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High Prevalence of Tetracycline Resistance Genes among *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis* Clinical Isolates Causing Infections in Europe (2019)

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Introduction

- Tetracycline antibiotics have been in clinical use since the discovery of chlortetracycline in 1948.
- Over the next two decades, other natural and semisynthetic derivatives of this drug class (e.g., demethylchlortetracycline, doxycycline, lymecycline, methacycline, minocycline, and rolitetracycline) were introduced with improved antibacterial potency, oral bioavailability, resistance coverage, solubility, and spectrum.
- Tetracyclines exhibit broad-spectrum of activity against gram-positive and -negative bacteria as well as obligate intracellular bacteria, protozoan, parasites, and spirochetes.
- Resistance to the older generation of tetracycline agents is due to long and widespread use of tetracycline compounds to treat infections as well as their addition to livestock feed to promote growth and improve productivity.
- This study updates the literature on the distribution of tetracycline resistance (e) genes among *E c e c a ç ˙* , *K eb ë¨a e , ae*, and *P, e ab˙* recovered from patients in European medical centres that met the CLSI MIC criteria for the screening of β-lactamase genes.
- All isolates were submitted to the SENTRY Antimicrobial Surveillance Program in 2019.

– Each raw data set was quality assured, error corrected, and *de , ,* assembled using SPAdes v. 3.11.1.
- Sequencing data was screened ˙ ç for β-lactamase and *e* genes using an in-house proprietary bioinformatic pipeline.

Results

- The isolates selected for β-lactamase, and *e* gene screening by WGS, were highly resistant, showing >90% susceptibility only to ceftazidime-avibactam and tigecycline (Table 1).
  – Meropenem (82.8%/85.0% susceptible per CLSI/EUCAST), amikacin (87.0%/78.4% susceptible per CLSI/EUCAST), and colistin (89.5% susceptible per EUCAST) showed moderate activity.
  – Nitrofurantoin (47.3% susceptible per CLSI) and trimethoprim-sulfamethoxazole (28.1% susceptible) showed modest activity.
  – Only 36.5% of isolates were susceptible to tetracycline according to CLSI criteria.
- Among the 592 isolates sequenced, 294 (49.7%) carried 1 or more *e* genes, including (Figure 1):
  – 149 (52.6% tested isolates) *E. ç ˙* ,
  – 140 (49.6%) *K. e , ae*, and
  – 5 (18.5%) *P. ab˙* .

  e (A) was observed in 40.2% of all sequenced isolates, followed by *e* (D) (5.1%), *e* (B) (4.7%), and *e* (G) (0.2%).
  – *e* (A) was similarly prevalent in *E. ç ˙* (42.8% of tested isolates) and *K. e , ae* (39.7%), whereas *e* (B) was only detected in *E. ç ˙* (9.9%; Figure 1).
  – *e* (D) was more prevalent in *K. e , ae* (9.9% of tested isolates) than in *E. ç ˙* (0.7%).
- The distribution of *e* and β-lactamase genes among species is shown in Figure 2.
  – The majority (270/294; 91.8%) of isolates positive for *e* genes also carried *b˙a*$_{CTX-M}$.
  – 209 (83.6%) of the *b˙a*$_{CTX-M}$ alleles were *b˙a*$_{CTX-M-15}$.
- Carbapenemase genes were noted in (Figure 2):
  – 111/282 sequenced *K. e , ae* (39.4%): 38 *b˙a*$_{KPC}$, 15 *b˙a*$_{NDM}$, 1 *b˙a*$_{VIM-1}$, and 58 *b˙a*$_{OXA-48}$-like.
  – 6/283 sequenced *E. ç ˙* (2.1%): 3 *b˙a*$_{KPC-3}$, 1 *b˙a*$_{VIM-1}$, and 2 *b˙a*$_{OXA-48}$-like.
  – 46/117 carbapenemase producing isolates also carried a *e* gene (39.3%).

Conclusions

e genes were commonly encountered among *E. ç ˙* ofx.587 0 lc0 1eiAX75 –

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