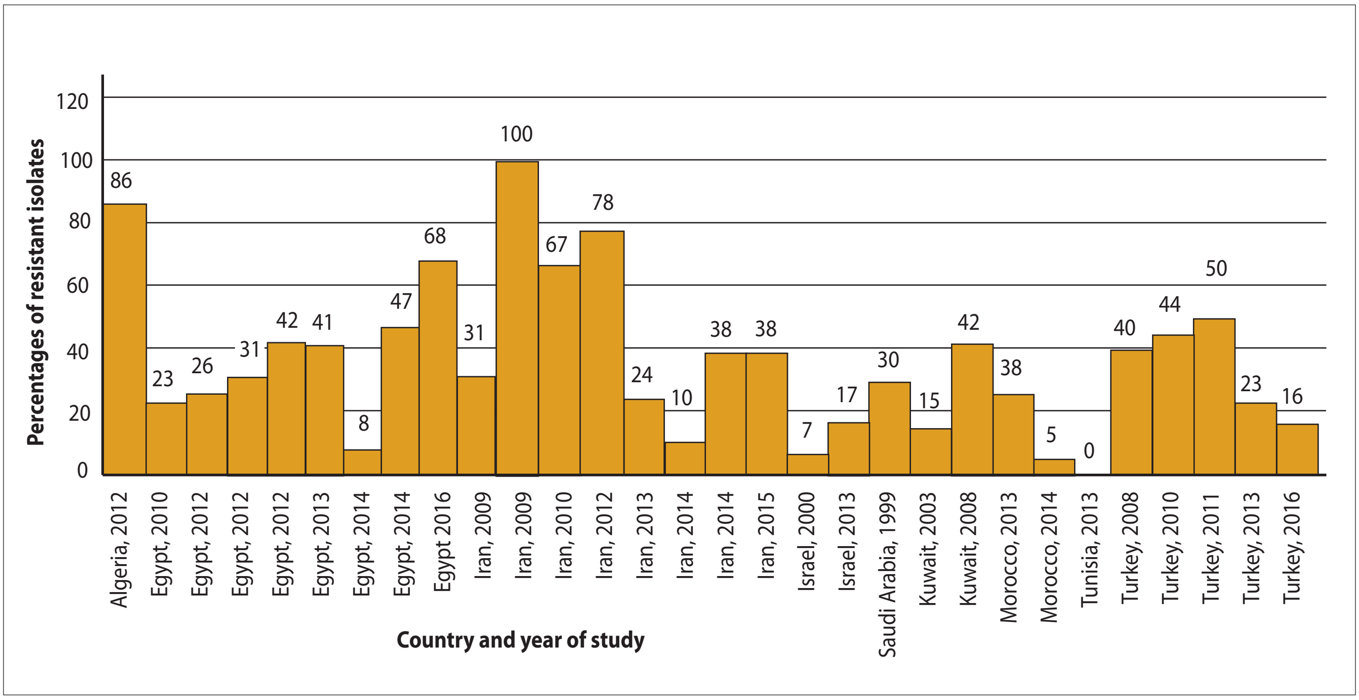

Figure 2. Proportions of methicillin resistance among Staphylococcus aureus in Middle East and North African countries.

method, transportation and processing of samples (Roberts and Simon, 2012). The available literature did not determine the clinical role of anaerobes in DFI and whether anaerobes are associated with worse outcomes or not.

This systematic review found a large discrepancy in the prevalence of anaerobes over time and between countries. Anaerobes were present in 0–21% of isolates. Ahmed et al (2013) isolated anaerobes from high-grade ulcers only and Bozkurt et al (2011) from deep ulcers with osteomyelitis, but not from soft tissue infections.

Fungi are rarely the principle pathogen in DFI. They are usually cultivated from long-standing and deep ulcers, but the clinical implication is not clear (Missoni et al, 2006; Uçkay et al, 2014). In this review, fungi were isolated in 14 studies and their prevalence ranged between 1% and 9% of total isolates. *Candida* was the most common genus in all studies. Anvarinejad et al (2015) reported that all fungi were cultured from high-grade ulcers (Wagner 3 and 4). Raiesi et al (2017) studied fungal prevalence in cutaneous lesions in patients with diabetes, and found 19% of diabetic foot ulcers had a fungal infection, with *Candida* spp being the most common. There is a wide variation in fungi prevalence in DFI and it is most likely related to chronic wounds.

MDROs are an increasing problem in DFI treatment. They are associated with more complications and longer hospital stay (El-Sheikh et al, 2014). Risk factors for MDRO were assessed in many studies and included previous hospitalisation and antibiotic use, osteomyelitis, neuro-ischaemic ulcers, high-grade ulcers, chronic wounds of greater than 1-month duration, previous surgical procedure and random blood glucose level of >200 mg/dl (Alavi et al, 2007; Ahmed et la, 2013; Amini et al, 2013; Grigoropoulou et al, 2017). The most important MDROs in DFI are ESBL-producing GNR, MRSA and vancomycin-resistant *Entercoccus*.

MRSA is a challenging pathogen in DFI. Studies related MRSA to poor outcomes in DFI, such as increasing duration of hospital stay and increasing surgery recurrence rate (Ozkara et al, 2008; Saltoglu et al, 2015). Risk factors for MRSA infection include: prior antibiotic treatment, prior hospitalisation, chronic wounds, osteomyelitis, nasal carriage of MRSA, and previous history of MRSA (Lipsky et al, 2012). From a clinical point of view, MRSA represented between 0% and 26% of the total isolates (median: 6%) in this review. IDSA guidelines recommended empirical MRSA coverage if the local prevalence exceeds 50% for mild infection and 30% of moderate infection (Lipsky et al, 2012). This relatively low prevalence in the MENA region may eliminate the need for empiric MRSA coverage except for patients with a previous history of or patients with a risk factor for MRSA and severe infection that will lead to poor outcomes if empirical treatment is delayed.

Limitations

This review had many limitations. As most of the studies were conducted in hospitalised patients in large centres, this may affect the ability to generalise findings. Some concepts were not uniformly used in the studies, such as the definition of MDRO and the reporting of antibiotic susceptibility, which makes comparison between studies impractical. Furthermore, some studies did not clarify the stage or chronicity of the ulcers studied. Most studies were conducted in Iran, Turkey and Egypt, with a lack of data from many other countries.

Conclusion

There is a high prevalence of GNR in DFI in the MENA countries. This could be related to patients presenting late with high-grade ulcers and severe infections. Raising awareness among patients with diabetes to seek medical care early is highly important. Establishing a primary prevention programme and implementing a multidisciplinary approach to detect the at-risk foot early and avoid late presentation and complicated ulcers is recommended. Although there are enough studies from Egypt, Turkey and Iran, more studies from other countries are needed. Data from this review could be used to establish regional guidelines for the antibiotic treatment of DFI. DFJME

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Further information

Should any readers wish to see a detailed description of the studies, the authors are happy to send a copy over. Please email lead author Lamia Jouhar at *lj24@aub.edu.lb* and he will get back to you.

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