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Control of an Outbreak of Linezolid-Resistant

Staphyococcus Aureus in a Spanish Intensive Care Department

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A 12-patient outbreak with linezolid-resistant Staphylococcus aureus (LRSA) developed in our intensive care department. A combination of interventions, in close collaboration with the microbiology and the preventive medicine services, were effective in controlling the outbreak within two months.

Introduction

Linezolid resistance was first reported in 2001 in a clinical isolate of S. aureus in the USA (Tsiodras et al. 2001), although it still is very uncommon in surveillance programmes (Cuevas et al. 2008; Jones et al. 2008; Jones et al. 2009). Nonetheless, linezolid and methicillin- resistant Staphylococcus aureus (LRSA) is increasingly being identified as a colonising and infecting microorganism agent both in ambulatory and hospitalised patients. At the time of writing this manuscript, 77 strains/cases of colonised and/or infected patients have been published, mostly in the years 2009, 2010 and 2011. The importance of this development resides both in the fact that MRSA is a frequent aetiology of severe, mainly respiratory tract and bloodstream, healthcare- associated and ICU infections (Alvarez-

Lerma et al. 2007; Klevens et al. 2007) and that therapeutic options for severe MRSA infections are limited. Linezolid has a favourable safety profile in short-term administration, provides multi-drug resistant Gram-positive coverage and has proven to be an effective antimicrobial tool. An additional and recent factor driving its use is the rising concern about the decreasing effectiveness of vancomycin (Haque et al. 2010; Soriano et al. 2008). Linezolid is therefore widely employed as empiric and directed therapy, both in critically ill patients in ICUs, as well as in hospitalised or ambulatory patients. Antimicrobial activity of linezolid is due to protein synthesis inhibition by binding to the domain V of the 23S rRNA of the 50S subunit of bacterial ribosomes (Diekema and Jones 2001). The reported principle mechanisms of linezolid resistance documented in human isolates of S. aureus are mutations in the domain V of the 23S ribosomal RNA and, more recently, the existence of a plasmidic cfr gene (Long et al. 2006; Morales et al. 2010) encoding a methyl-transferase which modifies the binding site of linezolid on the bacterial 23S rRNA. In April 2008, we were alerted by the Microbiology Service about a positive blood culture growing LRSA and 4 weeks later, at the third isolate identified in a third patient, an LRSA outbreak was officially declared in our Intensive Care Department (Sanchez Garcia et al. 2010); to our knowledge, this was the first LRSA outbreak to be reported.

Outbreak

Our centre is a referral tertiary-care university teaching hospital in Madrid. The Intensive Care Department consists of three closed dedicated ICUs with a high mean bed occupancy rate. The outbreak involved 12 patients and the predominant clone was transmitted to the three ICUs (Figure 1) causing primary bacteraemia in three patients and ventilator-associated pneumonia in six. Affected patients had been in intensive care for approximately one month at LRSA index culture, half of them required vasopressor support and all were mechanically ventilated. 11 of the 12 patients had linezolid-susceptible MRSA prior to the detection of LRSA and had received a relatively short period of a median of 7.5 days of linezolid therapy. Infections with LRSA were treated with vancomycin and tigecycline. Hospital mortality was 50%, with one death possibly related to infection with LRSA.

Management Measures

The short duration of two months of this outbreak suggests that an effective combination of control measures was in place. Some of these measures are routinely implemented in our department and tend to limit the spread of resistant bacteria, while other, more specific interventions, were instituted upon identification of LRSA.

Disinfection

Extensive cleaning and disinfection of the patient area and equipment is daily practice in our units and it is also performed after discharge of a patient. Actually, investigation of environmental spread of LRSA resulted in negative cultures in 90 of 91 randomly selected surfaces (bedside equipment, furniture, clinical devices and the nursing station).

Prevention / Collaboration

Immediate communication of identification of bacterial multi-drug resistance (MDR) to the attending physicians and the preventive medicine service is of utmost importance for the swift implementation of the strict barrier precautions issued by the preventivists. The MRSA protocol reinforces hand washing and the use of gloves, masks and disposable gowns for patient contact, daily 4% chlorhexidine body wash, and five days of intranasal mupirocin ointment in nasal carriers.

Isolation

Specific measures implemented during this LRSA and other MDR bacterial outbreaks start with immediate placement of patients in isolation rooms under strict barrier precautions, as detailed above, until three consecutive negative weekly surveillance samples are documented. If more than two cases occur simultaneously, they are cohorted and nursed in a separate four bed ICU area.

Use of Linezolid

An important characteristic of the management of this outbreak, which should be pointed out is that the prescription of linezolid by intensivists was not restricted in any way or, much less, prohibited. Daily updates of the outbreak data were provided and discussed on clinical rounds with the attending intensivists in each unit and linezolid was reserved for documented respiratory tract and complicated skin and soft tissue infections caused by linezolid–susceptible microorganisms to take advantage of the excellent efficacy and safety profile of linezolid in selected cases. As a result, an immediate, marked, approximately 8-fold, reduction of linezolid use occurred within few weeks (Figure 2), which after definitive control of the outbreak has settled at approximately 40 to 50% of prior usage. The reduction of linezolid pressure in the ICU environment seemed a logical outbreak control measure to implement, as it is apparently, the most specific risk factor for the development of linezolid resistance. Of note is, however, that linezolid was administered to outpatients for months (Gales et al. 2006; Hentschke et al. 2008) and even years (Meka et al. 2004b; Roberts et al. 2006) before it induced mutations leading to resistance in MRSA, while inpatients had received linezolid therapy for much shorter periods of time (Kola et al. 2007; Meka et al. 2004a; Paterson et al. 2003; Peeters and Sarria 2005; Tsiodras et al. 2001; Wilson et al. 2003). Also, strains of LRSA with resistance mediated by the cfr gene, which doesn't seem to be directly induced by the presence of linezolid, are detected after relatively short durations of therapy. Cfr-mediated linezolid resistance was shown in an LRSA isolate after only two doses in the first Colombian isolate (Toh et al. 2007), without prior exposure in the US strain (Mendes et al. 2008) and after a median of 7.5 days of linezolid therapy in our outbreak. Therefore, although LRSA strains with the cfr gene may emerge due to a survival advantage in the presence of linezolid, other, yet unknown, risk factors may contribute to the emergence of LRSA. It may be speculated that cross-resistance, transmission of the plasmid from an undetected LRSA patient, or transferral of the cfr plasmid from an undetected linezolid-resistant microorganism, like coagulase-negative staphylococci, may be the mechanisms of acquisition of resistance. This implies that further studies are needed in order to identify additional effective outbreak control measures or the prevention of emergence of LRSA.

Conclusion

Finally, the characteristics and interventions which specifically may have facilitated the rapid control of the outbreak that occurred at our institution were the absence of stable exogenous reservoirs on the hands of ICU staff and environment, with only five patients harbouring LRSA in their GI tract, and the strict barrier precautions, respectively. In conclusion, the efficient rapid control of an outbreak with LRSA in the ICU department was attained by a combination of control measures mainly consisting of barrier precautions, environmental cleaning and reduction of linezolid use.

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