Real-life Experience with Ceftobiprole in Canada: Results from the CLEAR (Canadian LEadership on Antimicrobial Real-life Usage) Registry

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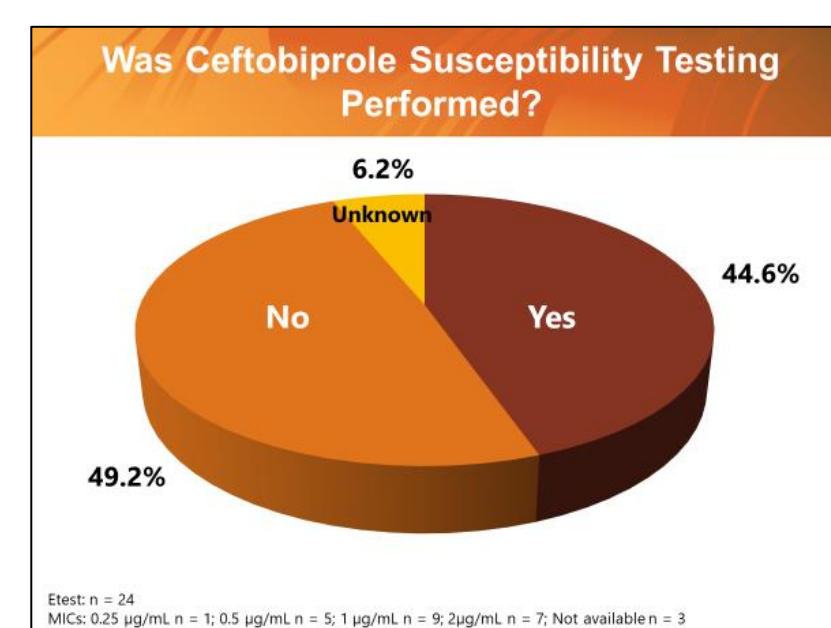Winnipeg, MB R3A 1R9
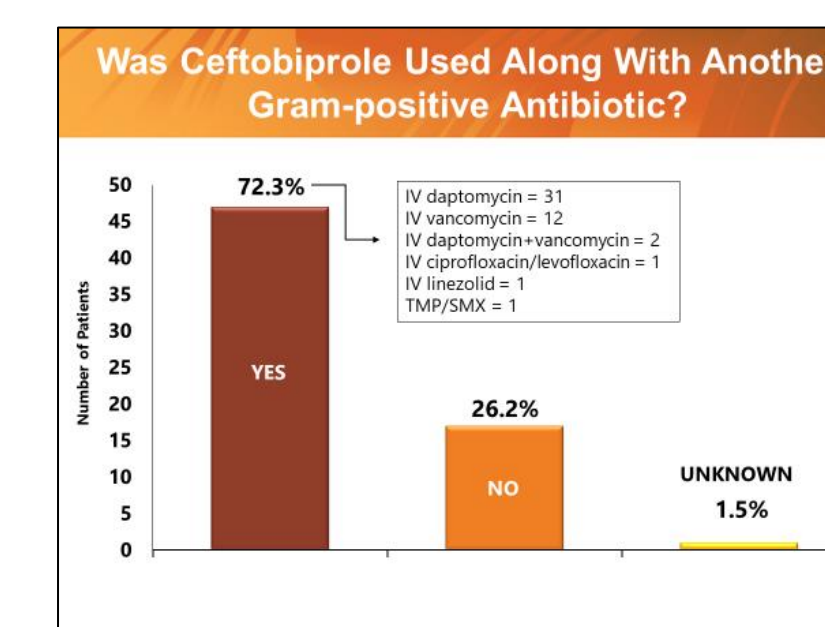Email: ggzhanel@pcsinternet.ca

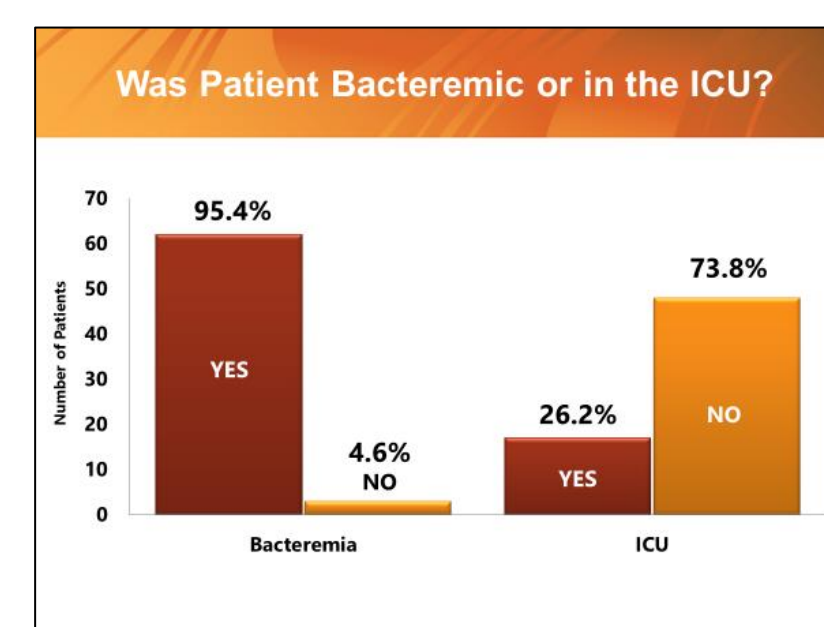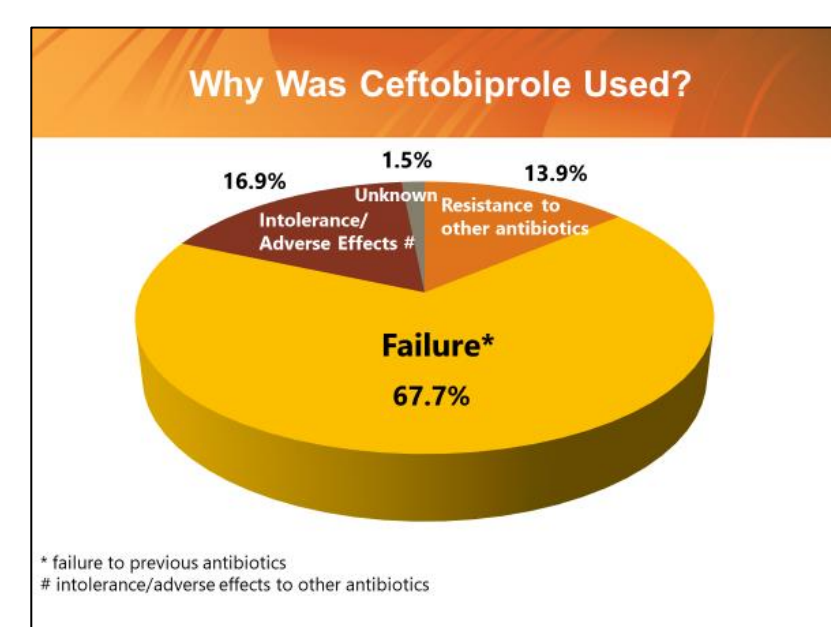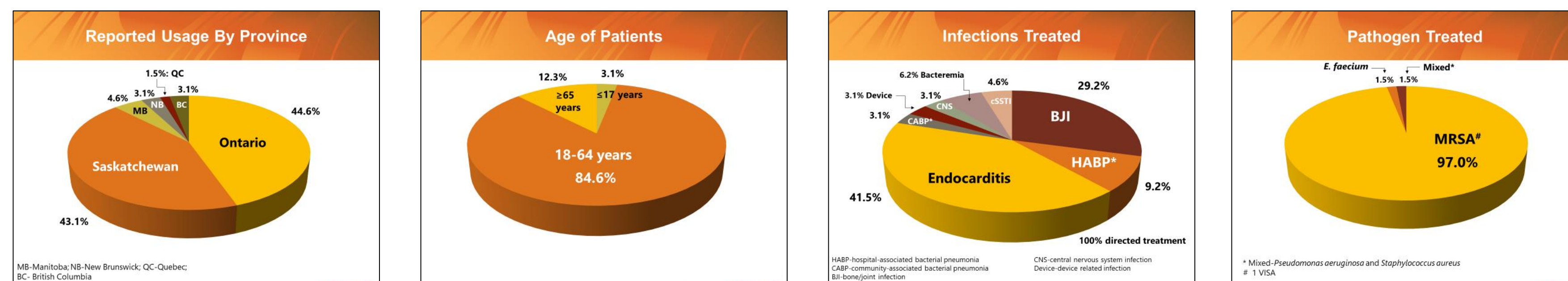www.can-r.com

Introduction

Over the past several years in Canada, when new IV antimicrobials are approved and introduced onto the market, they are used primarily by infectious diseases/medical microbiology specialists and frequently used to treat "off-label" infectious indications. There is commonly limited data sharing between clinicians regarding why they chose to use these new IV antimicrobials (i.e., because of failure, resistance, or adverse effects associated with use of other antimicrobial agents), the types of infections treated, and how (i.e., dosage regimen, duration of therapy, as monotherapy or in combination with one or more other antimicrobial agents) they use new IV antimicrobial agents in real world scenarios. The CLEAR (Canadian LEadership on Antimicrobial Real-life Usage) registry is an initiative coordinated by the Canadian Antimicrobial Resistance Alliance (CARA). CLEAR is a national usage registry platform that enables the accumulation of knowledge regarding the clinical usage of new IV antimicrobials recently introduced into the Canadian marketplace. In this study, CLEAR is accumulating data on the usage of IV ceftobiprole across Canada (https://rcsurvey.radyfhs.umanitoba.ca/surveys/?s=A8EHM8JJRF). CLEAR also has IV ceftolozane/tazobactam and IV fosfomycin in the registry. Links to access these surveys:
https://rcsurvey.radyfhs.umanitoba.ca/surveys/?s=F7JXNDFXEF
https://rcsurvey.radyfhs.umanitoba.ca/surveys/?s=WHWT7RDK7X

Materials and Methods

An IV ceftobiprole usage questionnaire was developed using the input of infectious disease/medical microbiology specialists (physicians and pharmacists) across Canada. The CLEAR registry protocol/questionnaire was submitted to and received approval by the Human Ethics Committee at the University of Manitoba (Winnipeg, Canada; April 2019).

Using the web-based research data management program, REDCap[TM] (Research Electronic Data Capture), clinicians (physicians and clinical pharmacists) responded directly to the usage questionnaire online starting June 2019. The REDCap[TM] online survey link (https://rcsurvey.radyfhs.umanitoba.ca/surveys/?s=A8EHM8JJRF) was distributed via email to >330 CLEAR participants (members of the Association of Medical Microbiology and Infectious Diseases Canada [AMMI] and Canadian Society of Hospital Pharmacists [CSHP]). Clinicians were sent an email every 2 months encouraging their participation in CLEAR. A series of drop-down menus and short answer questions allowed for rapid (~3 minutes) completion of the survey. Clinicians were encouraged to voluntarily complete usage questionnaires for as many patients as possible. The CLEAR ceftobiprole questionnaires received by March 1, 2022 were tabulated and results presented are based on 65 patient treatment surveys.
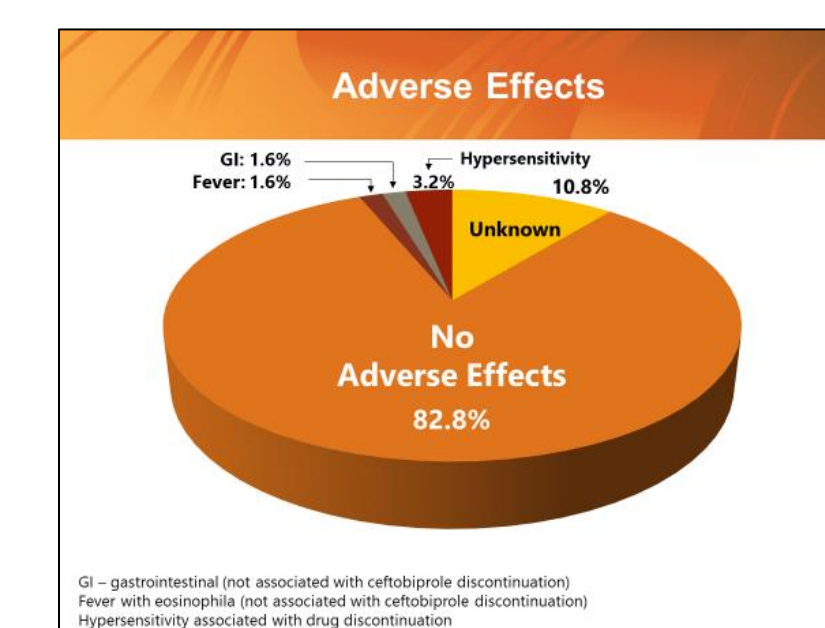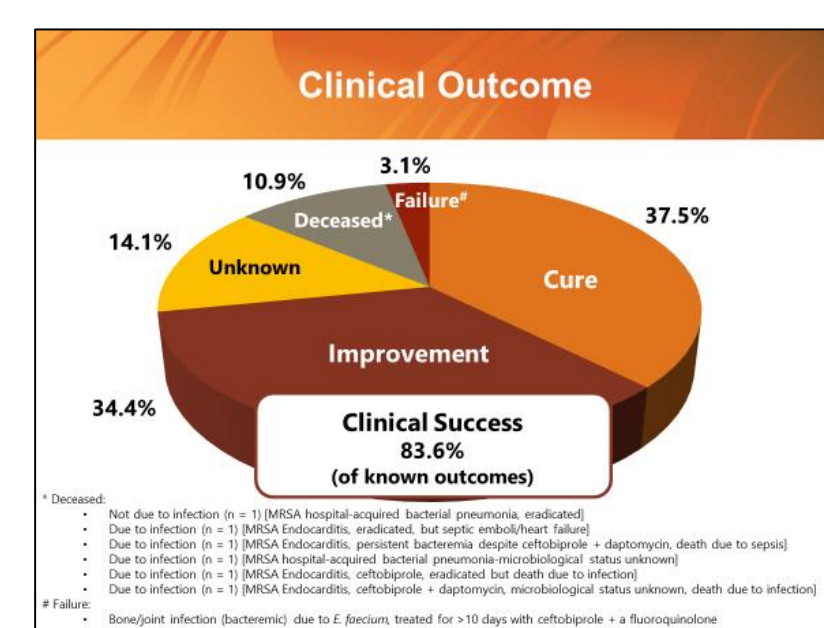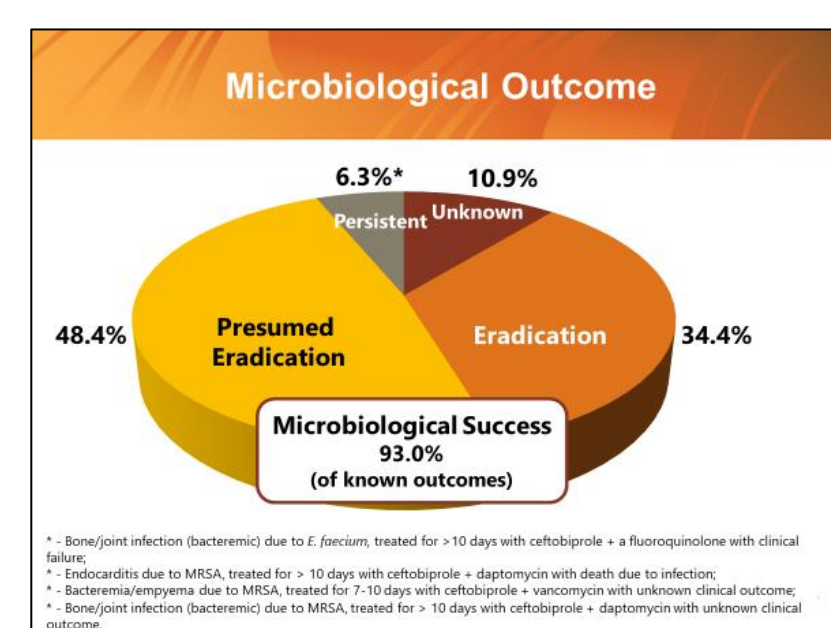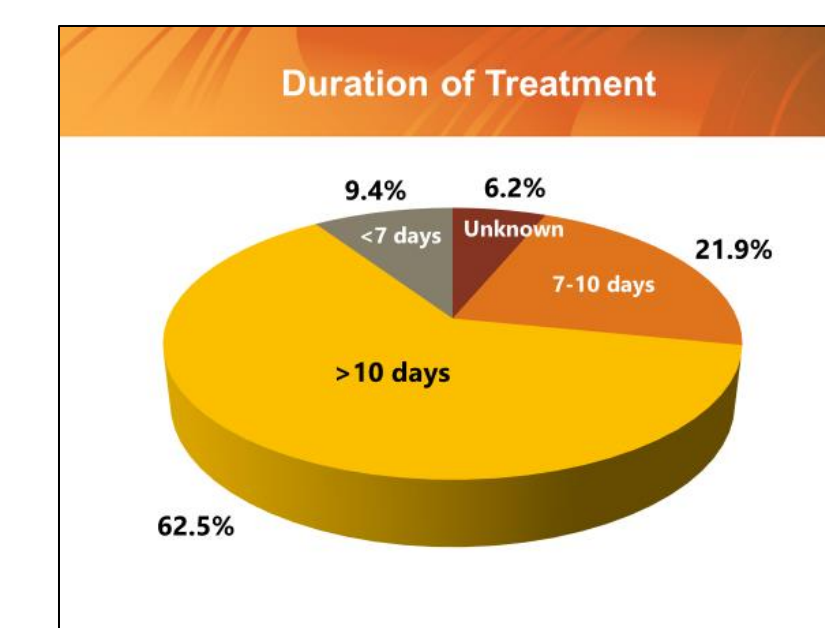
Results

Below are the cumulative tabulated results of the questions asked in the CLEAR ceftobiprole usage survey questionnaires as of March 1, 2022. The following tables are based on a total of 65 patient treatment surveys.

Reported Usage By Province
- Ontario 44.6%
- Saskatchewan 43.1%
- MB 4.6%, NB 3.1%, BC 3.1%, QC 1.5%

MB-Manitoba; NB-New Brunswick; QC-Quebec; BC- British Columbia

Age of Patients
- 18-64 years 84.6%
- ≥65 years 12.3%
- ≤17 years 3.1%

Infections Treated
- BJI 29.2%
- HABP* 9.2%
- Endocarditis 41.5%
- Bacteremia 6.2%, Device 3.1%, CNS 3.1%, CABP* 3.1%, ≤SSTI 4.6%

100% directed treatment

HABP- hospital-associated bacterial pneumonia
CABP- community-associated bacterial pneumonia
BJI- bone/joint infection
CNS- central nervous system infection
Device- device related infection

Pathogen Treated
- MRSA# 97.0%
- E. faecium 1.5%, Mixed* 1.5%

* Mixed-Pseudomonas aeruginosa and Staphylococcus aureus
# 1 VISA

Why Was Ceftobiprole Used?
- Failure* 67.7%
- Intolerance/Adverse Effects # 16.9%
- Resistance to other antibiotics 13.9%
- Unknown 1.5%

* failure to previous antibiotics
# intolerance/adverse effects to other antibiotics

Was Patient Bacteremic or in the ICU?
- Bacteremia: YES 95.4%, NO 4.6%
- ICU: YES 26.2%, NO 73.8%

Was Ceftobiprole Used Along With Another Gram-positive Antibiotic?
- YES 72.3%
- NO 26.2%
- UNKNOWN 1.5%

IV daptomycin = 12
IV vancomycin = 12
IV daptomycin+vancomycin = 2
IV ciprofloxacin/levofloxacin = 1
IV linezolid = 1
TMP/SMX = 1

Was Ceftobiprole Susceptibility Testing Performed?
- Yes 44.6%
- No 49.2%
- Unknown 6.2%

Etest: n = 24
MICs: 0.25 μg/mL n = 1; 0.5 μg/mL n = 5; 1 μg/mL n = 9; 2μg/mL n = 7; Not available n = 3

How Was Ceftobiprole Dosed / Infused?

# (%) of Patients	Ceftobiprole Dose
2 (3.1%)	1 Gram Q8H
1 (1.5%)	1 Gram Q12H
43 (66.2%)	500mg Q8H
8 (12.3%)	500mg Q12H
10 (15.4%)	250mg Q24H
1 (1.5%)	250mg Q12H

Creatinine clearance measured in 98.5% (64/65) patients
Infusion time:
- Short (15 min – 1 hour) 16.9% (11/65)
- Prolonged* (≥2 hours) 78.5% (51/65)
- Unknown 4.6% (3/65)
* On label: 2 hour infusion

Duration of Treatment
- >10 days 62.5%
- 7-10 days 21.9%
- <7 days 9.4%
- Unknown 6.2%

Microbiological Outcome
- Presumed Eradication 48.4%
- Eradication 34.4%
- Persistent 6.3%*
- Unknown 10.9%

Microbiological Success 93.0% (of known outcomes)

Clinical Outcome
- Cure 37.5%
- Improvement 34.4%
- Unknown 14.1%
- Failure† 10.9%
- Deceased# 3.1%

Clinical Success 83.6% (of known outcomes)

Adverse Effects
- No Adverse Effects 82.8%
- Hypersensitivity 10.8%
- Unknown 3.2%
- GI 1.6%, Fever 1.6%

GI – gastrointestinal (not associated with ceftobiprole discontinuation)
Fever with eosinophilia (not associated with ceftobiprole discontinuation)
Hypersensitivity associated with drug discontinuation

Conclusions

1. Ceftobiprole is used to treat a variety of infections including endocarditis, healthcare-acquired bacterial pneumonia, and bone and joint infections with the majority of patients having bacteremia

2. Ceftobiprole is almost exclusively used for the treatment of infections caused by MRSA

3. Ceftobiprole is primarily used due to failure of previously prescribed antibiotics

4. Ceftobiprole is frequently used without antimicrobial susceptibility testing

5. Ceftobiprole is frequently combined with a second MRSA agent such as daptomycin or vancomycin

6. The most common IV dosage administered was 500mg Q8H and the most administration was using prolonged (on label) infusion (≥2 hours)

7. Ceftobiprole is frequently used for durations >10 days

8. Ceftobiprole treatment is associated with high rates of microbiological and clinical efficacy

9. Ceftobiprole is associated with an excellent safety profile

Acknowledgements

Survey Access

CLEAR – ceftobiprole link
https://rcsurvey.radyfhs.umanitoba.ca/surveys/?s=A8EHM8JJRF