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Original Article

Increasing trend of healthcare-associated infections due to vancomycin-resistant *Enterococcus faecium* (VRE-fm) paralleling escalating community-acquired VRE-fm infections in a medical center implementing strict contact precautions: An epidemiologic and pathogenic genotype analysis and its implications

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KEYWORDS
Vancomycin-resistant *Enterococcus*;
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Multilocus sequence typing (MLST);

Abstract *Objective:* To clarify whether there were clandestine intra-hospital spreads of vancomycin-resistant *Enterococcus faecium* (VRE-fm) isolates that led to specific strain of VRE lingering in the hospital and/or developing outbreaks that rendered a progressively increasing trend of healthcare-associated infections due to VRE-fm (VRE-fm-HAIs).
Setting: Despite implementing strict contact precautions for hospitalized patients with VRE-fm-infection/colonization, number of VRE-fm-HAIs in a medical centre in southern Taiwan were escalating in 2009—2019, paralleling an increasing trend of community-acquired VRE-fm- infections.
Methods: We analyzed epidemiologic data and genotypes of non-duplicate VRE-fm isolates each grown from a normally sterile site of 89 patients between December 2016 and October 2018;

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Pulse-field gel electrophoresis typing

multilocus sequence typing (MLST) and pulse-field gel electrophoresis (PFGE) typing were performed.
Results: Totally 13 sequence types (STs) were found, and the 3 leading STs were ST17 (44%), ST78 (37%), and ST18 (6%); 66 pulsotypes were generated by PFGE. Four VRE-fm isolates grouped as ST17/pulsotype S, 2 as ST17/pulsotype AS, 2 as ST17/pulsotype AU, and 3 as ST78/pulsotype V grew from clinical specimens sampled less than one week apart from patients staying at different wards/departments and/or on different floors of the hospital.
Conclusions: Despite possible small transitory clusters of intra-hospital VRE-fm spreads, there was no specific VRE-fm strain lingering in the hospital leading to increasing trend of VRE-fm-HAIs during the study period. Strict contact precautions were able to curb intra-hospital VRE-fm spreads, but unable to curb the increasing trend of VRE-fm-HAIs with the backdrop of progressively increasing VRE-fm-infections/colorizations in the community.

Introduction

Since vancomycin-resistant *Enterococcus* (VRE) isolates were first identified in Europe in 1986 and were found later in North America in 1988,[1,2] globally distributed infections due to VRE isolates of differing strains have been increasingly reported.[2] VRE isolates are often multidrug-resistant,[2–4] and vancomycin-resistant *Enterococcus faecium* (VRE-fm) isolates are especially clinically important,[2–5] as they often caused healthcare-associated infections (HAIs) in vulnerable patients with multiple comorbidities, leading to substantial mortality.[2–4,6] Proposed recommendations for curbing increasing trends of VRE infections included prudent antibiotic use within the framework of antimicrobial stewardship to minimize antibiotic selective pressure,[7,8] taking care of patients with standard precautions, and strict contact/isolation precautions.[9,10]

As for Taiwan, the first VRE-fm infection case was reported in 1996, and increasingly erupting VRE-fm infections have been found ever since.[2] Surveillance data disclosed a marked increase in VRE-fm isolates from 12.4% in 2007 to 40.6% in 2016 among the overall enterococci isolated from patients staying at intensive-care units of medical centers in Taiwan.[4]

Despite adopting strict contact precautions for hospitalized patients with VRE-fm infection/colonization, number of HAIs due to VRE-fm (VRE-fm-HAIs) in Kaohsiung Chang Gung Memorial Hospital (KSCGMH), a large medical centre in southern Taiwan, have been escalating, paralleling the increasing trend of community-acquired VRE-fm-infections.[4,11] To clarify whether or not there were clandestine intra-hospital spreads of VRE-fm that led to specific strain(s) of VRE-fm lingering in the hospital or developing nosocomial outbreaks that rendered a progressively increasing trend of healthcare associated VRE-fm-HAIs, VRE-fm isolates grew from culture of specimens sampled from normally sterile sites of patients suffering HAI between December 2016 and October 2018 at KSCGMH were genotyped for analysis[12]; specifically, multilocus sequence typing (MLST) was performed to evaluate the epidemiological clonal relatedness of the VRE-fm isolates, and pulse-field gel electrophoresis (PFGE) typing was carried out to clarify whether there were intra-hospital VRE spreads or outbreaks of HAIs due to VRE-fm during this time period.[12] The implications of results would be discussed.

Methods

Hospital setting, infection control practice and surveillance, and antimicrobial stewardship

KSCGMH is a 2680-bed facility serving as a primary care and tertiary referral medical centre, in which infection control practice has been implemented following the principle recommended by the CDC.[10] Clinical specimens that grew VRE-fm in this report were sampled based on diagnostic attempts made by clinicians during their daily clinical practices. Specimen sampling was carried out at any time point during patients' hospitalization, beginning from patients' arrival at the hospital to being released from the facility. Hospitalization referred to patients' overall stay at the facility receiving medical treatment; for some patients, the overall stay included an initial stay at KSCGMH's Emergency Services and subsequent admission to ward for continuous treatment. A specimen for bacterial culture sampled upon a patient's admission to hospital ward from the community or upon a patient's arrival at our Emergency Services referred to one that was sampled at day zero when it comes to evaluate the timing of VRE-fm being isolated in hospitalized patients.

According to the standard operation procedure of the KSCGMH's clinical microbiology laboratory, once a bacterium was grown from a specimen sampled from a patient's normally sterile sites (i.e., blood, cerebrospinal fluid, pleural effusion, pericardial effusion, ascites and synovial fluid), in addition to clinically reporting the results of bacterial culture and antibiotic susceptibility tests, the isolated bacterium would be stored at −70 °C in skim milk until the laboratory storage capacity being full; the storage of a bacterium usually spanned approximate 3 years before the microbe was discarded. In case a VRE or other multidrug-resistant microbes (e.g., methicillin-resistant *Staphylococcus aureus*, carbapenem-resistant *Acinetobacter baumannii*, and carbapenem-resistant *Enterobacteriaceae*) were isolated, the clinical microbiology

laboratory personnel would immediately notify the medical staff caring for the patient and the nursing staff in the ward where the patient was staying for rapidly starting contact precautions.

Strict contact precautions adopted for hospitalized patients with VRE-fm infection/colonization by KSCGMH included immediate transferal of the patient in question to an isolation room upon receiving the clinical microbiology laboratory's notification of the growth of VRE-fm from whatever specimen, adherence to strict hand hygiene by caretakers, medical/nursing staff wearing a gown and gloves before entering the isolation room, and follow-up evaluation of VRE-fm carriage by sampling specimen literally one week apart from the patient's original infection site, or from feces if the improved infection site made sampling from it no longer possible, for bacterial culture. Contact precautions were lifted only when 2 successive culture results were negative for VRE-fm. Regular active HAI surveillance was carried out by the experienced staff composed of the same senior infection-control practitioners throughout the study period under the supervision of an infectious-diseases specialist (Dr. J-W Liu).[13,14] HAIs and their pathogens were identified based on the CDC diagnostic criteria for nosocomial infections at the hospital's regular active surveillance[15]; each infection was assessed for evidence linking to acquisition at hospitalization to determine whether the infection was healthcare-associated.[15] VRE-fm infections lacking evidence of acquisition at hospitalization referred to community-acquired VRE-fm infections. Medical records of patients with VRE-fm-HAI were retrospectively reviewed for retrievals of demographic and clinical information for analysis. In comparisons of demographic and clinic data with hypothesis testing between different groups, the Student's *t*-test was used for continuous variables, and the χ^2 test or Fisher's exact test was used for categorical variables, wherever applicable. The chi-squared test for trend was used, with post hoc comparisons, if necessary. Results were considered statistically significant at a 2-tailed *P* value < 0.05. Data in this study were analyzed anonymously; the study was conducted with a waiver of patient consent, approved by the Institutional Review Board of Chang Gung Memorial Hospital.

A HAI cluster referred to an incident in which two or more patients were experiencing temporally linked HAIs caused by the same strain of a bacterium. An HAI outbreak was defined as an increase in the number of HAI cases due to the same strain of bacterium, which was characterized by a prolonged, high-caseload, and temporally-related surge.[16]

All antimicrobial prescriptions in KSCGMH have had to be made online, as described elsewhere.[13,14] With the exception of a small number of antibiotics, such as penicillin, ampicillin, clindamycin, cefazolin, gentamicin and metronidazole, prescribed antimicrobials were subjected to review by an infectious-diseases specialist. The prescribed antimicrobial(s) would be dispensed immediately from the hospital's pharmacy, while awaiting decisions made by the online reviewer. The dispensing antimicrobial(s) would continue only when the prescription was approved by the reviewer; otherwise, the antimicrobial dispensing would be discontinued 48 h later. The reviewer was able to access the clinical, laboratory, radiographic information of the reviewed case online for evaluation to make a decision on approval or disapproval of the prescribed antimicrobial(s). The reviewer's decision and comment/suggestion were automatically immediately texted to the antimicrobial prescriber and the pharmacy.

Identification of clinical VRE isolates, susceptibility testing, DNA extractions and genotyping

E. faecium isolates were identified using matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) technology[17] with Bruker BioTyper (microflex LT; Bruker Daltonik GmbH, Bremen, Germany). Vancomycin susceptibility tests for *E. faecium* isolates were performed with Becton Dickinson BD Phoenix 100 Automated Microbiology System (Becton Dickinson Diagnostic Systems, Sparks, MD, USA). *E. faecium* against which the minimum inhibitory concentration (MIC) of vancomycin $\geq$32 μg/mL was defined as a VRE-fm isolate.[18] DNAs of the VRE-fm isolates were extracted using Qiagen DNeasy Blood and Tissue Kit (Qiagen, Hilden, Germany) for genotyping. MLST and PFGE were performed as reported previously,[19,20] with modifications.

For MLST, primer sequences of housekeep genes reported elsewhere were used; internal 400- to 600-bp fragments of these genes (*adk*, *atpA*, *ddl*, *gyd*, *gdh*, *purK*, and *pstS*) were amplified by PCR.[19] The amplification procedure was carried out in 25 μL buffered solution (Fast-Run™ Taq Master Mix; Protech, Taiwan), with denaturation at 95 °C for 5 min, annealing for 35 cycles (30 s per cycle) each at 95 °C, 50 °C and 72 °C, and extension for 5 min at 72 °C, using Veriti™ 96-Well Fast Thermal Cycler (ABI, Singapore).

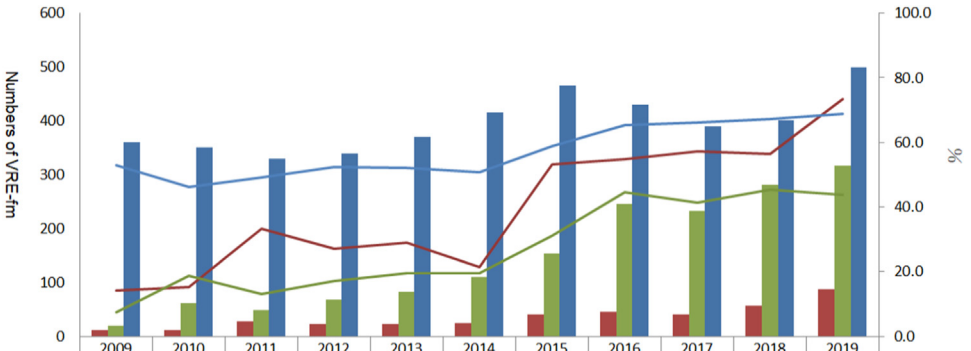
MLST and PFGE

Sequence type (ST) of a VRE-fm was determined by matching the sequences of its seven housekeeping genes with the counterparts found from the *E. faecium* isolates in the online *E. faecium* MLST database (http://efaecium.mlst.net).[19] Based on the eBURST program provided from the website, clustering analysis for the STs was depicted.[19,21]

The restriction enzyme *SmaI* was specifically used for cleavages of DNA sequences in PFGE typing.[20] The results of PFGE were analyzed using BioNumerics (version 7.6, Applied Maths, Austin, TX, USA). Based on the Unweighted Pair Group Method with Arithmetic Mean (UPGMA) analysis, PFGE patterns bearing more than 80% similarity were regarded as the same pulsotype.[2,22]

Results

Increasing trends for both VRE-fm-HAIs and community-acquired VRE-fm infections were found between 2009 and 2019 in KSCGMH ($P < 0.001$ for linear trends); post hoc multiple comparisons indicated significantly higher incidence rates of VRE-fm infections in the later half of this time period for both categorized infections (Fig. 1). In KSCGMH, among the annual overall *E. faecium* HAIs, VRE-fm-HAIs were increased from 14.1% in 2009 to 21.6% in 2014, and to 73.3% in 2019; among the annual overall *E. faecium* non-HAIs, community-acquired VRE-fm infections were increased from 7.6% in 2009 to 19.6% in 2014, and to



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
VRE-fm-HAIs in KSCGMH (No.)	11	11	27	22	22	24	40	46	40	57	87
VRE-fm-community-acquired infections in KSCGMH (No.)	19	61	48	68	82	110	153	245	233	281	317
Mean of VRE-fm-HAIs in medical centers in Taiwan (No.)	360	350	330	340	370	415	465	430	390	400	500
VRE-fm-HAIs in KSCGMH (%)	14.1	15.3	33.3	27.2	28.9	21.6	53.3	54.8	57.1	56.4	73.3
VRE-fm-community-acquired infections in KSCGMH (%)	7.6	18.7	13.2	17.3	19.6	19.6	31.1	44.6	41.2	45.4	43.8
Mean of VRE-fm-HAIs in medical centers in Taiwan (%)	52.8	46.1	49.1	52.4	52	50.7	58.9	65.3	66.1	67.1	68.7

Fig. 1. Secular trends of VRE-fm-HAIs and community-acquired VRE-fm-infections in Kaohsiung Chang Gung Memorial Hospital (KSCGMH) ($P < 0.001$ for both trends) and of VRE-fm-HAIs in medical centers in Taiwan.[11] Percentages of each categorized VRE-fm-infections were calculated by (categorized VRE-fm-infections/overall categorized *E. faeciium* infections) $\times$ 100.

43.8% in 2019. Trends for VRE-fm infections in KSCGMH and the trend for VRE-fm-HAIs in medical centers in Taiwan between 2009 and 2019 are detailed in Fig. 1.[11]

From the database of the clinical microbiology laboratory of KSCGMH, an overall 902 non-duplicate VRE-fm isolates were found between 2016 and 2018 to grow from whatever specimens. Of those, 89 non-duplicate VRE-fm isolates were each found to grow from a normally sterile site of an individual patient, and all of these VRE-fm isolates and patients were included for analysis. Of these 89 VRE-fm isolates, 33 (37%) were from blood, 53 (60%) from ascites, and 3 (3%) from pleural effusion. The timing of specimens sampled that grew VRE-fm in these hospitalized patients greatly varied, with a median of 27 days (range, 0—348 days).

Of the overall 89 patients (54 males [60.7%] and 35 females [39.3%]; mean age $\pm$ SD $=$ 67 $\pm$ 13 years), 21 (27%) were either staying at a nursing home or regional medical facility immediately prior to their admission to KSCGMH. All of these patients had at least one comorbidity, and the leading ones included solid tumors (44%), chronic renal diseases (36%), diabetes mellitus (31%), and liver cirrhosis (20%). Strict precautions were lifted in only 4 cases and patients were therefore transferred to general hospital room; eighty-five patients either died at hospitalization or were released from hospital as they underwent strict contact precautions staying at an isolation room. Forty-six patients died at their hospitalization, accounting for an all-cause mortality rate of 51.7%. Between the fatal group (n $=$ 46) and survival group (n $=$ 43), there were no significant differences in age (70 $\pm$ 12 vs. 64 $\pm$ 13 years; $P = 0.935$), gender (58.7% vs. 63.8% men; $P = 0.693$), and any one of the many comorbidities ($P \geq 0.05$). Of note, VRE-fm isolates belonged to ST18 were significantly outnumbered in fatal cases (5 isolates vs. 0 isolate; $P = 0.035$).

There were 13 STs found in these 89 VRE-fm isolates (Fig. 2). The leading STs, in decreasing order, were ST17 (n $=$ 39 [44%]) and ST78 (n $=$ 33 [37%]), followed by ST18 (n $=$ 5 [6%]) and ST80 (n $=$ 3 [3%]); the rest included ST9, ST22, ST39, ST71, ST80, ST97, ST202, ST323, ST341, and ST789, which were each found in one VRE-fm isolate.

An overall 66 pulsotypes were generated by PFGE from the 89 VRE-fm isolates. Of them, 28 pulsotypes were found from VRE-fm isolates belonged to ST17, and 27 pulsotypes from VRE-fm isolates belonged to ST78. The PFGE dendrogram with pulsotypes, the corresponding STs of the VRE-fm isolates and the VRE-fm number are shown in Fig. 3.

There were two or more VRE-fm isolates found in each of 8 pulsotypes among the overall 39 VRE-fm isolates belonged to ST17, and in each of 5 pulsotypes among the 33 VRE-fm isolates belonged to ST78 (Table 1). Of note, 4 VRE-fm isolates grouped as ST17/pulsotype S (VRE-fm nos. 8, 9, 11 and 19), 2 as ST17/pulsotype AS (VRE-fm nos. 33 and 34), 2 as ST17/pulsotype AU (VRE-fm nos. 35 and 37), and 3 as ST78/pulsotype V (VRE-fm nos. 38, 39 and 47) were identified from clinical specimens sampled less than one week apart, remarkably, from patients staying at different wards/departments and/or on different floors of the hospital. There was no specific strain of VRE-fm lingering in the hospital that led to the development of a progressively increasing trend of VRE-fm-HAIs in KSCGMH during the study period.

Discussion

With the exception of those belonged to ST39, ST9 and ST97, all of VRE-fm isolates in this report were diverged members of a special genetic lineage of *E. faecium* currently known as clonal complex-17 (CC17) (http://efaecium.mlst.net). CC17 plays an important role in globally distributed VRE-fm-infections, especially in infections acquired in hospital settings.[2,23,24] The adaption to the hospital environments of *E. faecium* isolates belonged to this genetic lineage was assumed to result from the cumulative evolutionary process with the insertion of sequence elements leading to increase in its genome plasticity.[24]

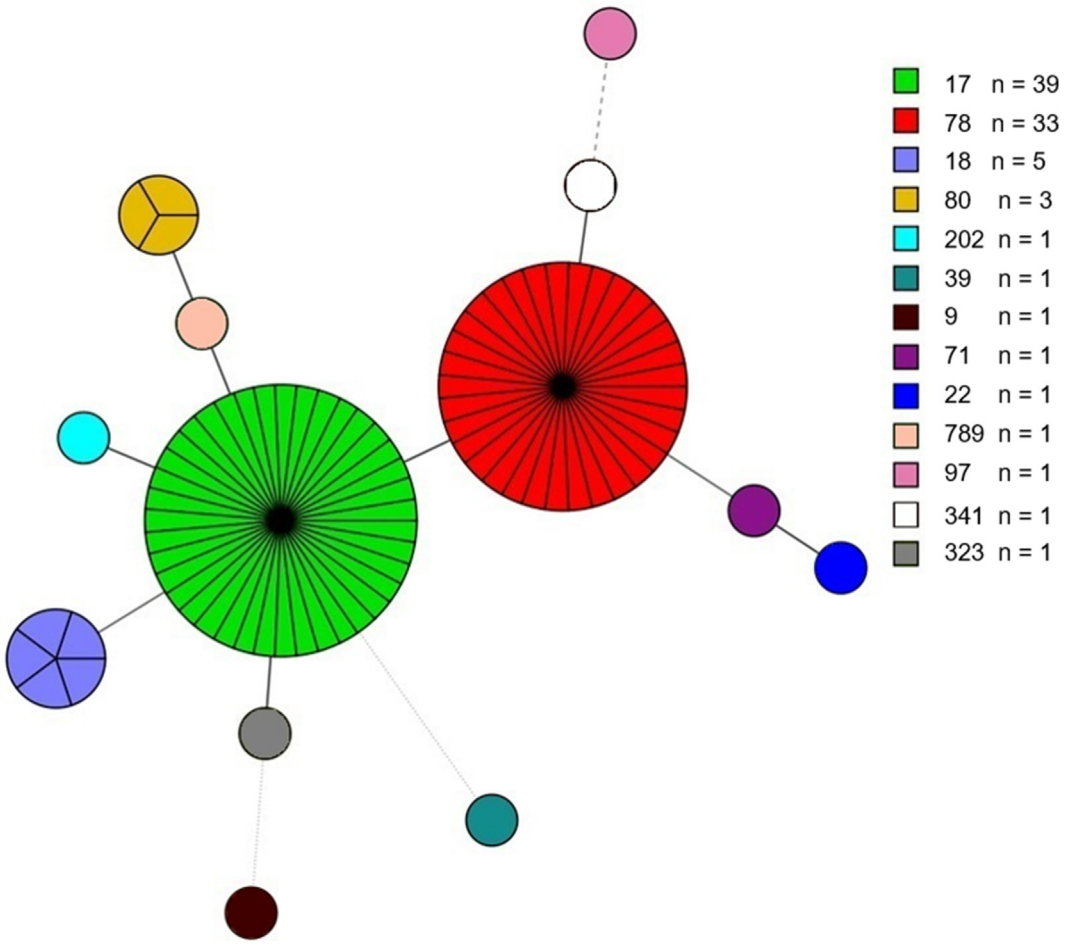


Fig. 2. eBURST analysis of the 89 VRE-fm isolates with multilocus sequence typing (MLST) in the current study. Each circle with a specific color denotes a particular sequence type (ST). The larger the number of a specific ST, the bigger the circle is. ST17 and ST38 are the dominant STs. The number of the partitioned space inside a circle indicates the number of the STs. A circle with no partition inside indicates one ST. VRE-fm isolates belonged to ST39, ST9 and ST97 were not diverged members of clonal complex-17 (CC17).

Starting from 2008, marked increase in VRE-HAI incidences has been reported in Taiwan[22,25]; CC17 members, mainly VRE-fm isolates belonged to ST17, ST78 and ST414 have been found to be predominant epidemic strains of VRE-fm-HAI clusters/outbreaks,[2—4,22,25] which resulted from either intra-hospital or inter-hospital spreads of VRE-fm isolates. Most of these VRE-fm-HAIs in the early days occurred in northern and central Taiwan.[2—4,22,25,26]

Between 2009 and 2019, the increasing trends of VRE-fm-HAIs and community-acquired VRE-fm-infections in KSCGMH ($P < 0.001$, for both trends) paralleled the escalating trend of VRE-fm-HAIs in other medical centers in Taiwan (Fig. 1).[11] It was not until 2014 that the slowly escalating trends of VRE-fm-HAIs and community-acquired VRE-fm-infections in KSCGMH became steeply risen.

Although a small number of VRE-fm isolates belonged to the same pulsotypes were found from specimens of patients admitted at different wards/departments and/or on different floors, the time proximity of sampling these specimens suggested that there were possibly small transitory clusters of intra-hospital VRE-fm spreads during the study period. If this is the case, our data suggested that although conventional active infection surveillance might fail to detect small clusters of intra-hospital VRE-fm spreads, the implementation of strict contact precautions at KSCGMH be able to curb the potentially developed large-scale hospital outbreaks of VRE-fm-HAIs. However, when the rates of incidence of VRE-fm infection/colonization in the community were rapidly rising, VRE-fm-infections in hospital were inevitably quickly soaring, which would result from the increase in potential infection sources due to the carriage of VRE-fm by newly admitted patients.[5,25,26] There are 2 limitations in this study. First, data regarding bacterial carriage in our staff were not available in this retrospective analysis, making it impossible to clarify whether or not our staff members played a role in horizontal transmissions of VRE-fm between hospitalized patients. Second, given the relatively small scale and short duration of the study, it is possible that only certain strains of VRE-fm were captured in the analysis, leading to a potential bias in the epidemiological findings.

Previous publications showed conflicting impacts of contact precautions on curbing increasing trends of VRE-fm-HAIs; some showed that contact precautions were

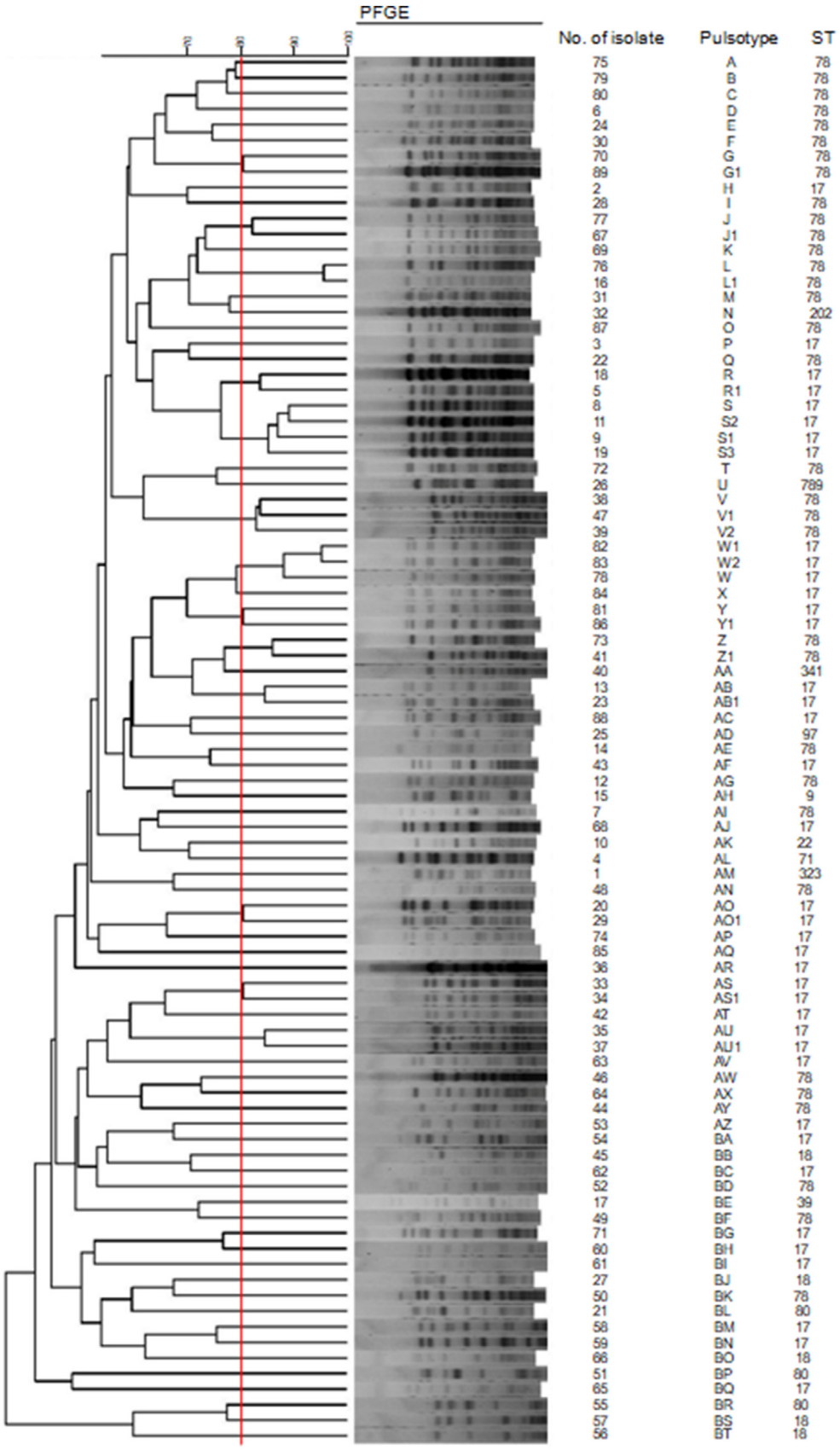


Fig. 3. Dendrogram of pulse-field gel electrophoresis (PFGE) with pulsotypes, the corresponding sequence types (STs) derived from multilocus sequence typing (MLST), and the VRE-fm isolate number are shown. Each row represents a pulsotype with its unique PFGE pattern.

Table 1 MLST sequence types (STs) and PFGE types (pulsotypes) of VRE-fm isolates grew from specimens sampled from normally sterile sites.

MLST-ST	Pulsotype	VRE-fm isolate no. and the date of sampling specimen for culture that subsequently grew VRE-fm (y/m/d)
17 (n = 39)	R	18 (2018/01/14)
		05 (2017/12/12)
	S*	08 (2017/12/15)
		11 (2017/12/26)
		09 (2017/12/21)
		19 (2018/01/18)
	W	82 (2017/07/16)
		83 (2017/09/29)
		78 (2017/05/01)
	Y	81 (2017/07/09)
		86 (2016/12/18)
	AB	13 (2017/12/27)
		23 (2018/01/29)
	AO	20 (2018/01/17)
		29 (2018/02/26)
	AS*	33 (2018/03/15)
		34 (2018/03/17)
	AU*	35 (2018/03/23)
		37 (2018/03/27)
78 (n = 33)	G	70 (2018/08/31)
		89 (2017/02/06)
	J	77 (2017/04/11)
		67 (2018/08/20)
	L	76 (2017/03/11)
		16 (2018/01/04)
	V*	38 (2018/04/05)
		47 (2018/04/23)
		39 (2018/04/06)
	Z	73 (2018/09/24)
		41 (2018/04/13)

Each VRE-fm isolate grew from one individual patient. Asterisks indicate pulsotypes in which two or more VRE-fm isolates grew from specimens that were sampled less than one week apart.

effective,[27] while others did not.[5,28] Of note, these studies did not analyze/evaluate the impacts of contact precautions on curbing VRE-fm-HAIs in the context of concurrent rapidly and progressively increasing incidences of VRE-fm-infection in the community.[5,27,28]

Contact precautions were first recommended by the CDC in 1970,[9,10] which have been globally adopted by medical facilities for decades to contain spreads of multidrug-resistant bacteria including VRE-fm isolates.[2—5,22,25,27,28] However, the progressively increasing trends of VRE-fm spreads in communities worldwide indicate that contact precautions failed to suppress the globally soaring trend of VRE-fm-infections as a whole.[2—5,22—25,27,28] Most of patients experiencing VRE-fm-infection have comorbid conditions and are immunocompromised.[2—4,14,22,25,28] When being released from hospital, these patients often harbored VRE-fm in their intestinal lumens,[5,29] which would lead to insidious yet progressive disseminations of VRE-fm isolates in the community over time,[29—33] and would cause inter-hospital spreads of VRE-fm isolates in case these vulnerable patients who are subject to high chances of repetitive infections seek medical help at other medical facilities.[29—33]

When it comes to fatalities in VRE-fm-HAIs versus vancomycin-susceptible *Enterococcus* (VSE)-HAIs, robust data supporting a meaningfully higher attributable mortality rate in VRE-HAIs are lacking[34—36]; it is reasonable to believe that the comorbid conditions and immunocompromise-inherent vulnerability found in most patients suffering VRE-fm-HAIs contribute substantially to a high crude mortality rate in this patient population.[4—6,35,36]

In summary, epidemiologic analysis with genotyping of pathogens for VRE-fm-infections in this study suggest that strict contact precautions be able to curb intra-hospital spreads of VRE, but unable to contain the increasing trend of VRE-fm-HAIs against a backdrop of progressively increasing VRE-fm infections/colorizations in the community.

Higher prevalence of VRE-infection/colonization in the community settings should be regarded a new norm. Under these circumstances, strict contact precautions should not necessarily be regarded as routine infection control measures for curbing VRE-fm-HAIs; preventions of horizontal spreads of VRE-fm isolates with staff's strict hand hygiene and minimizing antibiotic selective pressure with antimicrobial stewardship should never be overemphasized, and strict contact precautions should only be reserved for uncontrolled VRE-fm-infection outbreaks to interrupt VRE-fm transmissions. Cancellation of unnecessary strict contact precautions will minimize the potentially developed anxiety and depression in the isolated patients and improve their satisfactions with healthcare,[9] decline other potential non-infectious adverse events (e.g., postoperative respiratory failure, hemorrhage, deep vein thrombosis, decubitus ulcers, and/or trauma),[37] and will render cost savings on healthcare delivery.[38]

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