# ETS AND SUDDEN INFANT DEATH SYNDROME

## Trends in SIDS

Sudden infant death syndrome (SIDS), defined as the sudden death of an infant that remains unexplained by clinical or necropsy evidence, is the most common single cause of death in the postneonatal period (1-12 months) in most developed countries[1]. Following campaigns discouraging parents from putting babies to sleep in the prone position, SIDS deaths have reduced substantially in several countries, including the UK, Ireland, USA, New Zealand, Australia, Scandinavia, Germany and the Netherlands[2-10]. In the UK the rate of SIDS fell by 70% between 1987 and 1992, from 2.2 to 0.7 per 1000 live births[7]. This decline continued between 1995 and 2003, with rates in England and Wales falling from 0.61 to 0.29. However, during the same period there was an increase, from 0.02 to 0.19, in the rate of infant deaths classified as "unascertained", a term that is to some extent used interchangeably with SIDS[11], complicating interpretation of the apparent decline in SIDS deaths. Although the rate of SIDS is now about 50% what it was in the late 1990s[12], in recent years the rate of decline has experienced a plateau[13].

## Factors associated with SIDS

Epidemiological studies have identified a large number of factors that are associated with SIDS e.g.[1,9,10,14,15]. Other than prone sleeping position, these factors include the use of soft mattresses, overheating, head covering, season, having had a recent illness (gastro-intestinal as well as respiratory), complications of pregnancy, low birthweight, premature birth, not being immunised, male sex, central nervous system abnormalities, lack of breast-feeding, using a pacifier, sharing a bed with the parents, intrauterine growth retardation, alcohol consumption and illicit drug use by the mother during pregnancy, young age of the mother, no pre-natal care, size of family, race, the mother's education, and socio-economic status. The role of smoking by the parents, with particular relevance to possible effects of ETS exposure, is the main interest of this summary.

## Maternal postnatal smoking

Although it has been claimed that exposure of infants to ETS is associated with SIDS, there are difficulties in interpreting the epidemiological data. Studies have compared the incidence of SIDS among infants exposed to ETS by a parent who smokes after the birth with the incidence among infants who have not been so exposed.

Some 32 studies on SIDS and ETS exposure from smoking by the mother after pregnancy have been published[8,10,12,16-44]. Of these, 14 studies[8,10,16,21,22,24,25,27,28,30,33,39,41,43] reported a statistically significant increased risk of SIDS among exposed infants based on adjusted analyses, four[32,34,35,40] reported a significant increase in unadjusted but not adjusted analyses, and seven[17,19,23,26,29,38,42] reported a significant unadjusted increase but did not report adjusted findings (Table 1). One further study[18] reported a raised unadjusted relative risk per cigarette per day that was of borderline significance. In addition, nine of these studies[16,22,24,27,28,30,34,35,43] also reported evidence of a dose-response relationship (data not shown), although in one of these studies[43] this was by the number of smokers the child was exposed to.

**Maternal smoking in pregnancy**

As ETS exposure is the main interest of this review, a detailed presentation of the evidence relating SIDS risk to maternal smoking in pregnancy is not provided. In any case, it is usually difficult to separate out the effects of smoking during pregnancy, as most women who smoke during pregnancy continue to do so after the birth of their child[45-47]. Indeed the only study identified as presenting results jointly by prenatal and postnatal maternal smoking[34] included only two SIDS cases exposed only prenatally and one exposed only postnatally, as against 25 exposed at both times, the numbers being far too small to estimate the individual effects reliably. Not surprisingly, therefore, many studies[8,22,24,29,30,32,34] report very similar relative risks for maternal smoking during and after pregnancy, though some studies[12,31,37,40] report rather higher estimates for smoking in pregnancy. A large multi centre European case-control study[9] reported results only for maternal smoking in pregnancy as this explained SIDS risk better than did maternal smoking after pregnancy. Most of the more recently published studies on smoking and SIDS appear to have concentrated solely on maternal smoking during pregnancy[45,46,48-61]. Relative risks for an outcome of SIDS from the majority of these studies were similar to those previously reported by other studies for maternal smoking after pregnancy, although three studies[49,57,60] reported relative risks that were substantially higher. However, two of these studies[49,57] were based on very small numbers, and one of these studies[57] was restricted to infants who had already had a life-threatening event, while in the third study the very elevated relative risk was seen among Asian participants only, with relative risks for other ethnic groups showing a similar pattern to other studies.

### Smoking by the father

Nineteen studies on the risk of SIDS and paternal smoking have been published[8,9,16,17,19,20,22,24,27,28,32-34,40,41,62-65] (Table 2). Of these, 13[8,9,17,22,24,27,28,32,33,40,41,64,65] reported a statistically significant increase in the risk of SIDS among infants whose fathers smoked, although in four of these[17,32,40,41] this was only in unadjusted analyses. In the majority of studies the risk estimates for paternal smoking are less than the corresponding risk estimates for maternal postnatal exposure shown in Table 1. However, there are some exceptions[24,32,41]. (Note that Table 2 excludes some publications considered in Table 1, to avoid duplication with the combined analyses of Carpenter *et al*[9]). It should also be noted that although three studies[8,32,33] do overlap, they are included in their own right as they are based on a longer study periods and/or a larger number of cases and controls than those considered by Carpenter *et al*.

### Smoking by other household members

In addition, six studies investigated the relationship between ETS and smoking by other members of the household (data not shown). Two of these reported a significant unadjusted relative risk that became non-significant after adjustment[22,30], one reported a significant adjusted association in whites but not blacks[21], two reported significant adjusted associations using various indices[8,24], and one reported no significant association[25].

### Interpretation of the results

A number of reviews of the association between SIDS and parental smoking have previously been published[1,13,14,28,66-71]. When attempting to interpret the results relating to ETS exposure, various points should be borne in mind.

<u>Limited attention to potential confounding factors</u>

Fourteen of the studies[12,17-20,23,26,29,37,38,42,44,62,63] reporting an association between SIDS and ETS exposure have not adjusted for any other risk factors, while many others[8,10,16,21,24,25,30,31,33-35,40,41,43,64,65] have only taken a few of them into account. Only nine studies[9,22,27,28,32,36,39,72,73] have taken a fairly extensive list of potential confounders into account in at least some of their analyses.

Effect of adjustment for multiple risk factors

Six publications[9,22,27,28,72,73] based on large studies (of at least 200 SIDS cases) have reported both unadjusted risk estimates and risk estimates adjusted for a large number of potential confounding variables. With the exception of one study[73], all have found that a major part of the unadjusted association can be explained by confounding. Thus, for example, the Mitchell I study[22] found that adjustment reduced the relative risk for maternal smoking after pregnancy from 4.24 to 1.70, i.e. explained 78.4% of the excess risk.[1] Other studies of maternal smoking after pregnancy found that the percentage of the excess risk explained was 75.5% or 84.9%, depending on the index used[28], and 38.7%[27]. For paternal smoking, corresponding estimates were 73.8%[22], 39.3%[27], 66.9%[9], 66.2%[72] and 13%[73]. Since such adjustments will inevitably be incomplete, partly because not all relevant factors will have been considered and partly because data errors or the use of surrogate variables limit the ability to control for confounding, it is not implausible that most, if not all, of the claimed SIDS/ETS association could, in fact, be explained by confounding. It has been observed that multiple concurrent risks are a characteristic of the majority of SIDS cases[74], and it has also been suggested that risk factors such as prematurity, multiple births, large family size, birth order and lack of breastfeeding have become more important features in SIDS cases in recent years[53], so adjustment for potential confounders in any study of ETS and SIDS needs to be carried out before an accurate assessment of the role of smoking can be obtained.

Relevance of other possible causal factors

In a study involving over 30,000 infants in which electrocardiograph measurements were made shortly after birth[75], prolongation of the QT interval was associated with a more than 40-fold increased risk of SIDS, with this abnormality being seen in 50% of the infants dying of SIDS. These findings have been confirmed by more recent studies[76-78], although the proportion of infants with the disorder is somewhat lower than first reported, at around 12-20%[76,78,79]. Long QT interval is a major risk factor that could not have been caused by postnatal ETS exposure and which has not been taken into account in any of the epidemiological studies of ETS and SIDS.

[1] If $RR_U$, $RR_A$ are the unadjusted and adjusted relative risks, the ratio of excess risks given by $S = (RR_A-1)/(RR_U-1)$ and the percentage of the excess risk explained by adjustment is $100(1-S)$.

Elsewhere, it has been suggested that there may be a genetic basis for SIDS, with results from several studies supporting the involvement of genes responsible for the embryologic origin and development of the autonomic nervous system[80]. Again, none of the published studies on ETS and SIDS appear to have considered this possibility.

Disentangling effects of ETS exposure and of maternal smoking in pregnancy

Even if the association between parental smoking and SIDS cannot be fully explained by uncontrolled confounding by other risk factors, it may result not from ETS exposure but from an effect of maternal smoking during pregnancy. Most studies[8,22,24,28,30,34,72,73], though not all[21], have found that the association of SIDS with postnatal maternal smoking or paternal smoking is reduced if adjustment is made for maternal smoking in pregnancy, or if attention is restricted to non-smoking mothers. Also, as noted above, some recent studies have reported higher relative risks for maternal smoking during pregnancy than for postnatal parental smoking.

## Conclusion

Despite extensive research, the causes of SIDS, and the mechanisms by which such causes may act, are far from clear. Furthermore, the epidemiological data are difficult to interpret. It is concluded that the scientific evidence, considered as a whole, does not adequately demonstrate that exposure to ETS is a cause of SIDS.

## ETS AND SIDS

## THE DATA

The tables that follow summarize the key evidence on SIDS and parental smoking, as indexed by maternal smoking after pregnancy (Table 1) and paternal smoking (Table 2). The tables show, for each successive study providing data, relative risks (RRs) and 95% confidence intervals (CIs), unadjusted, and adjusted for the factors listed. The tables are adapted and extended from tables presented by Thornton and Lee[14] and include all the relevant studies considered in previous reviews of this subject[1,13,28,66-71].

# TABLE 1 Maternal smoking after pregnancy and SIDS

| Study Ref | Author | Year | Location | Unadjusted RR (95% CI) | Adjusted RR (95% CI) | Adjustment factors |
|---|---|---|---|---|---|---|
| [16] | Bergman | 1976 | USA, Washington State | 2.42(1.22-4.82)[a] | 2.38(1.17-4.83)<br>2.05(1.00-4.24) | MA<br>ED |
| [17] | Cameron | 1986 | Australia, Victoria | 4.04(2.63-6.20)[a,b] | - | - |
| [18] | Victora | 1987 | Brazil | 1.06(1.00-1.11)[c] | - | - |
| [19] | McGlashan | 1989 | Australia, Tasmania | 1.92(1.26-2.92)[a] | - | - |
| [20] | Engelberts | 1991 | Netherlands | 1.47(0.97-2.23)[a] | - | - |
| [21] | Schoendorf | 1992 | USA, National | | | |
| | (i) after or during pregnancy | | | | | |
| | - Black | | | 2.77(2.08-3.70)[a,d] | 2.78(2.12-3.64) | ED,MA,MS,MSA,MSP |
| | - White | | | 3.65(2.27-4.81) | 2.66(2.04-3.48) | As above |
| | (ii) only after pregnancy | | | | | |
| | - Black | | | 2.40(1.49-3.83)[d] | 2.33(1.48-3.67) | As above |
| | - White | | | 2.22(1.29-3.78) | 1.75(1.04-2.93) | As above |
| [22] | Mitchell I | 1993 | New Zealand | | | |
| | - any | | | 4.24(3.39-5.31)[e] | 1.70(1.21-2.37) | A,AN,BF,BS,BW,CAN, GA,MA,MAP,MS,P,R, REG,S,SA,SE,SES,SL,TD |
| | - in house | | | 2.20(1.38-3.51)[f] | - | - |
| | - never in house | | | 5.07(1.50-15.41) | - | - |
| [23] | Jorch | 1994 | Germany | 3.30 (2.30-4.80)[g] | - | - |
| [24] | Klonoff-Cohen | 1995 | USA, California | | | |
| | - any | | | 3.13(1.75-5.60) | 2.28(1.04-4.98) | AN,BF,BW,MC,MSP,SL |
| | - same room | | | 6.17(2.60-14.61) | 4.62(1.82-11.77) | As above |
| [25] | Ponsonby | 1995 | Australia, Tasmania | 3.96(1.91-8.24) | 3.82(1.43-10.2)<br>2.39(1.01-6.00) | BH,FAS,MA,SL,VHC<br>EMP,FAS,MA,SL |
| [26] | Wigfield | 1995 | England, Avon | | | |
| | - study 1 | | | 2.90(1.60-5.40) | - | - |
| | - study 2 | | | 4.60(1.90-11.40) | - | - |
| [27] | Brooke | 1997 | Scotland | 5.91(3.61-9.68) | 4.01(2.19-7.33)[a] | BF,BW,CBP,DEP,DRG, ED,GA,MA,MS,MTO, OID,P,S,SES,SL,SPR,SS, SWD,SYM,TOG |
| [28] | Mitchell II | 1997 | New Zealand | | | |
| | - after birth | | | 6.56(4.32-9.95)[a] | 6.26(4.07-9.63)[a]<br>2.36(1.27-4.37)[a] | BS<br>BF,BS,BW,MA,MS,P,R,S, SA,SL |
| | - 2 months after birth | | | 5.85(3.37-10.20)[a] | 5.42(3.10-9.47)[a]<br>1.73(0.75-3.95)[a] | BS<br>BF,BS,BW,MA,MS,P,R,S, SA,SL |
| [29] | Schellscheidt | 1997 | Germany | 5.90(2.60-13.90)[g] | - | - |
| [30] | Alm | 1998 | Norway, Sweden, Denmark | 3.80(2.80-5.30) | 3.70(2.50-5.50) | A,ED,MA |
| [31] | Kohlendorfer | 1998 | Austria | | | |
| | - early SIDS | | | 1.90(0.90-4.00) | Not significant | AN,BW,FID,GA,MA,NS, RAE,SL |
| | - late SIDS | | | 1.00(0.50-1.80) | Not significant | As above |
| [32] | L'Hoir | 1998 | Netherlands | 2.80(1.51-5.18)[a] | 3.53(0.73-16.99)[a,g] | A,AL,BF,BW,CR,D,DU, MA,MB,SES,SL,SSU |
| [33] | Blair | 1999 | England, 5 areas | 5.91(4.30-8.12)[a,g] | 6.05(4.23-8.66)[a] | A,BS |
| [34] | Dwyer | 1999 | Australia, Tasmania | 3.38(1.58-7.23) | 2.20(0.67-7.23)[a] | MSP |

| Study Ref | Author | Year | Location | Unadjusted RR (95% CI) | Adjusted RR (95% CI) | Adjustment factors |
|---|---|---|---|---|---|---|
| [35] | Jonville-Bera | 2001 | France | 1.72(1.09-2.72)[a] | 1.72(0.95-3.11) | BF,BW,PI,S,SL,TM,V |
| [36] | Toro | 2001 | Hungary | 0.85(0.27-2.67)[a] | 0.90(0.20-3.00) | AL,AP,BOF,BW,DEP,GA, IP,MA,MC,MI,P,PI,SL |
| [37] | Iyasu | 2002 | USA, 3 states | 1.20(0.50-2.40) | - | - |
| [8] | McDonnell | 2002 | Ireland | 7.52(4.78-11.81) | 4.16(2.48-6.97) | AL,DEP,ED,MA,MSP |
| [38] | McMartin | 2002 | USA, Maryland | 4.36(1.60-11.88)[a,g] | - | - |
| [39] | Sanderson | 2002 | England, Sheffield | - | 7.24(2.76-19.01) | BF,BW,DEP,DP,GA,HV, MA,MB,MPH,MSF,P,S, SB,YB |
| [40] | Nelson | 2005 | Hong Kong | 4.90(1.20-20.10) | 4.60(0.90-22.70) | S,SES |
| [41] | Stray-Pederson | 2005 | Norway | 11.63(3.92-34.49)[a] | 6.60(1.10-37.50) | BF,BS |
| [42] | Tappin | 2005 | Scotland | 5.81(3.01-11.23)[a] | - | - |
| [10] | Howard | 2007 | United Kingdom | 3.39(2.19-5.26) | 2.50(1.29-4.88) | DP,S |
| [43] | Ruys | 2007 | Netherlands | - | 5.00(3.10-8.00)[h] | BS |
| [12] | Blair | 2009 | England, 6 counties | 2.89(0.95-8.80)[ag] | - | - |
| [44] | Machaalani | 2009 | Australia, New South Wales | 3.07(0.81-11.71)[a] | - | - |

[a] Estimated from data given
[b] Women smoking 20 or more cigarettes per day
[c] Relative risk per cigarette per day, but not clear whether data refers to maternal smoking during or after pregnancy
[d] Relative risk compared to mothers smoking neither during pregnancy nor after infant's birth
[e] Data came from reference [81]. An alternative reference [82] gave an unadjusted estimate of 4.24(3.33-5.40) and an estimate of 1.79(1.30-2.48), adjusted for a similar list of factors but including INT and MP and excluding CAN
[f] Data came from reference [83]
[g] Postnatal ETS exposure of child
[h] Postnatal smoking by both parents

Key to adjustment factors:
A = Postnatal age; AL = Alcohol consumption by mother; AN = Antenatal classes; AP = Apgar score <7; BF = Breast feeding; BH = Bedroom heating; BOF = Bottle feeding; BS = Bed sharing; BW = Birthweight; CAN = Cannabis use by mother since birth; CBP = Cot bumper used; CR = Change in routine; D = Dummy use; DEP = Deprivation; DP = Depression; DRG = Drug treatment; DU = Duvet use; ED = Education; EMP = Employment status; FAS = Family history of asthma; FID = Family history of infant death; GA = Gestational age; HV = Number of visits by health visitor; IP = Interval between pregnancies; MA = Maternal age; MAP = Mother's age at first pregnancy; MB = Multiple birth; MC = Medical conditions at birth; MI = Maternal illness; MPH = Maternal psychiatric history; MS = Marital status; MSA = Maternal postnatal smoking; MSF = Maternal satisfaction with infant feeding; MSP = Maternal smoking in pregnancy; MTO = Old mattress used; NS = Night sweating; OID = Other infant death; P = Parity; PI = Previous illness; R = Race; RAE = Repeated apnoea episodes; REG = Region; S = Sex; SA = School leaving age; SB = Season of birth; SE = Season; SES = Socio-economic status; SL = Sleep position; SPR = Sleeps with parents; SS = Sweating during sleep; SSU = Use of sleep sack; SWD = Usually swaddled; SYM = Symptoms; TD = Time of day; TM = Type of mattress used; TOG = Tog value; V = Vaccinations; VHC = Visits to health clinic; YB = Year of birth within study

## TABLE 2 Paternal smoking and SIDS

| Study Ref | Author | Location | Year | Unadjusted RR (95% CI) | Adjusted RR (95% CI) | Adjustment factors |
|---|---|---|---|---|---|---|
| [16] | Bergman | USA, Washington State | 1976 | 1.53(0.78-3.01)[a] | - | - |
| [62] | Lewak | USA, California | 1979 | No association | - | - |
| [17] | Cameron | Australia, Victoria | 1986 | 1.85(1.32-2.60)[a] | - | - |
| [63] | Lee | Hong Kong | 1989 | 3.57(0.98-13.0) | - | - |
| [19] | McGlashan | Australia, Tasmania | 1989 | 1.73 [p=0.05] | - | - |
| [20] | Engelberts | Netherlands | 1991 | | | |
| | - during pregnancy | | | 1.02(0.68-1.55)[a] | - | - |
| | - after birth | | | 0.96(0.63-1.45)[a] | - | - |
| [64] | Nicholl | UK, 8 centres | 1992 | 1.99(1.38-2.86) | 1.63(1.11-2.40) | BW,MA,P,SRA |
| [65] | Gilbert | UK, Bristol | 1993 | 2.78(1.59-4.87)[a] | 2.43(1.32-4.48)[a] | SES |
| [22] | Mitchell I | New Zealand | 1993 | 2.41(1.92-3.02) | 1.37(1.02-1.84) | A,BF,BS,BW,MA,MS,MSP,R, REG,S,SE,SES,SL,TD |
| [24] | Klonoff-Cohen | USA, California | 1995 | | | |
| | - during pregnancy (around mother) | | | 3.56(2.11-6.00) | - | - |
| | - after birth | | | 3.53(1.99-6.27) | 3.46(1.91-6.28) | AN,BF,BW,MC,MSP,SL |
| | - after birth, in same room | | | 9.20(3.66-23.15) | 8.49(3.33-21.63) | As above |
| [27] | Brooke | Scotland | 1997 | 2.40(1.57-3.65)[a] | 1.85(1.08-3.18)[a] | BF,BW,CBP,DEP,DRG,ED, GA,MA,MS,MTO,OID,P,S, SES,SL,SPR,SS,SWD,SYM, TOG |
| [28] | Mitchell II | New Zealand | 1997 | | | |
| | - after birth | | | 3.84(2.54-5.80)[a] | - | |
| | - 2 months after birth | | | 3.21(1.87-5.52)[a] | - | |
| | - time not stated | | | - | 2.1(1.3-3.40)[a] | MSA |
| [32] | L'Hoir[b] | Netherlands | 1998 | 3.76(2.08-6.82)[a] | - | - |
| [33] | Blair[c] | England, 5 areas | 1999 | 3.16(2.45-4.08)[a,d] | 2.88(1.72-4.83)[a,d] | A,AL,BW,DU,EMP,FS,GA, HC,II,MA,MSP,PDU,S,SL, SPR,TD |
| | - post-matched controls | | | 2.25(1.60-3.16)[e] | 1.89(1.23-2.90)[e] | AL,BW,DU,GA,LBP,MB,MC, MSP,P,PAL,PDU,RD,S,SCBU |
| [34] | Dwyer | Australia, Tasmania | 1999 | 1.10(0.56-2.16)[f] | - | - |
| [8] | McDonnell[g] | Ireland | 2002 | | | |
| | - father during pregnancy | | | 4.60(3.04-6.92) | 2.65(1.49-4.72) | AL,DEP,ED,MA,MSP |
| | - father after birth | | | 4.40(2.92-6.63) | 2.64(1.49-4.67) | As above |
| [9] | Carpenter | Europe, 20 regions | 2004 | 2.69(2.24-3.23)[a,f] | 1.56(1.24-1.97)[a,f] | A,ALTE,BW,D,EMP,MA,MB, MS,MSP,P,S,SC,SCBU,SL,UP |
| [40] | Nelson | Hong Kong | 2005 | | | |
| | - before pregnancy | | | 3.40(1.20-9.80) | 2.90(0.96-8.80) | S,SES |
| | - 2nd trimester | | | 3.40(1.20-9.80) | 2.90(0.96-8.80) | As above |
| | - since birth | | | 3.50(1.20-10.00) | 3.00(0.99-9.10) | As above |
| [41] | Stray-Pedersen | Norway | 2005 | 3.48(1.29-9.43)[a] | 6.90(1.00-47.00) | BF,BS |

[a] Estimated from data given
[b] Based on 73 cases and 146 controls, 31 cases and 61 controls appear to have been included in study by reference[9]
[c] Based on 325 cases and 1300 controls, 195 cases and 780 controls included in study by reference[9]

[d] Data came from reference[73]
[e] Data came from reference[72], based on 195 cases and 780 controls
[f] Smoking postnatally by any household resident other than the mother
[g] Based on 203 cases and 608 controls, 92 cases and 322 controls appear to have been included in study by reference[9]

Key to adjustment factors:
A = Postnatal age; AL = Maternal alcohol consumption; ALTE = Apparent life-threatening events; AN = Antenatal classes; BF = Breast feeding; BS = Bed sharing; BW = Birthweight; CBP = Cot bumper used; D = Dummy use; DEP = Deprivation; DRG = Drug treatment; DU = Use of illegal drugs; ED = Education; EMP = Employment status; FS = Family size; GA = Gestational age; HC = Head covering; II = Infant illness; LBP = Late booking of pregnancy; MA = Maternal age; MB = Multiple birth; MC = Medical conditions at birth; MS = Marital status; MSA = Maternal postnatal smoking; MSP = Maternal smoking in pregnancy; MTO = Old mattress used; OID = Other infant death; P = Parity; PAL = Paternal alcohol consumption; PDU = Paternal use of illegal drugs; PSB = Previous stillbirth; R = Race; RD = Resuscitation at delivery; REG = Region; S = Sex; SC = Study centre; SCBU = Admission to special care baby unit; SE = Season; SES = Socio-economic status; SL = Sleep position; SPR = Sleeps with parents; SRA = State of major accommodation; SS = Sweating during sleep; SWD = Usually swaddled; SYM = Symptoms; TD = Time of day; TOG = Tog value; UP = Urinary tract infection in pregnancy.

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