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Managing Escherichia coli sepsis and the Tarragona strategy

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Title figure:
The Ferreres Aqueduct (Catalan: Aqüeducte de les Ferreres), also known as the Pont del Diable), is an ancient bridge, part of the Roman aqueduct built to supply water to the ancient city of Tarraco, today Tarragona in Catalonia, Spain (source: www.wikipedia.org).

INTRODUCTION

Early onset sepsis is one of the leading causes of neonatal death – worldwide as well as in high-resource countries (1). The incidence (2) of early-onset sepsis and the case fatality rate (3) are even higher among preterm infants, in whom a shift towards gram-negative bacteria, predominantly Escherichia coli, occurs (4). For life-threatening diseases, empiric antibiotic therapy regimens must cover the most relevant pathogens and, at the same time, avoid any unnecessary use of reserve antibiotics (5, 6). In most cases of early-onset neonatal sepsis, the pathogens colonizing the neonate or its previous environment, the mother's womb, are not known when treatment is initiated.

CASE REPORT

This male preterm infant was born to a 25-year-old G1/P1 at 27 5/7 weeks of gestation with a birth weight of 1060 g (P 25 – 50), a body length of 38 cm (P 50 – 75) and a head circumference of 27 cm (P 50 – 75). The pregnancy had been uneventful until 26 weeks, when the mother was hospitalized secondary to contractions. A complete course of antenatal corticosteroids was administered. At 27 2/7 weeks, premature preterm rupture of the membranes (PPROM) occurred. A vaginal swab revealed gram-positive cocci and gram-negative rods. Beta-hemolytic streptococcus group C/G could be cultivated in addition to undifferentiated vaginal flora. In addition to tocolytic therapy with hexoprenaline, erythromycin 500 mg twice daily was administered until Cesarean section became necessary due to contractions refractory to escalating tocolysis and signs of amniotic infection syndrome.

The Apgar scores were 8, 9 and 9 at 1, 5 and 10 minutes, respectively. Non-invasive respiratory support was started (CPAP at 8 cmH_2O, FiO_2 0.23). An empiric regimen for early-onset sepsis with amoxicillin and gentamicin was initiated in the delivery room taking into consideration the available microbiological results of the maternal swab.

In the neonatal intensive care unit (NICU), respiratory distress and desaturations occurred, requiring mechanical ventilation and administration of surfactant on the first day of life (DOL). Arterial hypotension was

managed with fluid boluses. Interleukin-6 from cord blood was slightly elevated (201 ng/l), while C-reactive protein (CRP) was within normal range (1 mg/l). With a time to positivity of 6 hours, aerobic blood culture, collected prior to the administration of antibiotics, turned positive with pan-sensitive Escherichia coli (E. coli). Routine screening with nasal, pharyngeal, perianal, umbilical, and tracheal swabs was completed on admission to the NICU. Prior to extubation on DOL 2, a lumbar puncture was performed and yielded no evidence of meningitis (9 cells/µl, negative gram stain). Therefore, the empiric antibiotic regimen was continued at non-meningitic doses.

On DOL 3, prolonged capillary refill time and peripheral hypothermia were noted. An echocardiogram revealed reduced myocardial contractility, near-systemic pulmonary hypertension and a hemodynamically relevant persistent ductus arteriosus (PDA). Dobutamine was administered at 15 µg/kg/min. The baby remained stable on CPAP with an FiO_2 of 0.21.

Later that day, however, blood gases deteriorated with marked metabolic acidosis (pH 6.9, lactate 13 mmol/l, and base excess -19 mmol/l). At this time, the medical chart was reviewed again. It was noted that the routine skin swab obtained as part of routine microbiological surveillance had revealed growth of an E. coli, still multi-sensitive but resistant to the administered antibiotic regimen of amoxicillin and gentamicin.

Source	Date of collection Specimen		Pathogen	Resistance to amoxicillin / gentamicin	Date reported	Date noted
Mother	Aug 12	vaginal swab	gram negative rods	no		
Infant	Aug 14	umbilical / perianal swab	E. coli (1)	no	Aug 16 15:00	Aug 16 21:00
			E. coli (2)	yes	Aug 16 15:00	Aug 16 21:00
	Aug 14	blood culture	E. coli (1)	no	Aug 16 10:00	reported by phone
	Aug 15	tracheal aspirate	E. coli (2)	yes	Aug 17 15:00	
	Aug 16	blood culture	E. coli (2)	yes	Aug 18 10:00	reported by phone

Unfortunately, the results of the routine skin swab had not been recognized in time but only with a delay of 6 hours. Consequently, antibiotics were then switched from amoxicillin to piperacillin-tazobactam after retrieval of another aerobic blood culture. This blood culture confirmed the same E. coli with a resistance pattern as documented in the skin swab.

Regrettably, despite change of antibiotics and escalation to maximum intensive care measures including high frequency oscillatory ventilation, adrenalin, noradrenalin and milrinone, the patient developed refractory septic shock (Fig. 1), necrotizing enterocolitis, intraventricular hemorrhage, seizures, and died on DOL 5 despite ongoing intensive care therapy. In the aftermath, the histological report of the placenta confirmed acute chorioamnionitis.

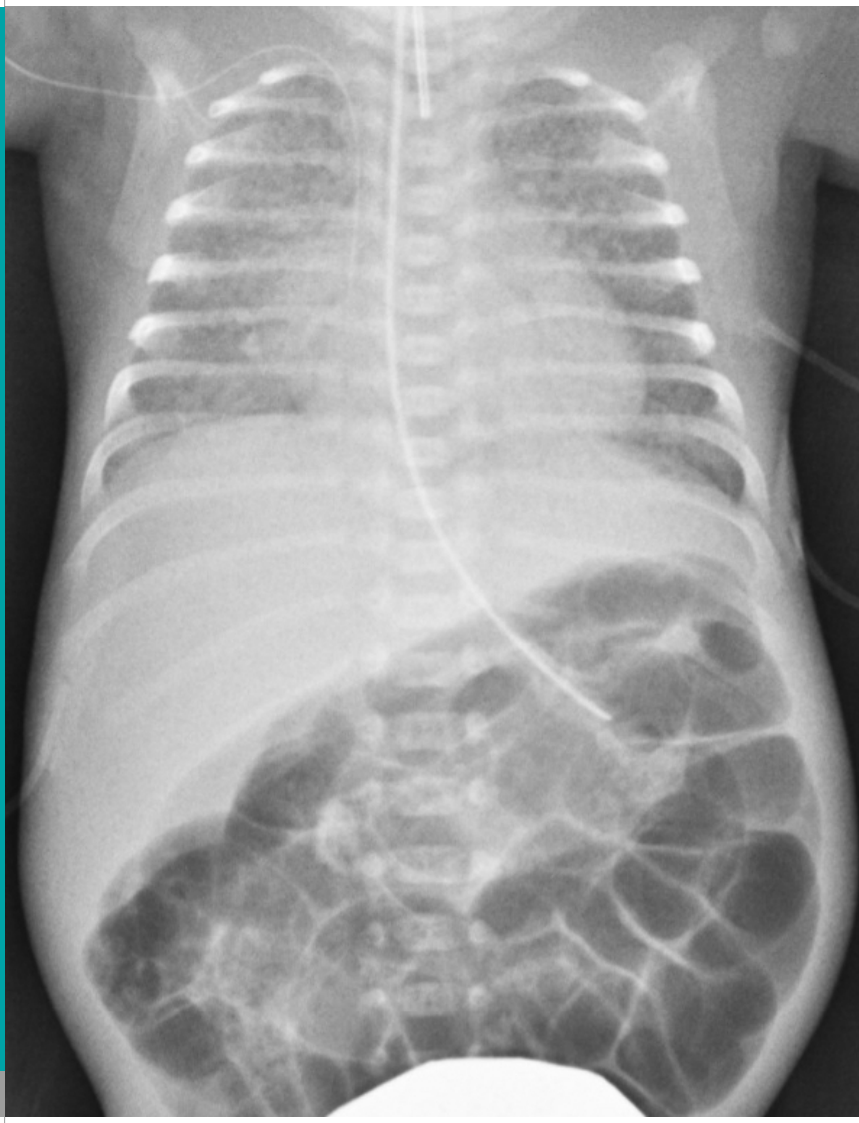

Fig. 1

Babygram following intubation under conventional ventilation (SIMV, PIP 25 cmH_2O, PEEP 8 cmH_2O, FiO_2 0.65): signs of pneumonia and possible intestinal pneumatosis.

DISCUSSION

Almost 20 years ago, the "Tarragona Strategy" was published, addressing ineffective as well as unnecessary antibiotic therapy of ventilator-associated pneumonia (7, 8). Since then, five key principles of the Tarragona Strategy have been applied to antibiotic therapy in intensive care services in general (9):

- Look at your patient
- Listen to your hospital (the patient's environment)
- Hit hard (and early)
- Get to the point
- Focus, focus, focus

Although our local guidelines for diagnosis and management of early- and late-onset neonatal sepsis follow these principles, they failed to prevent the fatal course in this particular case. Thus, it is important to learn from this situation, to analyze the process, and to develop future strategies for the prevention of similar events.

In reviewing this case, the following questions arose:

- Was the timing of the Cesarean section the most appropriate?
- Could the resistant bacteria in the mother have been detected earlier?
- Was the first line antibiotic regimen appropriate?
- Was the management to detect clinical deterioration under therapy appropriate?

- Was the process of reporting available information in a timely manner appropriate?

Retrospectively, the answer to the first question is „no“, it should have been done earlier in order to avoid chorioamnionitis; however, prospective decision-making is challenging. Every additional day of prolongation of pregnancy from the limit of viability to the end of prematurity is beneficial, except for the one day, when chorioamnionitis develops and pathogens reach the fetus. There is no international consensus about the indication, optimal and maximal duration of tocolysis in preterm labor, and guidelines and current practice at times disagree (10 – 12). While there is a strong consensus to administer tocolytics until the completion of antenatal corticosteroid administration, there is no proof for the effectiveness of prolonging pregnancy until 34 or even 37 weeks of gestation. Clinical experience, however, demonstrates, that in the absence of contraindications, prolonging tocolysis beyond 48 hours is common and, in certain cases, appears to prolong gestation (13). Maintaining tocolytic therapy in the presence of PPROM, however, is even more controversial because of an increased incidence of amniotic infection syndrome. There is a strong consensus that intrauterine inflammation or infection is a contraindication for prolongation of pregnancy and that timely delivery is indicated in such cases (14). Of course, the challenge is the recognition of reliable evidence of intrauterine infection. There are efforts

to unify definitions and thereby simplify management strategies, but still, uncertainties prevail (15). For these situations, each institution should develop clinical management guidelines that are applicable 24 hours a day to facilitate decision-making ("Look at your patient").

Could the resistant bacteria in the mother have been detected earlier? Possibly, yes, if the microscopically detected gram-negative rods had been differentiated ("Look at your patient" and "Listen to your hospital"). The current aim of vaginal swabs in PPROM is to guide antibiotic therapy of the mother. If these vaginal swabs, however, would be regarded as colonization screening of the newborn-to-be, it would need cultural differentiation and determination of resistances of all pathogens, similar to what is performed in neonatal colonization screening after birth (16 – 18). Knowing the bacteria colonizing a patient should not only increase the rate of appropriate antibiotic therapies but also reduce the use of unnecessary broad-spectrum antibiotics ("Focus, Focus, Focus"). Colonization should, however, never trigger antibiotic therapy in the absence of an infection.

Was the first line antibiotic regimen appropriate? In our hospital, based on the annual analysis of resistances of the specimens collected in the whole hospital, the intensive care units, and the neonatal department, about 7 – 8 % of all isolated E. coli are

resistant to gentamicin ("Listen to your hospital"). All isolates resistant to gentamicin are also resistant to amoxicillin. For patients infected by these isolates, our initial regimen will be ineffective. E. coli accounts for about one quarter of all cases of early-onset sepsis (19), in preterm infants the incidence is somewhat higher (20). Many infants receive empiric antibiotic treatment without fulfilling the full criteria of early onset sepsis. Therefore, the number-needed-to-treat with an alternative (broader) regimen in order to achieve one additional effective treatment would be clearly higher than 100 patients – which seems inappropriate to us. We believe, it is more appropriate to ensure awareness of this gap in antibiotic effectiveness among our staff and make sure that second line treatment is initiated in a timely manner in case of clinical non-response to the first line treatment ("Look at your patient" and "Hit hard").

Was the management to detect clinical deterioration under therapy appropriate? In this case, it was obviously not: clinical deterioration on DOL 3 was apparent many hours before antibiotics were changed. Gradients of peripheral-to-core-temperature, reduced stability to nursing procedures and cardiac dysfunction were recognized many hours prior to the recognition that the antibiotic treatment was ineffective. Analysis of C-reactive protein 48 hours after initiation of therapy showed only a slight elevation (13 mg/l), the results of the initial blood culture

suggested appropriate choice of antibiotics. Finally, the rareness of colonization (and even more: infection) with two different strains of the same pathogen likely contributed to misinterpretation of the new symptoms. This type of error, namely assuming that the infection is treated with the correct antibiotics and therefore under control, neglecting the possibility of a "second hit infection", is known as „fixation error". It can be overcome by strategies described in Crew Resource Management, e.g. stepping back and re-evaluating the situation ("10 for 10" principle in CRM (21)).

Was the process of reporting available information in a timely manner appropriate? The answer is „no". The system of microbiological surveillance had just been implemented in routine clinical practice. Several factors may have contributed to this failure: 1) The initial detection of the second strain of E. coli came from a skin swab (and not from sterile material); 2) the strain was not multi-resistant but "only" resistant to gentamicin and amoxicillin; 3) results were not communicated by phone due to perceived lack of urgency by the microbiologist; 4) the patient initially improved. Since then, this case has become a "teaching case" and is used on a regular basis to teach how to use and interpret the findings of the microbiologic surveillance system – hoping to prevent a re-occurrence of such a course.

One question remaining unanswered is the origin of the second strain of E. coli. It seems very unlikely that aminoglycoside resistance could have developed within two days under the pressure of antibiotic therapy. Most likely, it was present in the mother together with the pan-sensitive first strain, but it is also possible that the second strain was only transferred after birth. The first strain may have facilitated bloodstream invasion of the second strain.

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