Ceftriaxone-resistant *Salmonella* spp. in Singapore

Dear Editor,

The utility of ceftriaxone for the treatment of *Salmonella typhi* bacteraemia was first demonstrated in Singapore as early as 1985.[1] Since then, ceftriaxone has become established as first-line treatment for typhoid fever and serious non-typhoidal *Salmonella* infections. However, in recent years, we have noticed sporadic cases of non-typhoidal *Salmonella* with reduced susceptibility to ceftriaxone.

Fifteen *Salmonella* spp. with diminished susceptibility to ceftriaxone were collected from 2 public hospitals from 2003 to 2006 (out of approximately 640 isolates of all *Salmonella* spp. per annum). DNA was extracted and subjected to multiplex PCR looking for plasmid AmpC (pAmpC) cephalosporinase and CTX-M extended spectrum β-lactamase (ESBL) genes.[2,3] We also amplified and sequenced TEM and SHV β-lactamase genes using the methods of Mabilat and Rasheed respectively.[4,5]

The patient and isolate details together with the results are summarised in Table 1. All SHV β-lactamase genes coded for the ESBL SHV-5, whereas all TEM β-lactamase genes coded for TEM-1, which is not an ESBL. In addition, 2 types of CTX-M ESBL ($bla_{\text{CTX-M group 1}}$ and $bla_{\text{CTX-M group 9}}$) and pAmpC genes ($bla_{\text{CMY-2-like}}$ and $bla_{\text{DHA-like}}$) were detected. There was a distinction between isolates from adult and paediatric patients with SHV-5 and CTX-M genes being more common in the former and CMY-2-like pAmpC genes in the latter.

Non-typhoidal *Salmonella* usually cause gastroenteritis that resolves spontaneously. However, they may cause more serious infections in children, the elderly and the immunocompromised. One strain (DS3583) was obtained at post-mortem although it could not be confirmed that death was attributable to infection. The choice of antimicrobials for the treatment of invasive salmonellosis is relatively limited. It is noteworthy that 8 of the isolates also showed diminished susceptibility to nalidixic acid. This is predictive of therapeutic failure with ciprofloxacin (the alternative first choice therapy in adults).

There are increasing reports of ceftriaxone resistant *Salmonella* worldwide particularly due to the production of CMY-2 and CTX-M-1 group β-lactamases. On the other hand, *Salmonella* producing the CTX-M-14 β-lactamase (belonging to CTX-M group 9) seem to be more common in Asia (Hong Kong, Japan, Korea, Taiwan, Thailand).[6] SHV-5 ESBLs and DHA type pAmpC β-lactamases are more typically associated with multi-resistant *Klebsiella pneumoniae* in the hospital setting.

Table 1. Characteristics of Ceftriaxone Resistant *Salmonella* spp.

Strain no.	Year	Identification	Source	Age (y)	Sex	Ethnic origin	NA	β-lactamase gene
DM18275	2003	*S. typhimurium*	Wound	39	M	Chinese	S	$bla_{\text{CTX-M group 9}}$
3165-509	2003	*S. typhimurium*	Stool	30	M	Chinese	I	$bla_{\text{CTX-M group 9}}$
DS3583	2003	*S. typhimurium*	Stool	1	F	Malay	R	$bla_{\text{TEM-1}}$, $bla_{\text{CTX-M group 1}}$
M4-04-6638	2004	*Salmonella* Gp B	Stool	1	M	Chinese	I	$bla_{\text{CMY-2-like}}$
DS29	2004	*Salmonella* spp.	Stool	41	M	Chinese	S	$bla_{\text{SHV-5}}$
DS5907	2005	*Salmonella* Gp C	Stool	74	M	Chinese	I	$bla_{\text{SHV-5}}$
DS12328	2005	*Salmonella* Gp C	Stool	61	F	Malay	I	$bla_{\text{SHV-5}}$
DS909	2006	*S. enteritidis*	Stool	95	F	Chinese	R	$bla_{\text{SHV-5}}$
DB23970	2006	*Salmonella* Gp D	Blood	52	F	Indian	S	$bla_{\text{CTX-M group 1}}$
M4-06-8425	2006	*Salmonella* Gp E	Stool	1	M	Indonesian	S	$bla_{\text{TEM-1}}$, $bla_{\text{SHV-5}}$
M4-06-7527	2006	*Salmonella* Gp B	Stool	2	M	Chinese	S	$bla_{\text{CMY-2-like}}$
M4-06-6695	2006	*Salmonella* Gp D	Stool	3	F	Chinese	S	$bla_{\text{TEM-1}}$, $bla_{\text{CMY-2-like}}$
M4-06-8446	2006	*Salmonella* Gp D	Stool	15	F	Malay	S	$bla_{\text{TEM-1}}$, $bla_{\text{CMY-2-like}}$
M4-06-8700	2006	*Salmonella* Gp D	Stool	1	M	Chinese	R	$bla_{\text{DHA-like}}$
DS2941	2006	*Salmonella* Gp C	Stool	61	F	Chinese	R	$bla_{\text{TEM-1,}}$ $bla_{\text{DHA-like}}$

I: intermediate susceptibility; NA: nalidixic acid; R: resistant; S: susceptible

The origins of ceftriaxone resistance in *Salmonella* spp. pose an intriguing question given that *Salmonella* are not usually nosocomial pathogens and are therefore not subject to antibiotic pressure in hospitals. It has been suggested that animals and food products may be involved in some cases. Extended-spectrum cephalosporins like cefiofur and cefquinone are used to treat diseases in cattle and poultry, usually by mass oral medication.[7] In the United States, CMY-2-producing *Salmonella* have been found in beef and poultry products. There is also evidence that plasmids bearing the CMY-2 gene have transferred between animal-associated *Salmonella* spp. and *Escherichia coli*.[8] With increasing globalisation of food sources and the availability of oral third generation cephalosporins locally, there is the real possibility of ceftriaxone resistance emerging in the community in *Enterobacteriaceae* other than *Salmonella* spp.

While ceftriaxone resistant *Salmonella* spp. are still rare in Singapore, clinicians should be aware that susceptibility to this antimicrobial can no longer be assumed. Even though antimicrobials are not required for uncomplicated salmonella gastroenteritis, microbiology laboratories should continue susceptibility testing of stool isolates so that surveillance for the emergence of resistance can be maintained

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