

Thromboxane-Associated Pulmonary Hypertension during Three Types of Gram-Positive Bacteremia in Piglets

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ABSTRACT. Thromboxane-associated pulmonary hypertension occurs in animals during intravenous infusion of group B streptococcus (GBS), a gram-positive neonatal pathogen. We postulated that other gram-positive neonatal pathogens, such as *Streptococcus fecalis* (Ent) and *Staphylococcus epidermidis* (S. epi) would also induce increased thromboxane synthesis and pulmonary hypertension when infused into piglets. We observed similar hemodynamic and gas exchange abnormalities during stepwise increases in the dose of GBS, Ent, and S. epi ($n = 3, 4,$ and 4 piglets receiving each bacteria, respectively). Pulmonary vascular resistance increased significantly in the absence of acidosis or reduced arterial or mixed venous pO_2 at a dose of 2.5×10^8 cfu/kg/h for Ent and S. epi. In 14 additional piglets, pulmonary vascular resistance increased markedly after 60 min of intravenous infusion of $4 \pm 1 \times 10^8$ cfu/kg/h for each organism ($p < 0.05$, GBS: 11.7 ± 1.8 to 75.6 ± 18.4 mm Hg/liter/min, Ent: 12.7 ± 1.7 to 64.9 ± 10.6 mm Hg/liter/min, S. epi: 10.5 ± 0.8 to 56.9 ± 6.0 mm Hg/liter/min), and blood thromboxane B2 levels increased ($p < 0.05$, GBS: 30 ± 10 to 1830 ± 330 pg/ml, Ent: 20 ± 7 to 1110 ± 300 pg/ml, S. epi: 31 ± 9 to 1260 ± 350 pg/ml). This dose of each bacteria caused a similar degree of mild arterial hypoxemia (57–66 mm Hg). The thromboxane synthetase inhibitor, dazmegrel, completely reversed pulmonary hypertension, reduced TxB2 levels to near baseline values, and partially reversed arterial hypoxemia despite ongoing bacterial infusion. We conclude that thromboxane-associated pulmonary hypertension occurs in piglets during infusion of different gram-positive neonatal pathogens. (*Pediatr Res* 23: 553–556, 1988)

Abbreviations

cfu, colony forming units
C.O., cardiac output
DAZ, dazmegrel
Ent, *Streptococcus fecalis* (enterococcus)
GBS, group B streptococcus
 P_{pa} , pulmonary artery pressure
PVR, pulmonary vascular resistance
 P_w , pulmonary capillary wedge pressure
S. epi, *Staphylococcus epidermidis*
TxB2, thromboxane B2
TxA2, thromboxane A2
IV, intravenous

P_{aw} , proximal airway pressure
 P_{sa} , systemic arterial pressure

GBS, a common gram-positive neonatal pathogen, causes acute pulmonary hypertension, arterial hypoxemia, and decreased cardiac output when infused into both adult and neonatal animals (1–3). In animals with GBS bacteremia and in some human newborns with GBS sepsis, pulmonary hypertension is associated with elevated blood levels of TxB2, the stable metabolite of the potent vasoconstrictor thromboxane A₂ (2, 4, 5). Inhibitors of thromboxane synthesis, such as DAZ (UK 38, 485), can prevent or reverse pulmonary hypertension in animals with GBS bacteremia (4, 6).

The fact that both gram-positive bacteria, e.g. GBS, and some gram-negative bacteria, e.g. *Escherichia coli* and *Aeromonas hydrophilia* (7, 8), can cause thromboxane-associated pulmonary hypertension suggests a lack of bacterial specificity for this pulmonary vascular response. Gram-positive neonatal pathogens other than GBS, such as Ent and S. epi, can contribute to respiratory failure and morbidity in human newborns (9, 10). However, there are no reports on the pulmonary hemodynamic effects of these other gram-positive bacteria.

We postulated that the intravenous infusion of gram-positive neonatal pathogens other than GBS into neonatal piglets might also cause elevation of blood thromboxane levels and pulmonary hypertension. Therefore, we also postulated that the administration of DAZ during ongoing infusion of bacteria other than GBS would reverse the pulmonary hypertension. Our hypothesis was tested by measuring pulmonary vascular responses and thromboxane levels in piglets before and during infusion of (1) GBS, (2) Ent, an enterococcal species containing the Lancefield group D antigen, and (3) S. epi, a nonstreptococcal species.

METHODS

Twenty-five piglets, 18 ± 4 days of age, and weighing 3.5 ± 0.3 kg were anesthetized (20 mg/kg pentobarbital IV), paralyzed (0.3 mg/kg pancuronium bromide IV), heparinized (1000 IU IV), and mechanically ventilated via a metal tracheostomy with a large animal Harvard ventilator adjusted to deliver a tidal volume of 10 ± 2 ml/kg at a rate to maintain $PaCO_2$ at 40 ± 5 mm Hg during baseline conditions. All animals were ventilated with room air throughout each experiment. A 5 Fr Swan-Ganz thermodilution catheter was positioned in a branch of the left pulmonary artery under fluoroscopy to measure P_{pa} and P_w and C.O. by thermodilution using an Edwards cardiac output computer, and to sample mixed venous blood. A polyethylene (PE 160) catheter was placed in the aorta via the left internal carotid

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artery to measure P_{sa} and sample arterial blood for pH, blood gas tensions, and arachidonic acid metabolite measurements. A polyethylene catheter (PE 90) was inserted into the left external jugular vein for infusion of bacteria. After instrumentation, anesthesia and muscle paralysis were maintained with pentobarbital (3 mg/kg IV q 1–2 h) and pancuronium bromide (0.3 mg/kg IV q 1–2 h), respectively. All piglets demonstrated a PaO_2 of more than 80 mm Hg and a pulmonary artery pressure less than 20 mm Hg while breathing room air after instrumentation. Animals received sighs to 30 cm H_2O every 20 min to minimize spontaneous development of atelectasis. All vascular pressures were measured using Hewlett-Packard 1280 transducers and referenced to mid-chest; P_{aw} was measured with a Statham P50 transducer at the tracheostomy port. Rectal temperature was maintained between $38.5 \pm 0.5^\circ C$ with an overhead radiant heat source.

Group B β -hemolytic streptococcus (type III, COH-1), Ent (CG 110), and *S. epi* (V.L. strain) were originally clinical isolates from neonates at Children's Hospital and Medical Center, Seattle, WA. Bacteria were inoculated into Todd-Hewitt broth and incubated at $36^\circ C$ for 18 h before each experiment. The broth culture was centrifuged at $1000 \times g$ at $2^\circ C$ for 15 min, the bacterial pellet was resuspended in sterile isotonic saline, recentrifuged at $1000 \times g$ for 15 min, and resuspended in sterile isotonic saline. The purity of each inoculum was assessed by colony morphology on blood agar. Bacterial concentration of the resuspensions was determined by measurement of optical density at 800 nm with comparison to previous plots of bacterial cfu on blood agar versus O.D. at 800 nm for each organism. The inoculum was then diluted with isotonic saline such that an infusion rate of 0.1 ml/min provided 5×10^8 cfu/kg/h. The diluted inoculum was inspected under light microscopy and showed no evidence of bacterial aggregation. Quantitative bacterial cultures were performed by serial dilution of arterial blood samples in sterile isotonic saline and subsequent plating onto blood agar.

In pilot experiments, a 1:50 dilution of Todd-Hewitt broth was infused via the central venous catheter at a rate of 0.1 ml/min for 20 min, and we observed no change in hemodynamic or gas exchange values in three piglets. This dilution of medium was selected as a generous estimate of possible contamination of the twice-washed bacterial pellet. In addition, undiluted supernatant from *S. epi* and Ent cultures was filtered (0.2- μ pore size) and infused at a rate of 0.1 ml/min with no change in hemodynamic or gas exchange values.

The relationship between IV bacterial infusion dose and pulmonary vascular resistance was first determined for each organism. Hemodynamic indices including P_{pa} , P_w , P_{sa} , C.O., and blood gas tensions were measured before bacterial infusion and at 20 min after each stepwise increase in the bacterial infusion doses beginning with 5×10^7 cfu/kg/h, and increasing to 1×10^8 cfu/kg/h, 2.5×10^8 cfu/kg/h, and finally 5×10^8 cfu/kg/h.

In each piglet, P_{pa} , P_w , P_{sa} , C.O., arterial and mixed venous blood gas tensions, proximal airway pressure, arterial blood samples for TxB2 measurement, and quantitative arterial blood cultures were subsequently obtained under three conditions: 1) before bacterial infusion (PRE), 2) 60 min after the onset of the bacterial infusion via the central venous catheter at a dose of $4 \pm 1 \times 10^8$ cfu/kg/h (60 min), and 3) 90 min after the onset of the bacterial infusion and 30 min after a 5-minute IV infusion of 8 mg/kg of DAZ, a thromboxane synthetase inhibitor. The powder from of DAZ (UK 38, 435 kindly provided by R. Uguilla, Pfizer Laboratories, Groton, CT) was dissolved in 1.5 ml of 0.1 N NaOH and 0.9% saline was added to a volume of 7.5 ml. For this part of the study, five additional piglets received Ent, five additional piglets received *S. epi*, and four additional piglets received GBS.

Under each experimental condition (PRE, 60 min, and DAZ), 2 ml of arterial blood were obtained for measurement of TxB2. The blood drawn into a cyclooxygenase inhibitor solution of 0.6

mg indomethacin and 2 mg EDTA/ml of blood. The inhibitor solution and the inhibitor solution-blood mixture were kept in an ice-water bath until centrifugation at $25,000 \times g$ for 20 min at $0^\circ C$. The decanted supernatant was promptly frozen at $-70^\circ C$ until analysis by radioimmunoassay in the laboratory of Dr. William Henderson, University of Washington, as previously reported (4).

Cardiac output was measured in triplicate during each experimental condition, and if there was a more than 10% variation in those values a fourth measurement was included for determining the average. PVR was calculated ($PVR = P_{pa} - P_w / C.O.$). The arterial blood samples for TxB2 measurement were analyzed in duplicate by radioimmunoassay; the average of the two assays was used to determine means for the different experimental groups. Paired *t* tests were used to ascertain statistical significance between prebacterial infusion values and the two subsequent experimental conditions for each type of bacteria. A *p* value of less than 0.05 was considered significant.

RESULTS

The relationship between bacterial infusion dose and pulmonary vascular resistance for each organism is shown in Figure 1. These experiments were performed to study the effects of increments in the bacterial infusion on pulmonary hemodynamics, C.O., and gas exchange. In addition these data were used to determine a common infusion dose for the three organisms that would cause sustained pulmonary hypertension in the absence of marked hypoxemia or hypotension. There was a similar dose-response relationship for each organism with a significant elevation in PVR at doses of 2.5×10^8 cfu/kg/h for Ent and *S. epi* and continued elevation in PVR at a dose of 5×10^8 cfu/kg/h for all types of bacteria. At a dose of 2.5×10^8 cfu/kg/h, PVR increased from preinfusion values predominantly due to a doubling of P_{pa} (GBS: 14.3 ± 0.9 to 30.0 ± 7.0 mm Hg, Ent: $15.2 \pm$

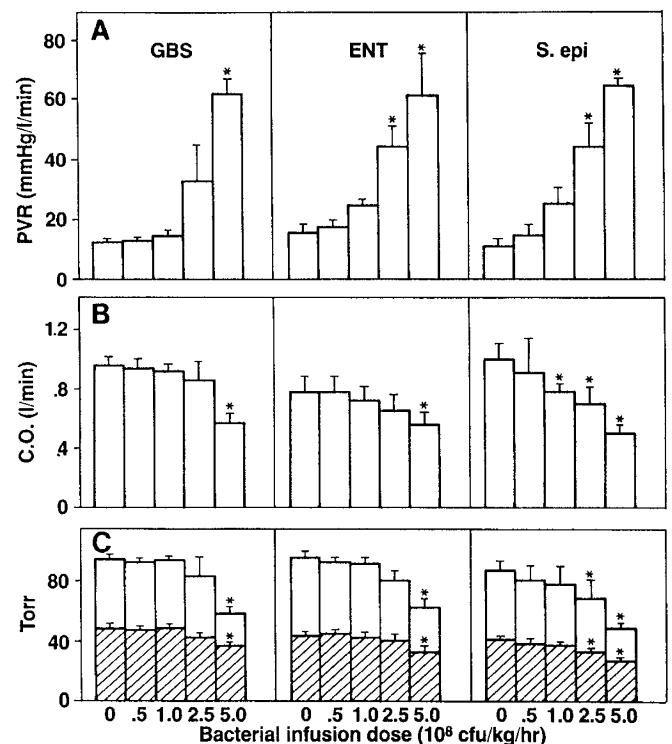


Fig. 1. Cardiopulmonary responses to increasing doses of three gram-positive bacteria. A, PVR versus bacterial infusion dose; B, C.O. versus bacterial infusion dose; C, blood gas tensions versus bacterial infusion dose. Open bars represent PaO_2 and cross-hatched bars represent PvO_2 . Values are expressed as mean \pm SEM, **p* < 0.05 compared to preinfusion value.

1.7 to 31.0 ± 1.4 mm Hg, and *S. epi*: 14.3 ± 2.3 to 35.2 ± 4.0 mm Hg), as well as a 15–30% decrease in C.O. (Fig. 1). The further increase in PVR at doses of 5×10^8 cfu/kg/h was due to both an increase in P_{pa} (GBS: 39.7 ± 2.2 mm Hg, Ent: 35.4 ± 1.1 mm Hg, and *S. epi*: 40.2 ± 2.5 mm Hg), and a 30–50% decrease in C.O. from preinfusion values.

The increase in PVR at a dose of 2.5×10^8 cfu/kg/h of Ent occurred in the absence of acidosis, arterial hypoxemia, or significant reduction in mixed venous oxygen tension (Fig. 1); the increase in PVR at a dose of 2.5×10^8 cfu/kg/h of *S. epi* was associated with statistically significant decreases in both arterial and mixed venous pO_2 , but values that remained within normal limits for piglets (Fig. 1). Due to the differences in the bacterial dose producing pulmonary hypertension for different types of bacteria, an infusion of $4 \pm 1 \times 10^8$ cfu/kg/h of each organism was selected for the remaining experiments to ensure significant elevation of P_{pa} in all animals during the entire 1-h infusion.

The pulmonary hemodynamic response to a 1-h infusion of $4 \pm 1 \times 10^8$ cfu/kg/h and the effect of the thromboxane synthetase inhibitor, DAZ, on pulmonary vascular resistance during bacterial infusion are shown in Table 1. For each gram-positive organism there was a similar and sustained elevation in PVR during the 1-h infusion, with marked increases in PVR above the preinfusion values. Thirty min after the administration of DAZ despite ongoing infusion of bacteria, PVR returned to preinfusion values for all three types of bacteria. All three bacteria caused a similar and significant increase in P_{pa} during the infusion, and there was a significant increase in P_w during both GBS and Ent infusion (Table 1). Elevated pulmonary artery and pulmonary capillary wedge pressures were reduced 30 min after administration of DAZ despite ongoing infusion of all three types of bacteria. C.O. was decreased to approximately 60% of baseline values 1 h after the onset of each infusion, with partial return to preinfusion values after infusion of DAZ (Table 1). This decrease in C.O. was associated with a 10–20% increase in heart rate, but no reduction in systemic arterial pressure. Although there were small but statistically significant reductions in pH and increases in $PaCO_2$ values after 60 min of bacterial infusion for all three organisms, no abnormal values for pH or $PaCO_2$ in piglets occurred (Table 2). In addition, after 60 min of infusion of each type of bacteria, there was a significant reduction in both PaO_2 and PvO_2 . After administration of DAZ values of both PaO_2 and PvO_2 partially returned to prebacterial infusion values (Table 2).

TxB2 levels are presented in Table 3. Arterial TxB2 levels were

Table 1. Similar hemodynamic responses to three gram-positive pathogens and DAZ in piglets (mean \pm SEM)*

	P_{pa} (mm Hg)	P_w (mm Hg)	C.O. (liter/min)	PVR (mm Hg/ liter/min)
GBS (<i>n</i> = 4)				
PRE	13.5 ± 1.0	2.6 ± 0.5	0.95 ± 0.06	11.7 ± 1.8
60'	$44.0 \pm 1.9^\dagger$	$6.3 \pm 0.6^\dagger$	$0.56 \pm 0.11^\dagger$	$75.6 \pm 18.4^\dagger$
DAZ	14.0 ± 1.6	2.8 ± 0.5	$0.75 \pm 0.05^\dagger$	14.3 ± 2.5
Ent (<i>n</i> = 5)				
PRE	14.3 ± 1.2	2.5 ± 0.2	0.96 ± 0.11	12.7 ± 1.7
60'	$39.6 \pm 2.3^\dagger$	$5.2 \pm 0.4^\dagger$	$0.57 \pm 0.07^\dagger$	$64.9 \pm 10.6^\dagger$
DAZ	13.6 ± 0.8	3.2 ± 0.3	$0.83 \pm 0.06^\dagger$	12.8 ± 1.4
<i>S. epi</i> (<i>n</i> = 5)				
PRE	13.4 ± 1.0	3.6 ± 0.6	0.99 ± 0.11	10.5 ± 0.8
60'	$37.3 \pm 2.2^\dagger$	4.6 ± 0.3	$0.59 \pm 0.08^\dagger$	$56.9 \pm 6.0^\dagger$
DAZ	12.4 ± 0.8	2.7 ± 0.5	0.79 ± 0.05	12.7 ± 0.9

* PRE, before bacterial infusion; 60', 60 min into bacterial infusion; DAZ, 30 min after administration of DAZ with ongoing bacterial infusion.

$^\dagger p < 0.05$ compared to baseline (PRE).

all less than 100 pg/ml before bacterial infusion, which represents the limit of TxB2 detection by radioimmunoassay. Arterial TxB2 levels increased significantly 60 min after the onset of infusion of each gram-positive organism ($p < 0.05$), and returned to near preinfusion values in all piglets 30 min after administration of DAZ.

Quantitative arterial blood cultures were performed to ensure sterility before experimental bacterial infusion, to determine the degree of bacteremia during these relatively low-dose infusions ($4 \pm 1 \times 10^8$ cfu/kg/h), and to ensure there were no antimicrobial effects of DAZ. No piglets had evidence of bacteremia before experimental bacterial infusion. One h after the onset of the same bacterial infusion dose, we observed similar arterial blood colony counts for *S. epi* ($6.6 \pm 1.5 \times 10^4$ cfu/ml) and Ent ($12.1 \pm 6.2 \times 10^4$ cfu/ml), but 5- to 10-fold lower blood colony counts for GBS ($1.3 \pm 0.4 \times 10^4$ cfu/ml). Due to variability of bacterial concentration in blood among different piglets receiving the same bacterial infusion dose, the GBS culture results were only significantly different from *S. epi* values. Blood colony counts of all three organisms did not change significantly after administration of DAZ (GBS: $2.0 \pm 0.5 \times 10^4$ cfu/ml, Ent: $6.7 \pm 3.0 \times 10^4$ cfu/ml, and *S. epi*: $5.9 \pm 1.9 \times 10^4$ cfu/ml).

DISCUSSION

Pulmonary hypertension and concomitant elevations of arterial blood TxB2 levels occurred in neonatal piglets during IV infusion of GBS, Ent, and *S. epi*. The increase in PVR and TxB2 levels were reversed after the administration of a thromboxane synthetase inhibitor, DAZ, providing further evidence for thromboxane-associated pulmonary hypertension during several forms

Table 2. Similar blood gas changes in response to three gram-positive pathogens and DAZ in piglets (mean \pm SEM)*

	pH	$PaCO_2$ (mm Hg)	PaO_2 (mm Hg)	PvO_2 (mm Hg)
GBS (<i>n</i> = 4)				
PRE	7.40 ± 0.03	41 ± 2	93 ± 3	48 ± 1
60'	7.34 ± 0.02	40 ± 3	$59 \pm 4^\dagger$	33 ± 7
DAZ	7.37 ± 0.01	38 ± 2	76 ± 9	44 ± 2
Ent (<i>n</i> = 5)				
PRE	7.44 ± 0.02	38 ± 1	94 ± 2	42 ± 1
60'	$7.36 \pm 0.03^\dagger$	$44 \pm 2^\dagger$	$57 \pm 2^\dagger$	$28 \pm 1^\dagger$
DAZ	7.39 ± 0.02	41 ± 2	$69 \pm 5^\dagger$	36 ± 3
<i>S. epi</i> (<i>n</i> = 5)				
PRE	7.43 ± 0.02	37 ± 1	95 ± 3	44 ± 2
60'	$7.36 \pm 0.02^\dagger$	$42 \pm 2^\dagger$	$66 \pm 8^\dagger$	$31 \pm 2^\dagger$
DAZ	7.41 ± 0.02	38 ± 2	$81 \pm 3^\dagger$	$39 \pm 1^\dagger$

* PRE, before bacterial infusion; 60', 60 min into the bacterial infusion; DAZ, 30 min after administration of DAZ with ongoing bacterial infusion.

$^\dagger p < 0.05$ compared to PRE value.

Table 3. TxB2 levels increase during infusion of three gram-positive bacteria in piglets (mean \pm SEM)*

	GBS (<i>n</i> = 4)	Ent (<i>n</i> = 5)	<i>S. epi</i> (<i>n</i> = 5)
PRE (pg/ml)	30 ± 10	20 ± 7	31 ± 9
60' (pg/ml)	$1830 \pm 330^\dagger$	$1110 \pm 300^\dagger$	$1260 \pm 350^\dagger$
DAZ (pg/ml)	310 ± 95	$110 \pm 20^\dagger$	160 ± 50

* PRE, before bacterial infusion; 60', 60 min after the onset of the bacterial infusion; and DAZ, 30 min after the administration of dazm-grel with ongoing bacterial infusion.

$^\dagger p < 0.05$ compared to PRE values.

of gram-positive bacteremia in piglets. Pulmonary hypertension in response to GBS infusion has previously been reported in piglets (1–4), but this study is the first to demonstrate similar degrees of pulmonary hypertension, elevated Tx_{B2} levels, arterial hypoxemia, and reduction in cardiac output during Ent and S. epi bacteremia in neonatal animals. Previous reports of hemodynamic changes in piglets due to GBS may be relevant to but not specific for GBS sepsis in human newborns.

The P_w was elevated during GBS and Ent infusion, and returned to normal values after administration of dazmegrel. Simultaneous P_w and left atrial pressures have not been measured during bacterial infusion in piglets, but there are previous independent observations of normal left atrial pressures and elevated P_w during GBS infusion in piglets (1, 3, 11, 12). There is indirect evidence that thromboxane can cause pulmonary vasoconstriction in sheep (13), which could explain an increase in P_w with no change in left atrial pressure during bacterial infusion.

A component of the increase in PVR observed 1 h into bacterial infusion may also be secondary to hypoxic pulmonary vasoconstriction, as PaO₂ fell from approximately 95 to 60 torr and PvO₂ decreased from approximately 45 to 30 torr (Table 1). However, for all organisms we observed a bacterial dose-dependent increase in PVR, and with Ent and S. epi a significant increase in PVR occurred before developing significant reductions in arterial or mixed venous pO₂ (Fig. 1). Furthermore, previous observations in our laboratory demonstrate a mean P_{pa} of approximately 20–25 mm Hg for piglets with a PaO₂ of 60 torr, which would not explain the observed increases in mean P_{pa} to 37–44 mm Hg during our experiments (14).

Why thromboxane-associated pulmonary hypertension occurs in several animal species receiving IV gram-positive or gram-negative bacteria is uncertain. Some possibilities include 1) different components specific for each organism are capable of inducing pulmonary hypertension, 2) a bacterial component common to all organisms can induce pulmonary hypertension, or 3) a nonspecific circulating particulate/embolic effect is responsible for the physiological changes observed during bacterial infusion in piglets. There are data to support the first contention based on the different structures of *E. coli* endotoxin compared to two identified GBS polysaccharide “toxins,” all of which produce pulmonary hypertension during IV infusion (15, 16). Two groups of investigators have identified two different GBS polysaccharide “toxins;” one is derived from the intact organism and apparently related to the GBS type and group specific polysaccharides (15), whereas the other is an unrelated mannan polysaccharide derived from GBS culture supernatant (16). No previous studies have described a common bacterial component that can induce pulmonary hypertension. In the piglet model used by several groups of investigators, a nonspecific particulate effect has not been excluded. A nonspecific embolic effect is less likely to explain our results due to the lack of bacterial aggregates in the inoculum. Furthermore, the lack of histological evidence for lung injury or pulmonary emboli by light microscopy in lung sections from related experiments in our laboratory (6), and the rapid reversal of pulmonary hypertension with administration of DAZ suggests a nonspecific particulate or embolic phenomenon is not responsible for pulmonary hypertension during gram-positive bacteremia in piglets.

It is uncertain if the degree of bacteremia that produces pulmonary hypertension in piglets (10⁴–10⁵ cfu/ml) is relevant to human newborns with sepsis due to GBS, Ent, or S. epi. There are no reports on quantitative blood cultures from septic human newborns with GBS, Ent, or S. Epi; other pediatric pathogens including *Hemophilus influenzae*, *Streptococcus pneumoniae*, and *E. coli* have been isolated in densities of more than 10³ cfu/ml from patients with sepsis of meningitis (17). The reason for a similar degree of pulmonary hypertension at a lower arterial blood colony density for GBS compared to Ent and S. epi is unclear. This finding suggests GBS may be a more potent stimulus for Tx_{B2} synthesis and pulmonary hypertension. Alternatively, piglets may clear GBS more rapidly than Ent or S. epi but

stimulate thromboxane-associated pulmonary vasoconstriction equally.

Our observations have potentially important clinical implications. Hammerman *et al.* (5) have reported elevated thromboxane levels in human infants with GBS sepsis and persistent pulmonary hypertension of the newborn, suggesting a pathogenic role for thromboxane in some of these cases. Therefore, it is possible that blood thromboxane levels may be elevated in human newborns with other forms of bacteremia. The clinical role of thromboxane synthetase inhibitors should be pursued as an adjunctive treatment for human newborns with hypoxemia, bacteremia, and pulmonary hypertension. Our results suggest there may be a common component in gram-positive organisms capable of inducing pulmonary hypertension. Identifying such a common component of gram-positive bacteria may offer new strategies for developing monoclonal antibody therapy to treat sepsis and pulmonary hypertension in newborns.

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