Antimicrobial co-resistance patterns of gram-negative bacilli isolated from bloodstream infections: a longitudinal epidemiological study from 2002-2011

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ABSTRACT

Background

Increasing multidrug resistance in gram-negative bacilli (GNB) infections poses a serious threat to public health. Few studies have analyzed co-resistance rates in detail, defined as an antimicrobial susceptibility profile in a subset resistant to one specific antibiotic. The epidemiologic and clinical utility of determining co-resistance rates are analyzed and discussed.

Methods

A 10-year retrospective study from 2001-2011 of bloodstream infections with GNB were analyzed from three hospitals in Greater Vancouver, BC, Canada. Descriptive statistics were calculated for antimicrobial resistance and co-resistance. Statistical analysis further described temporal trends of antimicrobial resistance, correlations of resistance between combinations of antimicrobials, and temporal trends in co-resistance patterns.

Results

The total number of unique blood stream isolates of GNB was 3280. Increasing resistance to individual antimicrobials was observed for *E. coli*, *K. pneumoniae*, *K. oxytoca*, *E. cloacae*, and *P. aeruginosa*. Ciprofloxacin resistance in *E. coli* peaked in 2006 at 40% and subsequently stabilized at 29% in 2011, corresponding to decreasing ciprofloxacin usage after 2007 as assessed by daily defined dose utilization data. High co-resistance rates were observed for ceftriaxone-resistant *E. coli* with ciprofloxacin (73%), ceftriaxone-resistant *K. pneumoniae* with trimethoprim-sulfamethoxazole (83%), ciprofloxacin-resistant *E. cloacae* with ticarcillin-clavulanate (91%), and piperacillin-tazobactam-resistant *P. aeruginosa* with ceftazidime (83%).

Conclusions

Increasing antimicrobial resistance was demonstrated over the study period, and may partially be associated with antimicrobial consumption. The study of co-resistance rates in multidrug resistant GNB provides insight into the epidemiology of resistance pattern development, and can be used as a clinical tool to aid prescribing empiric antimicrobial therapy.

METHODS

Data Extraction

- Report generated from VCH laboratory information system Sunquest® to identify all positive blood cultures with GNB from 2002-2011
- One bacterial isolate of the same identification (genus and species) and susceptibility pattern per patient per calendar study year
- Antibiotic susceptibility testing was performed and interpreted using guidelines established by the Clinical and Laboratory Standards Institute (CLSI).

Data Analysis

- Descriptive statistics used to present the resistance and co-resistance data
- Pharmacy data on inpatient antimicrobial consumption were compared against antimicrobial resistance results
- Statistical analysis was performed to determine linear-to-linear temporal trends of individual antimicrobial resistance and co-resistance patterns

RESULTS AND DISCUSSION

- Total number of unique blood stream isolates of GNB was 3,280
- Five most common GNB isolated were *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Enterobacter cloacae*, and *Pseudomonas aeruginosa*

Antimicrobial Resistance and Consumption Patterns over time

- Overall increasing rates of resistance to several antimicrobial agents in gram negative bacilli
- For *E. coli* (Figure 1a), resistance to ciprofloxacin and SMX-TMP peaked in 2006 (40%) and decreased to 29% and 34% in 2011.
- Ciprofloxacin consumption peaked in 2007 (23800 DDD) and decreased to 10100 DDD in 2011. SMX-TMP consumption peaked in 2007 (5100 DDD), decreased to 4200 DDD in 2009, and increased to 6700 DDD in 2011.
- Crude evidence heavy antimicrobial consumption driving increasing resistance - well known but little data showing this

Antimicrobial Co-resistance Patterns

- In *E. coli* (Table 1a), having resistance to ceftriaxone confers a 73% probability of also exhibiting resistance to ciprofloxacin. In contrast in those resistant to ciprofloxacin, only 25% are resistant to ceftriaxone.
- Useful clinically in empiric antimicrobial therapy, especially with MALDI-TOF technology identifying bacterial species average 1.5 days earlier (longer gap between identification and susceptibility results)
  - Choosing best combination empiric antimicrobial therapy in critically ill patient
  - Switching antimicrobial therapy empirically when recently failed another antibiotic

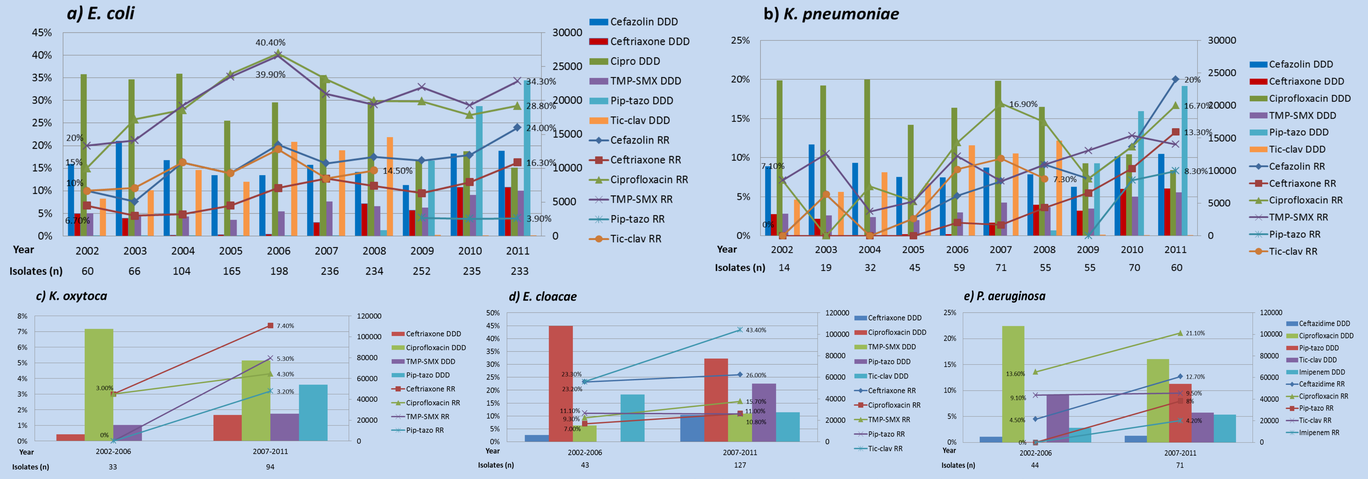

Figure 1. Temporal patterns of resistance to selected antimicrobial agents overlay with antimicrobial utilization data in daily defined doses (DDDs) for a) *E. coli*, **b)** *K. pneumoniae*, **c)** *K. oxytoca*, **d)** *E. cloacae*, and **e)** *P. aeruginosa*. Number of isolates for each GNB is listed below the corresponding year or time groups. Line graphs correspond with % resistance on left Y axis, and bar graphs correspond with DDD on right Y axis. Note that DDD data for ticarcillin-clavulanate is plotted in 00's.

a) ***E. coli***

No. of isolates (n)	Resistance to	Co-resistance Rate with Antibiotic (%)				
2002-06		**Ceftriaxone**	**Ciprofloxacin**	**Pip-tazo**	**TMP-SMX**	**Tic-clav**
44	**Ceftriaxone**	X	73	14	59	59
194	**Ciprofloxacin**	16	X	8	62	31
3	**Pip-tazo**	33	67	X	67	X
193	**TMP-SMX**	13	63	8	X	31
91	**Tic-clav**	29	67	X	66	X
2007-11		**Ceftriaxone**	**Ciprofloxacin**	**Pip-tazo**	**TMP-SMX**	**Tic-clav**
146	**Ceftriaxone**	X	73	18	72	48
357	**Ciprofloxacin**	30	X	10	58	26
28	**Pip-tazo**	57	71	X	79	X
373	**TMP-SMX**	28	56	10	X	27
64	**Tic-clav**	42	61	X	61	X
2002-11		**Ceftriaxone**	**Ciprofloxacin**	**Pip-tazo**	**TMP-SMX**	**Tic-clav**
190	**Ceftriaxone**	X	73	18	69	53
551	**Ciprofloxacin**	25	X	10	60	29
31	**Pip-tazo**	55	71	X	77	X
566	**TMP-SMX**	23	58	9	X	30
155	**Tic-clav**	34	65	X	64	X

b) ***K. pneumoniae***

No. of isolates (n)	Resistance to	Co-resistance Rate with Antibiotic (%)				
2002-11		**Ceftriaxone**	**Ciprofloxacin**	**Pip-tazo**	**TMP-SMX**	**Tic-clav**
20	**Ceftriaxone**	X	60	35	83	53
54	**Ciprofloxacin**	22	X	22	46	29
10	**Pip-tazo**	60	50	X	40	X
44	**TMP-SMX**	30	57	16	X	37
19	**Tic-clav**	26	58	X	53	X

c) ***K. oxytoca***

No. of isolates (n)	Resistance to	Co-resistance Rate with Antibiotic (%)				
2002-2011		**Ceftriaxone**	**Ciprofloxacin**	**Pip-tazo**	**TMP-SMX**	**Tic-clav**
8	**Ceftriaxone**	X	38	20	25	50
5	**Ciprofloxacin**	60	X	0	20	25
2	**Pip-tazo**	50	0	X	0	X
5	**TMP-SMX**	40	20	0	X	100
3	**Tic-clav**	67	33	X	33	X

d) ***E. cloacae***

No. of isolates (n)	Resistance to	Co-resistance Rate with Antibiotic (%)				
2002-2011		**Ceftriaxone**	**Ciprofloxacin**	**Pip-tazo**	**TMP-SMX**	**Tic-clav**
43	**Ceftriaxone**	X	26	47	37	81
17	**Ciprofloxacin**	65	X	17	59	91
9	**Pip-tazo**	100	11	X	11	X
24	**TMP-SMX**	67	42	6	X	80
33	**Tic-clav**	67	30	X	24	X

e) ***P. aeruginosa***

No. of isolates (n)	Resistance to	Co-resistance Rate with Antibiotic (%)				
2002-2011		**Ceftazidime**	**Ciprofloxacin**	**Pip-tazo**	**Imipenem**	**Gentamicin**
11	**Ceftazidime**	X	45	50	27	9
22	**Ciprofloxacin**	23	X	24	23	23
6	**Pip-tazo**	83	67	X	33	33
13	**Imipenem**	23	38	18	X	23
9	**Gentamicin**	11	56	29	33	X

Table 1. Summary of antimicrobial co-resistance rates determined for a) *E. coli*, **b)** *K. pneumoniae*, **c)** *K. oxytoca*, **d)** *E. cloacae*, and **e)** *P. aeruginosa*. Co-resistance rates were analyzed as a summary of isolates from 2002-2011 except for *E. coli*, where it was possible to analyze two time periods from 2002-06 and 2007-11 due to higher isolate numbers.

CONCLUSIONS

- Increasing rates of antimicrobial resistance for several GNB were observed over a 10-year period
- Antimicrobial consumption is associated with increasing antimicrobial resistance
- Study of co-resistance rates helps determine the epidemiology of resistance development
- One clinical utility of co-resistance rates include tailoring empiric antibiotic regimens to minimize risks of resistance when the susceptibility profile of a bacterial isolate is not yet known